**Effect of 1.5% Topical Diclofenac on Clinical Neuropathic Pain**


**ABSTRACT**

**Background:** Neuropathic pain is a condition resulting from injury to the peripheral and/or central nervous system. Despite extensive research over the last several decades, neuropathic pain remains difficult to manage.

**Methods:** The authors conducted a randomized, placebo-controlled, double-blinded, and crossover clinical trial to examine the effect of 1.5% topical diclofenac (TD) on neuropathic pain. The authors hypothesized that 1.5% TD would reduce the visual pain score and improve both quantitative sensory testing and functional status in subjects with neuropathic pain. The authors recruited subjects with postherpetic neuralgia and complex regional pain syndrome. The primary outcome was subject's visual pain score.

**Results:** Twenty-eight subjects completed the study (12 male and 16 female) with the mean age of 48.8 yr. After 2 weeks of topical application, subjects in 1.5% TD group showed lower overall visual pain score compared with placebo group (4.9 [1.9] vs. 5.6 [2.1], difference: 0.8; 95% CI, 0.1 to 1.3; \(P = 0.04\)) as well as decreased burning pain (2.9 [2.6] vs. 4.3 [2.8], difference, 1.4; 95% CI, 0.2 to 2.6; \(P = 0.01\)). There were no statistical differences in constant pain, shooting pain, or hypersensitivity over the painful area between the groups. This self-reported improvement of pain was corroborated by the decreased pain summation detected by quantitative sensory testing. There were no statistically significant changes in functional status in these subjects. There were no complications in both groups.

**Conclusion:** The findings indicate that 1.5% TD may serve as an effective treatment option for patients with neuropathic pain from postherpetic neuralgia and complex regional pain syndrome. (Anesthesiology 2015; 123:191-8)

**What We Already Know about This Topic**

- Neuropathic pain is not uncommon and is difficult to treat.
- Topical nonsteroidal antiinflammatory preparations have not been carefully evaluated for the treatment of neuropathic pain.

**What This Article Tells Us That Is New**

- Using a blinded, placebo-controlled, crossover trial design, lower pain scores were observed after treatment with topical diclofenac. Several secondary endpoints and functional status were unchanged.
- Topical diclofenac was not associated with complications within the timeframe of the study.

NEUROPATHIC pain is a chronic pain condition resulting from injury to the peripheral and/or central nervous system. Despite extensive research over the last several decades, neuropathic pain remains difficult to manage. One of the primary reasons is the lack of effective pharmacotherapy for neuropathic pain conditions. Although several categories of medications (e.g., tricyclic antidepressants, anticonvulsants, or opioids) are currently being used for the treatment of neuropathic pain, their effectiveness remains largely uncertain.1-4 Studies have found that nonsteroidal antiinflammatory drugs (NSAIDs) are consistently among the most commonly prescribed pain medications for neuropathic pain.5-6 In addition, there is a significant heterogeneity with regard to the clinical presentation and comorbidity associated with neuropathic pain, suggesting that there are diverse mechanisms of neuropathic pain, and new pharmacological tools would be needed to improve the current clinical management of neuropathic pain. In this regard, topical diclofenac (1.5%) may be an effective treatment for neuropathic pain such as postherpetic neuralgia (PHN) and complex regional pain syndrome (CRPS) because NSAIDs could modulate the mechanisms of neuropathic pain and provide effective analgesia.7 Moreover, topical diclofenac (1.5%) has been used in clinical subjects of osteoarthritis with a favorable systemic.
side effect profile. Both male and female subjects including elderly subjects have been treated with topical diclofenac (1.5%) with a safety record. Topical diclofenac (1.5%) has few drug–drug interactions due to its topical formulation and is well tolerated. This pharmacological feature is significant because patients with neuropathic pain are often treated with multiple medications.

We conducted a randomized, placebo-controlled, double-blinded, and crossover clinical trial to examine the effect of 1.5% topical diclofenac on neuropathic pain. In a crossover design, a subject was first assigned to the drug or placebo arm and then switched over to the opposite arm. This design improves the power of data analysis, requires fewer subjects, and allows subjects to maintain other pain medications without interruption. This design is possible in this study because 1.5% topical diclofenac has a short elimination time. This feature allowed us to propose a short washout period (1 week) between two arms of this crossover study design. We hypothesized that 1.5% topical diclofenac would reduce pain score (visual analog scale [VAS]) and improve both quantitative sensory testing (QST) and functional status in subjects with neuropathic pain.

Materials and Methods

Study Subjects

We conducted a double-blind, placebo-controlled, crossover clinical trial at the Massachusetts General Hospital (MGH) Center for Translational Pain Research affiliated with MGH, a tertiary referral center in Boston, Massachusetts. A study physician explained the protocol, answered any question, and obtained an institutional review board (IRB, MGH, Boston). The Inclusion and Exclusion Criteria

Study Protocol

The entire study took 5 weeks (phase I, washout, phase II) including four office visits and two phone interviews (fig. 1). Phase I (Weeks 1 and 2). During the initial visit, after obtaining the study consent, we gathered the data listed in figure 1. Baseline QST was performed. Subjects were randomized...
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Fig. 1. Study flow diagram. QST = quantitative sensory testing.

The second office visit was at the end of week 2. During this visit, the subject was asked to fill out Pain Questionnaire and Short Form (36) Health Survey (SF-36) as well as undergo QST. Instructions were then given regarding the following washout period.

Washout Period. This was a 1-week period. During this period, no study medication was applied. The third office visit was made at the end of the washout period. During this visit, the subject was asked to fill out Pain Questionnaire and SF-36 as well as undergo QST. The subject’s study medication was then switched over. For example, if the subject was applying 1.5% topical diclofenac in phase I, then he/she used placebo in phase II. At this visit, the study medication or placebo for phase II was given to the subject with the same instructions used in phase I.

Phase II. The same study procedure as that in phase I was followed in phase II, including the dose regimen. Each subject was interviewed over phone at the end of week 4 to confirm that he/she was complying with the study protocol and there were no significant issues with the study. The next office visit was at the end of week 5. During this visit, the subject was asked to fill out Pain Questionnaire and SF-36 as well as undergo QST. Subject was then discharged from the study.

To assess subject compliance, returned study or placebo medication bottles were weighed on a digital scale at the beginning and end of each phase (i.e., phase I and phase II each had documented weights of these medication or placebo bottles). In addition, all subjects were allowed to continue their current pain medications without changes during the entire study period. Because the study medication and placebo were tested in the same subjects using a crossover design, there were no differences in other medications between these study medication and placebo groups (i.e., between two phases of the same study in the same study subjects). Finally, the oversight regarding the data and safety of this study was provided according to the stipulations of our IRB. Our IRB mandates that investigators report all adverse events and any deviation from the approved protocol within 24 h of occurring to IRB. The review board will have the discretion to investigate further if deemed necessary. There were no adverse events reported during this trial.

Quantitative Sensory Testing

Quantitative sensory testing is a method to assess the psychophysical response to a set of calibrated stimulation. In this study, heat stimulation was used in all QST sessions following a protocol detailed in our previous publication. To detect heat pain threshold, a contact thermode was placed at a designated body part (e.g., forearm). The temperature at the thermode–skin interface increased at 1°C/s from a baseline of 32°C to a cutoff temperature of 52°C. A subject was asked to stop stimulation by pressing a computer mouse button when pain was first experienced. This same test was repeated three times with a 3-min interval and the average threshold temperature from three tests was used as the pain threshold temperature (in degree Celsius). To detect heat pain tolerance,
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Thirty-five subjects were consented and enrolled in the study. Twenty-eight subjects completed the study, including 12 male and 16 female subjects with the mean age of 48.8 yr (22 to 68 yr). Because of the length of our study period (5 weeks in total) and the well-known high dropout rate of chronic pain subjects, we had planned to recruit more subjects than what is needed based on our a priori sample size calculation. In the actual study, we had a lower dropout rate than we anticipated. Therefore, we stopped recruiting when the number of subjects who completed the study reached the precalculated sample size. The reasons for discontinuation (fig. 2) from the study in seven subjects included skin sensitivity to solution (n = 1), concurrent use of NSAIDs (n = 2), positive urine drug screen (n = 3), wrong type of pain (n = 1), and started new pain medication during the course of the study (n = 1). Some subjects were discontinued from the study due to more than one reason listed in figure 2. All subjects reported chronic pain with neuropathic characteristics. Subjects described their pain as “constant, burning, tingling, or shooting pain.” The specific etiology of their pain included trauma (n = 16), PHN (n = 3), surgical scar (n = 6), and idiopathic (n = 3). The location of pain included lower extremity (n = 3), upper extremity (n = 6), and trunk (n = 3). The duration of pain ranged from 6 months to 23 yr, with a mean duration of 7.2 yr and a median duration of 5 yr. Common comorbid illness included diabetes mellitus (n = 5), history of depression (n = 8), and anxiety (n = 7). Subjects work history revealed the following: currently working (n = 13), retired (n = 4), and on disability (n = 14). Some subjects checked more than one option in their work history.

Primary Outcome Measure (VAS Score)

After 2 weeks of topical application, subjects in 1.5% diclofenac group showed lower VAS scores (mean [SD]) compared with placebo group. 4.9 (1.9) versus 5.6 (2.1) (difference: 0.8; 95% CI, 0.1 to 1.3; P = 0.04; fig. 3).
Secondary Outcome Measures
Clinical Neuropathic Pain Features. After 2 weeks of topical application, the VAS score of burning pain was lower in 1.5% diclofenac group (mean [SD]) than in placebo group, 2.9 (2.6) versus 4.3 (2.8) (difference 1.4; 95% CI, 0.7 to 2.1; \( P = 0.01 \); fig 4). The VAS score of constant pain and hypersensitivity was also lower in 1.5% diclofenac group than in placebo group; however, statistical significance was not reached (fig 5—constant pain: 4.0 (2.9) vs. 4.3 (2.9), difference, 0.3; 95% CI, 0.7 to 1.3; \( P = 0.2 \); fig. 6—hypersensitivity: 3.0 (3.0) vs. 3.4 (3.3), difference, 0.4; 95% CI, 0.6 to 1.5; \( P = 0.2 \)). There were no significant changes in the intensity of shooting pain before and after 1.5% topical diclofenac treatment (data not shown).

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**Fig. 2.** Flowchart illustrating subject recruitment and withdrawal. DOA = drug of abuse; NSAIDs = nonsteroidal antiinflammatory drugs.

**Fig. 3.** Effect of 1.5% topical diclofenac on visual analog scale (VAS). Histograms of VAS pain scores before and after the application of 1.5% topical diclofenac or placebo solution. \( *P = 0.04 \), VAS score directly compared between 1.5% diclofenac group and placebo group after the treatments.

**Fig. 4.** Effect of 1.5% topical diclofenac on burning pain. Histograms of visual analog scale pain scores before and after the application of 1.5% topical diclofenac or placebo solution. \( *P = 0.01 \), visual analog scale score directly compared between 1.5% diclofenac group and placebo group after the treatments.
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Quantitative Sensory Testing. The effect of 1.5% topical diclofenac on neuropathic pain in these same subjects was further examined by using QST. There were no statistically significant changes in static QST parameters, including warm sensation threshold (39.4° + 0.9°C vs. 38.9° + 0.7°C; \(P = 0.28\)), heat pain threshold (46.6° + 0.7°C vs. 46.3° + 0.7°C; \(P = 0.55\)), and heat pain tolerance (50.6 + 0.5 s vs. 50.5 + 0.4 s; \(P = 0.92\)) before and after 1.5% topical diclofenac treatment. There were also no differences in these same QST parameters before and after placebo treatment (\(P = 0.20, 0.26, 0.33\), respectively). However, a 2-week treatment with 1.5% topical diclofenac decreased temporal pain summation as compared with the placebo arm (fig. 7; \(P = 0.01\)).

SF-36. There was no significant change in SF-36 scores (both physical pain scale and psychological scale) before and after 1.5% topical diclofenac treatment. The data showed that the 2-week use of 1.5% topical diclofenac did not change physical health scale (34.56 + 1.97 pretreatment vs. 34.76 + 2.08 posttreatment; \(P = 0.71\)) or psychological health scale (46.00 + 2.23 pretreatment vs. 46.96 + 2.51 posttreatments; \(P = 0.14\)). Similarly, 2 weeks of placebo did not change SF-36 physical health scale (33.37 + 1.84 pretreatment vs. 33.5 + 1.96 posttreatment; \(P = 0.97\)). However, there was a slight improvement of psychological health scale (44.03 + 1.85 pretreatment vs. 47.02 + 2.01 posttreatment) after 2 weeks of placebo application (\(P = 0.01\)).

Side Effect Profile. There were no reported complications or side effects in subjects treated with either 1.5% topical diclofenac or placebo.

Discussion

We conducted a randomized, placebo-controlled, double-blinded, and crossover clinical trial to examine the effect of 1.5% topical diclofenac on neuropathic pain. We included subjects with clinical features supportive of the diagnosis of PHN and CRPS. Twenty-eight subjects completed the study. After 2 weeks of topical application of 1.5% diclofenac, but not placebo lotion, subjects with neuropathic pain showed reduced overall pain score and a decrease in their burning pain component. There was also a decrease in constant pain and hypersensitivity of the painful area with application of 1.5% diclofenac lotion but not placebo. These decreases, however, did not reach statistical significance likely due to a small sample size. In addition to changes in self-reported pain, subjects receiving 1.5% diclofenac lotion also showed a decrease in temporal pain summation (reflective of the improvement of a wind-up phenomenon) as detected by QST. We did not detect statistically significant changes in functional status (SF-36 score) after 1.5% topical diclofenac treatment, which could be related to a relatively short study duration. Subjects tolerated topical diclofenac therapy without any side effects or complications. These findings indicate that 1.5% topical diclofenac may serve as an effective treatment option for patients with neuropathic pain of the PHN or CRPS origin.

The overall prevalence of neuropathic pain is considered between 0.9 and 8%.22–24 However, a certain patient

Fig. 5. Effect of 1.5% topical diclofenac on constant pain. Histograms of visual analog scale pain scores before and after the application of 1.5% topical diclofenac or placebo solution. \(P = 0.2\), visual analog scale score directly compared between 1.5% diclofenac group and placebo group after the treatments.

Fig. 6. Effect of 1.5% topical diclofenac on pain hypersensitivity. Histograms of pain hypersensitivity scores before and after the application of 1.5% topical diclofenac or placebo solution. \(P = 0.2\), visual analog scale score directly compared between 1.5% diclofenac group and placebo group after the treatments.

Fig. 7. Effect of 1.5% diclofenac on temporal pain summation. A scattered plot illustrating quantitative sensory testing responses to a train-of-four identical suprathreshold heat (47°C) stimuli after application of diclofenac lotion or placebo. Delta 1, delta 2, and delta 3 represent the percent increase in visual analog scale score in response to the second, third, and fourth stimulus over that to the first stimulus, respectively. * \(P = 0.01\), as compared between 1.5% diclofenac group and placebo solution group.
population has much higher prevalence. For example, neuropathic pain is reported to occur in 35% of patients with diabetic neuropathy, 60% with limb amputation, 30% with spinal cord injury, and 28% among multiple sclerosis patients. It has also been suggested that the neuropathic pain peaked between the ages 70 and 79 yr. In several preclinical models of neuropathic pain, cyclooxygenase inhibitors have been found to be effective. Chauhan et al. described the use of dipyrone (a cyclooxygenase inhibitor) on experimentally induced (injecting streptozocin) diabetes in rats. They found significant attenuation of thermal hyperalgesia, mechanical allodynia, and formalin-induced phase II flinching response. Kimura et al. also found that meloxicam, a cyclooxygenase inhibitor, exerts antiallodynic effects in diabetic mice, and the site of action is considered to be peripheral. Sulfasalazine, another cyclooxygenase inhibitor, also produces attenuation of tactile allodynia in diabetic rats.

Cochrane systemic review in 2010 indicates that topical NSAIDs are an effective and safe drug for acute musculoskeletal pain. This review included 47 trials involving 5,512 patients and 16 various topical NSAIDs in the forms of creams, gels, foams, or patches. The only reported side effects included mild and transient local irritation, and there were no significant differences with regard to withdrawing from studies due to side effects. It has been reported that topical NSAIDs can penetrate the skin and distribute to target tissues underneath the application site. Tissue levels of NSAIDs applied topically reach a level that is high enough to inhibit cyclooxygenase enzyme, but the plasma concentration of topical NSAIDs is only a fraction (usually much <5%) of the plasma level found in oral administration. This may explain why topical diclofenac solution, when compared with oral diclofenac, has a significantly reduced incidence of gastrointestinal complaints and abnormal liver function tests in a randomized trial of osteoarthritis treatment.

Two separate surveys over the past few years have found that NSAIDs are among the most commonly prescribed (31% and over 50%) medications for neuropathic pain. The current study was designed to investigate whether 1.5% topical diclofenac could reduce clinical pain with neuropathic characteristics along with improvement in QST and functional status after 2 weeks of therapy. We found that after 2 weeks of application, topical diclofenac (1.5%) reduced clinical pain (overall pain score as well as the burning component of neuropathic pain) as compared with placebo solution. It is possible that the improvement of burning sensation was due to the effect of diclofenac solution on peripheral nociceptors.

Quantitative sensory testing was performed on the painful area before and after the application of diclofenac (1.5%) and placebo solution for 2 weeks. There were no statistically significant changes in static QST parameters, including warm sensation threshold, heat pain sensation threshold, and heat pain tolerance, before and after 1.5% topical diclofenac treatment. However, a 2-week treatment with 1.5% topical diclofenac decreased temporal pain summation, a psychophysical correlate of the wind-up phenomenon of spinal cord dorsal horn neurons in response to peripheral noxious stimulation (sensitization) and a clinical hallmark of neuropathic pain conditions. Although the exact clinical implication of this finding remains to be seen, future studies in a larger group of similar subjects may provide further information to determine whether the change in temporal summation could be used as a prognostic tool for the clinical efficacy of neuropathic pain treatment including the use of topical NSAIDs.

In our study, no measureable improvement of SF-36 scores was detected after the treatment with diclofenac (1.5%) solution despite the reduction of clinical pain and improvement in QST outcomes. This may not be a surprise because many chronic pain patients experience despair and need multidisciplinary interventions to improve their psychological and physical functioning. In addition, improvement in functional status may take place after a much longer period of pain improvement. Of significance to note is that we did not find complications and side effects from topical application of diclofenac solution among our subjects, consistent with the findings from Cochrane review regarding the use of topical NSAIDs. Given this favorable side effect profile, it would be reasonable to suggest that topical diclofenac may be used for an extended period of time to improve clinical pain and functional status.

There are several limitations of this study including a relatively small sample size and a short duration of therapy (2 weeks) for subjects experiencing chronic neuropathic pain. In addition, the criteria for the diagnosis of CRPS allowed some heterogeneity among the subjects. Nonetheless, the current data indicate that a short-term treatment with topical diclofenac is beneficial for patients with neuropathic pain, including reduction of pain score and improvement in QST outcome characteristic of neuropathic pain conditions.

Acknowledgments
This work was supported by an investigator-initiated research proposal funded by Covidien, Minneapolis, Minnesota.

Competing Interests
The authors declare no competing interests.

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