Effect of 1.5% Topical Diclofenac on Clinical Neuropathic Pain

Shihab U. Ahmed, M.B.B.S., M.P.H., Yi Zhang, M.D., Ph.D., M.S., Lucy Chen, M.D., Abigail Cohen, B.S., Kristin St. Hillary, B.S., Trang Vo, B.S., Mary Houghton, B.S., Jianren Mao, M.D., Ph.D.

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)**

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

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.

Submitted for publication May 19, 2014. Accepted for publication March 11, 2015. From the Harvard Medical School, Massachusetts General Hospital Center for Translational Pain Research, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

 Anesthesiology 2015; 123:191-8

side effect profile.[8–11] Both male and female subjects including elderly subjects have been treated with topical diclofenac (1.5%) with a safety record.[10] Topical diclofenac (1.5%) has few drug–drug interactions due to its topical formulation[12] and is well tolerated.[13] 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.[14,15] 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 Massachusetts)–approved informed consent from the subject before enrolling him/her in the study. This trial was designed to identify the superiority of 1.5% diclofenac lotion to placebo. The study was included at ClinicalTrials.gov on January 04, 2012 (registration number is NCT01508676). Study subjects were recruited primarily from a pool of neuropathic pain patients under treatment at the MGH Center for Pain Medicine. We recruited neuropathic pain subjects with a history and clinical features supporting the diagnosis of PHN and CRPS.[16] We chose to include subjects with these neuropathic pain conditions because (1) these pain conditions are often encountered in the clinical setting and (2) patients with these conditions are subject to treatment with topical agents.

The recruitment processes began in February 2012 and ended in March 2013. During this period, we assessed a total of 147 patients with presumed neuropathic pain conditions due to PHN or CRPS. All 147 subjects underwent either a phone interview (IRB-approved phone interview check list) or an in-person visit at the MGH pain clinic with a research assistant. The screening excluded 112 subjects because (1) pain distribution and characteristics were not supportive of PHN or CRPS and (2) these subjects did not meet other inclusion criteria or met one or more exclusion criteria (table 1). Once a subject passed the initial screening, he or she was scheduled for visit 1.

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

Table 1. The Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Subject will be between 18 and 80 yr of age. Subject has not been on diclofenac or other topical NSAIDs for at least 1 month.	1. Subject has documented severe liver or renal disease that will affect the elimination of diclofenac or is subject to the adverse effect of diclofenac on these organs. Renal dysfunction is defined as eGFR <60. Hepatic dysfunction is defined as LFTs ≥3X ULN.)
2. Subject agrees to make no change in his/her current pain medications during the entire study period. This requirement will ensure that valid comparisons of primary and secondary measures can be made before and after the study.	2. Subject has pending litigation related to the neuropathic pain condition.
3. Subject has a VAS pain score of ≥4 at the beginning of the study.	3. Subject has active skin lesion or open wound at the site of diclofenac application (*e.g.*, active shingles with skin lesions).
4. Subject has had a neuropathic pain condition such as those listed above for at least 3 months. This requirement is to avoid clinical uncertainty from an unstable pain condition and to minimize the study variation.	4. Subject is pregnant or lactating.
5. Female subjects of childbearing age must have a negative urine pregnancy test at the initial visit.	5. Subject has scar tissue or sensory deficit at the site of QST.
	6. Subject is allergic to diclofenac or has cross-sensitivity to other NSAIDs.
	7. Subject has a positive urine (illicit) drug test.
	8. Subjects who experience asthma, urticaria, or an allergic type reaction when taking aspirin or NSAIDs.
	9. Subject with a known history of ulcer, gastrointestinal bleed, impaired renal function, or severe uncontrolled hypertension and major cardiovascular events such as stroke, unstable angina, myocardial infarction, coronary artery bypass graft, or placement of coronary stent within 6 months.
	10. Subjects currently using NSAIDs.

eGFR = estimated glomerular filtration rate; LFTs = liver function tests; NSAIDs = nonsteroidal antiinflammatory drugs; QST = quantitative sensory testing; ULN = upper limit of normal; VAS = visual analog scale.

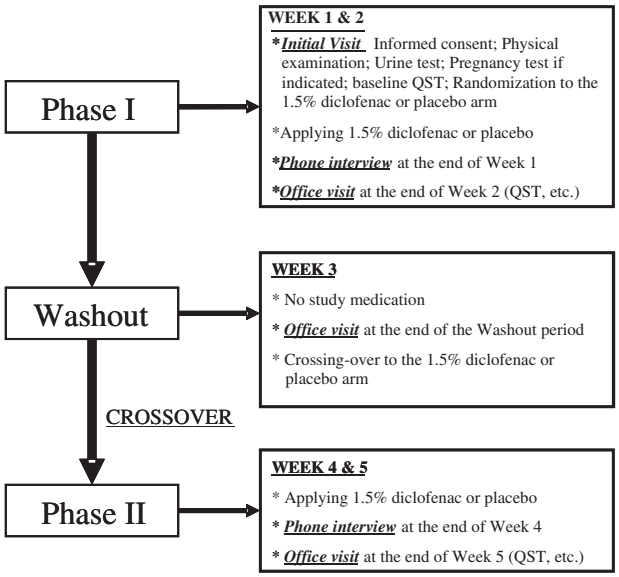

Fig. 1. Study flow diagram. QST = quantitative sensory testing.

into a placebo (with the same dimethyl sulfoxide [DMSO] base used in diclofenac solution) or diclofenac arm according to a computer-generated randomization scheme (www.randomization.com), carried out by the MGH Clinical Research Pharmacy. The randomization list was prepared for 48 participants. Participants were allocated in a 1:1 ratio in blocks of 12. There were no other restrictions used when creating the group assignments. Study staff and subjects were both blinded to medication (group) assignment.

Covidien (USA) prepared both active medication (1.5% [w/w]) diclofenac solution in a carrier 45.5% [w/w] DMSO) and placebo solution and shipped directly to the MGH Clinical Research Pharmacy. The placebo solution consisted of 0% (w/w) diclofenac sodium and 2.3% (w/w) DMSO. The preparations were both dispensed in 150 ml brown bottles and appeared the same on application. The study medication or placebo for phase I was given to the subject with instructions. Study subjects were allowed to continue their current pain medications, provided that there was no dose change and no addition of new pain medications during the entire study.

Study subjects topically applied 1.5% topical diclofenac or placebo solution (20 to 40 drops) three times daily to the painful area for the next 2 weeks. The actual dose (number of drops) was based on the size of painful area (approximately 10 drops for every 4 square inches) and was referenced from the published studies conducted on subjects with osteoarthritis of knee joints.[8–11] Subjects were asked to fill in a daily pain diary and report any side effects to the research center. Subjects completed the pain diary once daily. Diaries were reviewed by study staff at each office visit. Subjects reported their own average daily pain score. Each study subject was interviewed by phone at the end of week 1 to confirm that he/she was complying with the study protocol and there was no significant issue with the study.

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.[17] In this study, heat stimulation was used in all QST sessions following a protocol detailed in our previous publication.[18] *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*,

the same contact thermode was placed at the designated body site. 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. The subject was asked to stop stimulation by pressing a computer mouse button when pain was no longer tolerable (*i.e.*, just beyond pain threshold). The stimulation was fully escapable, and the subject was able to withdraw from the stimulation at any time. 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 tolerance temperature (in degree Celsius). *To detect temporal pain summation*, the same contact thermode was placed at the designated body site. A train-of-four identical 47°C suprathreshold heat stimuli were delivered at a 2-s interval. The subject was asked to rate VAS score at the peak of each of four stimuli. The degree of temporal summation was displayed at the percent increase in VAS score from the second, third, and fourth stimulus over that of the first stimulus.

Data Collection

A comprehensive set of information was collected during this study. The information falls into the following categories: (1) demographic data; (2) clinical pain improvement; (3) QST data; (4) functional status; and (5) side effects profile. This project was an investigator-initiated clinical research study funded by Covidien. Our research team designed the study, wrote the protocol, and collected, analyzed, and interpreted the data independently.

Statistical Analysis

Power Analysis. We expected subjects to have different baseline pain scores. To increase the statistical power of detecting a change in pain score, QST, and other measurement associated with 1.5% topical diclofenac treatment, we planned to use a within-subject crossover study design, using paired *t* test comparison because a paired *t* test has more statistical power when the difference between pretreatment and posttreatment may be small relative to the variation within groups (variation of patient's baseline pain score). We expected a 1.5-point change in VAS score after treatment with 1.5% diclofenac solution based on our previous clinical observations. We estimated the SD of VAS score in chronic pain patients to be 3, based on our previous studies.[18] We performed *a priori* sample size calculation using the statistical power estimation software G*Power to calculate the required sample size[19,20] with these parameters. Using paired *t* test, a sample size of 27 will give us 81% power to detect an effect size of 0.5 (a VAS difference of 1.5 after treatment, with a standard variation of VAS difference of 3), with an α value of 0.05. Assuming a dropout rate of 50% due to chronic pain study, we planned to enroll 48 subjects.

Data Analyses. Descriptive data analysis was used to describe demographic data. Quantitative data analysis was used to analyze parametric data including visual analog pain scale, SF-36 scales, and QST measurements. For SF-36, aggregate scales on physical health and mental health were computed according to the standard protocol.[21] Two tailed, paired *t* test was used to compare VAS pain scores, SF-36 scores, and QST measurement values. The primary outcome was the subject's VAS score. Secondary outcome measures included the changes in clinical pain characteristics such as burning and shooting pain, SF-36 scores, and QST findings. The *P* value of less than 0.05 was considered to be statistically significant. The statistical software STATA Version 12 (StataCorp LP, USA) was used for all statistical data analyses. The data presented in this article are from 28 subjects who completed both phases of the study, and there were no missing data.

Results

Demographic Data

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 = 18), upper extremity (n = 7), 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).

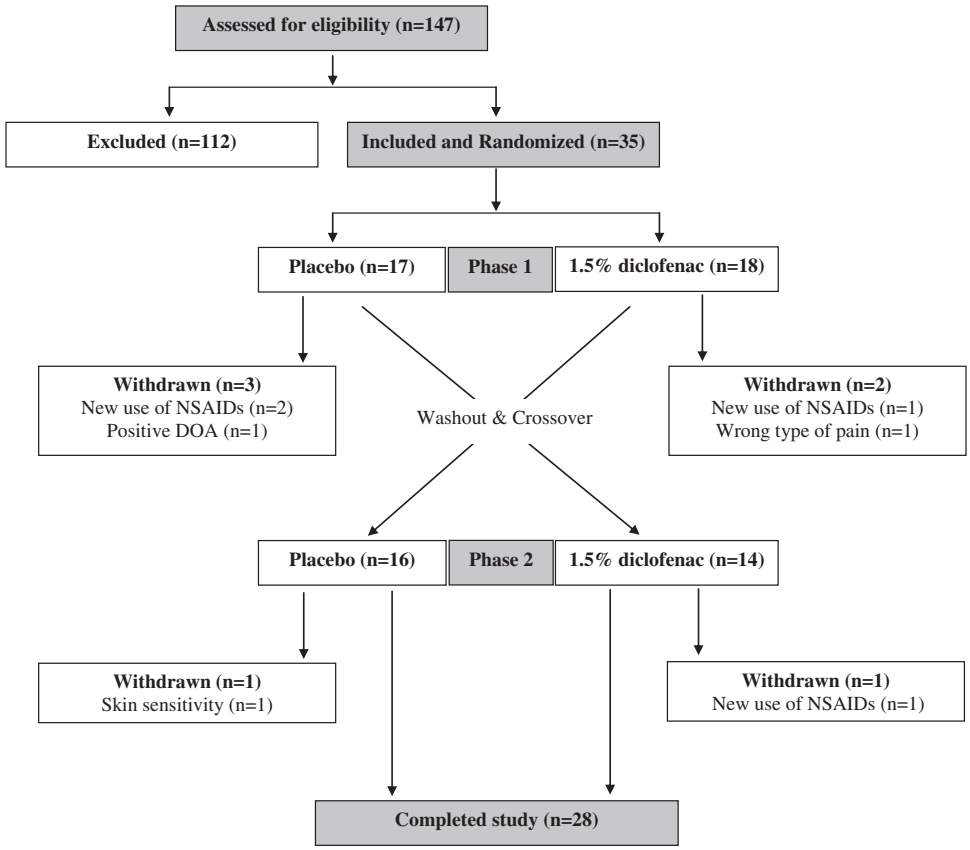

Fig. 2. Flowchart illustrating subject recruitment and withdrawal. DOA = drug of abuse; NSAIDs = nonsteroidal antiinflammatory drugs.

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, 0.2 to 2.6; 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).

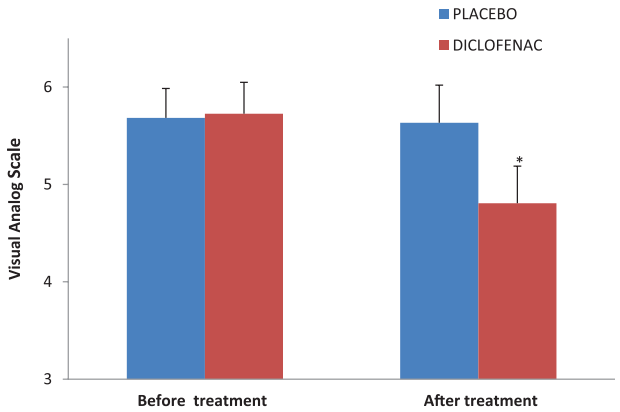

Fig. 3. Effect of 1.5% topical diclofenac on visual analog scale (VAS). Histograms of VAS pain scores before and after the application of 1.5% topical diclofenac or placebo solution. *P = 0.04, VAS score directly compared between 1.5% diclofenac group and placebo group after the treatments.

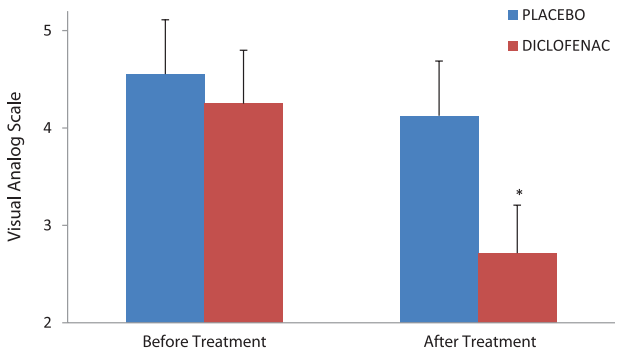

Fig. 4. Effect of 1.5% topical diclofenac on burning pain. Histograms of visual analog scale pain scores before and after the application of 1.5% topical diclofenac or placebo solution. *P = 0.01, visual analog scale score directly compared between 1.5% diclofenac group and placebo group after the treatments.

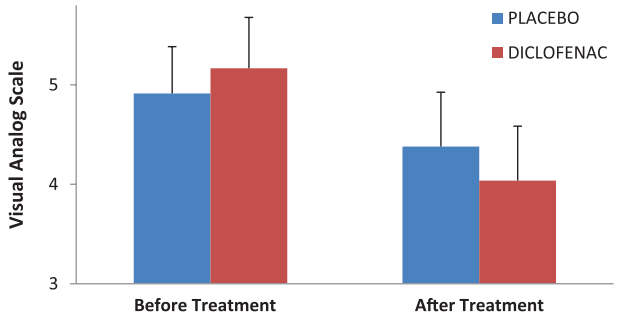

Fig. 5. Effect of 1.5% topical diclofenac on constant pain. Histograms of visual analog scale pain scores before and after the application of 1.5% topical diclofenac or placebo solution. $P = 0.2$, visual analog scale score directly compared between 1.5% diclofenac group and placebo group after the treatments.

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.* 33.35 + 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 ($P = 0.01$).

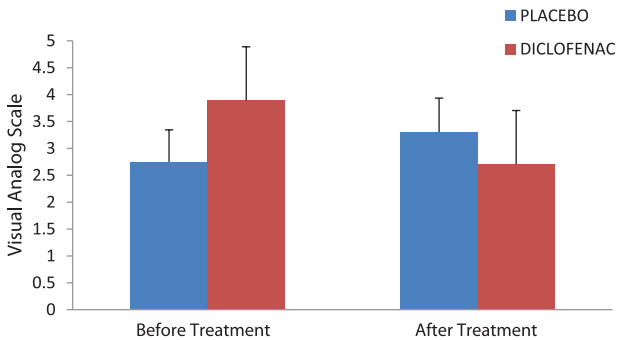

Fig. 6. Effect of 1.5% topical diclofenac on pain hypersensitivity. Histograms of pain hypersensitivity scores before and after the application of 1.5% topical diclofenac or placebo solution. $P = 0.2$, visual analog scale score directly compared between 1.5% diclofenac group and placebo group after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

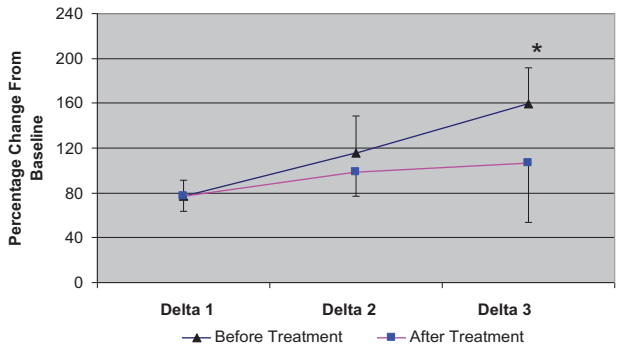

Fig. 7. Effect of 1.5% diclofenac on temporal pain summation. A scattered plot illustrating quantitative sensory testing responses to a train-of-four identical suprathreshold heat (47°C) stimuli after application of diclofenac lotion or placebo. Delta 1, delta 2, and delta 3 represent the percent increase 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.

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

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.[25] It has also been suggested that the neuropathic pain peaked between the ages 70 and 79 yr.[6] In several preclinical models of neuropathic pain, cyclooxygenase inhibitors have been found to be effective. Chauhan *et al.*[26] 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.*[27] 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[28] in diabetic rats.

Cochrane systemic review in 2010 indicates that topical NSAIDs are an effective and safe drug for acute musculoskeletal pain.[29] 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.[29] Tissue levels of NSAIDs applied topically reach a level that is high enough to inhibit cyclooxygenase enzyme,[29] 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.[8]

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.[5,6] 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.[29]

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.[29] 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.

Correspondence

Address correspondence to Dr. Ahmed: Harvard Medical School, Massachusetts General Hospital Center for Translational Pain Research, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, 101 Merrimac Street, Suite 610, Boston, Massachusetts 02114. sahmed@partners.org. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Sindrup SH, Jensen TS: Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. Pain 1999; 83:389–400
2. Mao J, Chen LL: Gabapentin in pain management. Anesth Analg 2000; 91:680–7
3. Mao J, Chen LL: Systemic lidocaine for neuropathic pain relief. Pain 2000; 87:7–17
4. Mao J, Gold MS, Backonja MM: Combination drug therapy for chronic pain: A call for more clinical studies. J Pain 2011; 12:157–66
5. Possidente CJ, Tandan R: A survey of treatment practices in diabetic peripheral neuropathy. Prim Care Diabetes 2009; 3:253–7
6. Dieleman JP, Kerklaan J, Huygen FJ, Bouma PA, Sturkenboom MC: Incidence rates and treatment of neuropathic pain conditions in the general population. Pain 2008; 137:681–8
7. Mao J: Translational pain research: Achievements and challenges. J Pain 2009; 10:1001–11
8. Tugwell PS, Wells GA, Shainhouse JZ: Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: A randomized controlled trial. J Rheumatol 2004; 31:2002–12
9. Baer PA, Thomas LM, Shainhouse Z: Treatment of osteoarthritis of the knee with a topical diclofenac solution: A randomised controlled, 6-week trial [ISRCTN53366886]. BMC Musculoskelet Disord 2005; 6:44
10. Towheed TE: Pennsaid therapy for osteoarthritis of the knee: A systematic review and metaanalysis of randomized controlled trials. J Rheumatol 2006; 33:567–73
11. Galer BS: A comparative subjective assessment study of PENNSAID® and Voltaren Gel®, two topical formulations of diclofenac sodium. Pain Pract 2011; 11:252–60
12. Roth SH, Shainhouse JZ: Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: A randomized, double-blind, vehicle-controlled clinical trial. Arch Intern Med 2004; 164:2017–23
13. Moen MD: Topical diclofenac sodium. Drugs 2009; 69:2621–32
14. Hui X, Hewitt PG, Poblete N, Maibach HI, Shainhouse JZ, Wester RC: *In vivo* bioavailability and metabolism of topical diclofenac lotion in human volunteers. Pharm Res 1998; 15:1589–95
15. Tanojo H, Wester RC, Shainhouse JZ, Maibach HI: Diclofenac metabolic profile following *in vitro* percutaneous absorption through viable human skin. Eur J Drug Metab Pharmacokinet 1999; 24:345–51
16. Merskey H, Bogduk N: Classifications of Chronic Pain, 2nd edition. Seattle, IASP Press, 1994
17. Yarnitsky D: Quantitative sensory testing. Muscle Nerve 1997; 20:198–204
18. Chen L, Malarick C, Seefeld L, Wang S, Houghton M, Mao J: Altered quantitative sensory testing outcome in subjects with chronic opioids. Pain 2009; 143:65–70
19. Faul F, Erdfelder E, Lang AG, Buchner A: G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39:175–91
20. Faul F, Erdfelder E, Buchner A, Lang AG: Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009; 41:1149–60
21. Ware JE, Kosinski M, Dewey JE: How to Score Version 2 of the SF-36® Health Survey. Lincoln, Quality Metric Incorporated, 2000
22. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS: Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain 2007; 132:237–51
23. Taylor RS: Epidemiology of refractory neuropathic pain. Pain Pract 2006; 6:22–6
24. Torrance N, Smith BH, Bennett MI, Lee AJ: The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006; 7:281–9
25. Niv D, Devor M: Refractory neuropathic pain: The nature and extent of the problem. Pain Pract 2006; 6:3–9
26. Chauhan N, Taliyan R, Sharma PL: Effect of dipyrone and thalidomide alone and in combination on STZ-induced diabetic neuropathic pain. Naunyn Schmiedebergs Arch Pharmacol 2012; 385:527–38
27. Kimura S, Kontani H: Demonstration of antiallodynic effects of the cyclooxygenase-2 inhibitor meloxicam on established diabetic neuropathic pain in mice. J Pharmacol Sci 2009; 110:213–7
28. Berti-Mattera LN, Kern TS, Siegel RE, Nemet I, Mitchell R: Sulfasalazine blocks the development of tactile allodynia in diabetic rats. Diabetes 2008; 57:2801–8
29. Massy T, Derry S, Moore RA, McQuay HJ: Topical NSAIDs for acute pain in adults. Cochrane Database Syst Rev 2010; 6:CD007402