Topical Capsaicin in the Management of HIV-Associated Peripheral Neuropathy

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Abstract
Distal symmetrical peripheral neuropathy (DSPN) is a particularly distressing pain syndrome associated with human immunodeficiency virus (HIV) disease. Capsaicin has been found to be effective in relieving pain associated with other neuropathic pain syndromes, and is mentioned as a possible topical adjuvant analgesic for the relief of DSPN. This multicenter, controlled, randomized, double-masked clinical trial studied patients with HIV-associated DSPN and compared measures of pain intensity, pain relief, sensory perception, quality of life, mood, and function for patients who received topical capsaicin to the corresponding measures for patients who received the vehicle only. Twenty-six subjects were enrolled in the study. At the end of 1 week, subjects receiving capsaicin tended to report higher current pain scores than did subjects receiving the vehicle (Mann-Whitney test; \( P = 0.042 \)). The dropout rate was higher for the capsaicin group (67%) than for the vehicle group (18%) (\( \chi^2 \) test of association; \( P = 0.014 \)). There were no other statistically significant differences between the capsaicin and vehicle groups with respect to current pain, worst pain, pain relief, sensory perception, quality of life, mood, or function at study entry or at any time during the 4-week trial. These results suggest capsaicin is ineffective in relieving pain associated with HIV-associated DSPN. J Pain Symptom Manage 2000;19:45–52. © U.S. Cancer Pain Relief Committee, 2000.

Key Words
Peripheral neuropathy, HIV, capsaicin, pain

Introduction
Pain is a common, frequently undertreated complication of human immunodeficiency vi-
peripheral nerve changes may occur before clinical manifestations of HIV infection. Hypothesized mechanisms of DSPN include altered immunity, metabolic factors, nutritional factors, nerve infiltration, infectious processes, increased macrophage numbers in peripheral nerves, and toxic effects of some of the antiretroviral agents used in the primary treatment of HIV disease (such as dideoxynosine [ddI] and dideoxycytosine [ddC]).

The chief clinical complaints associated with DSPN are burning and painful soles, paresthesias of the dorsum and soles, and numbness of the feet; these symptoms are typically symmetrical in distribution. Other symptoms are mild weakness, depressed or absent ankle reflexes, and an elevated threshold for vibration, pinprick, and cold in the foot. Electrodagnostic studies are consistent with distal symmetric degeneration of sensory and motor axons.

Treatment of DSPN may include discontinuing antiretrovirals, and correcting any infectious or nutritional deficits that may be present, such as vitamin B₁₂ deficiency. Pain management incorporates standard pharmacologic therapies, including opioids and adjuvant medications, such as tricyclic antidepressants, anticonvulsants, and local anesthetics. Despite these treatments, DSPN symptoms are often poorly relieved.

Capsaicin is frequently mentioned as a possible topical adjuvant analgesic for the relief of DSPN. Capsaicin binds to the vanilloid receptor, found in the human spinal cord and cloned in the laboratory. The initial mechanism of action of capsaicin is believed to be depolarization of C-fiber polymodal nociceptors. This effect may be due, in part, to the opening of nonspecific ion channels in the skin, airways, oral mucosa, and visceral organs. In particular, sodium and calcium show increased permeability, leading to depolarization and release of substance P. This initial release leads to an increased perception of pain when capsaicin is used topically. Repeated, regular topical application leads to further release and eventual depletion of substance P from the terminals of primary afferent neurons, potentially reducing pain. Levels of other neuropeptides are diminished as well, including calcitonin gene-related peptide, somatostatin, and vasoactive intestinal polypeptide. These diminished levels may be due to loss of C-fiber neurons in the treatment field. Repeated topical application of capsaicin in humans has been shown to cause degeneration of epidermal nerve fibers, which may contribute to the analgesia reported with capsaicin use.

Capsaicin has been studied in various models of pain and neuropathy. Using a randomized, double-masked design in patients with osteoarthritis or rheumatoid arthritis, topical capsaicin provided superior relief when compared to the vehicle. In an open trial of patients diagnosed with postherpetic neuropathy, 56% of 23 patients treated with topical capsaicin (0.025%) had good to excellent pain relief at 4 weeks. Two other open trials of postherpetic pain supported these findings. Several controlled trials of capsaicin in diabetic neuropathy suggested efficacy, although other investigators found no difference between capsaicin and placebo in this type of pain. In another open trial, women diagnosed with postmastectomy pain syndrome were given topical capsaicin (0.025%) for pain relief, and 12 of the 14 subjects showed improvement at 4 weeks. This report was followed by a randomized, parallel trial of topical capsaicin (0.075%) in women with postmastectomy pain syndrome. In this study, patients who received capsaicin obtained better pain relief than did patients who received the placebo. More recently, topical capsaicin (0.075%) was found to be effective in a randomized, controlled clinical trial of postsurgical neuropathic pain. However, Low and colleagues found no difference in pain relief in a controlled trial of capsaicin in patients with non-HIV-associated DSPN (e.g., idiopathic, diabetic, alcoholic, and other causes).

Despite the disparities in studies evaluating the efficacy of capsaicin, this compound is frequently suggested as an effective topical adjuvant analgesic in the treatment of HIV-associated DSPN. However, there have been no reported controlled trials supporting its use in these patients. The present study is a multicenter, controlled, randomized, double-masked clinical trial of the efficacy of topical capsaicin in patients with HIV-associated DSPN. Subjects who received topical capsaicin were compared to subjects who received the vehicle only with respect to measures of pain intensity, pain relief, sensory perception, quality of life, mood, and function.
Methods

Study Design
This was a multicenter, controlled, randomized, double-masked study designed to evaluate the effect of topical capsaicin on DSPN pain in persons with HIV-associated DSPN. Subjects were randomized to receive either topical capsaicin (0.075%) plus usual analgesic therapy, or the cream vehicle without capsaicin (placebo) plus usual analgesic therapy.

Subjects
The study included subjects 18 years and older with HIV-related DSPN. The exclusion criteria were pregnancy, lactation, inability to read or speak English, use of dideoxyinosine or dideoxycytosine, use of any topical medication on the lower extremities, and lesions on the feet or legs that might allow systemic uptake of the drug.

Drug
Capsaicin is a naturally occurring substance derived from chili peppers of the Solanaceae family. The chemical designation of capsaicin is trans-8-methyl-N-vanillyl-6-nonenamide (molecular weight 305.4). Capsaicin is a white powder that is insoluble in water and very soluble in alcohol, ether, and chloroform. The commercially available cream (Zostrix-HP; Gen-Derm Corporation, Lincolnshire, IL) contains capsaicin (0.075%) in an emollient base consisting of benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution, and white petrolatum. The vehicle was obtained from the manufacturer of the capsaicin cream used in the study and consisted of the emollient base without capsaicin.

Procedure
Potential subjects were identified from the rosters of inpatients and outpatients at two large urban hospitals: a private 800-bed hospital and a large veterans’ hospital. Only subjects with a documented diagnosis of HIV-associated DSPN, established by their primary care physician or neurologist, were considered for this study. After informed consent was obtained, subjects underwent evaluation of the feet and legs by a nurse with extensive training in conducting neurological examinations. The examination included sensory testing for paresthesia, hyperalgesia, and allodynia using standard measures such as light touch, pinprick, and Semmes-Weinstein monofilaments. The lower extremities were assessed for lesions that would preclude entry into the study. Subjects were then asked to complete the instruments described below. A trained nurse or research assistant instructed the subjects (and their caregivers, if present) in the correct method for applying the cream. Written instructions were also given to each subject.

Subjects were instructed to apply the capsaicin or vehicle 4 times each day for 4 weeks. They were also told to record their pain score 4 times each day on the daily diary form and to document the time of application of the cream. Subjects were directed to continue all supplemental opioids and adjuvant analgesics and record these drugs each day of the study on the daily diary form. At study entry and during the 6-week study period, at the time points described below, measurements were obtained for pain, pain relief, sensory perception, quality of life, mood, and function. At the end of 2 and 4 weeks, the skin was examined for adverse treatment effects. Used containers of medication were returned at the end of each week and replaced with the next week’s supply. The used containers allowed some verification of compliance with treatment.

Measures
Brief Pain Inventory. The Brief Pain Inventory (BPI) is a valid and reliable multidimensional measure of pain that has been used extensively in cancer patients and persons with HIV disease. This instrument was completed at entry into the study, at the end of each week, and at termination of the study.

Quality of Life. Perception of quality of life was measured using the Quality of Life Index (QLI). This instrument measures overall quality of life as well as the quality of four major life domains: health and physical functioning, social and economic, psychological/spiritual, and family. The instrument consists of a section that measures satisfaction with 37 aspects of life, and a section that measures the importance of each of these aspects to the subject. Scores are determined after weighting the satisfaction responses by the importance responses. Validity and reliability have been well
This instrument was completed at entry into the study and at termination of the study (the end of 4 weeks).

**Mood/Affective State.** Mood was measured using the Profile of Mood States (POMS), a valid and reliable tool that assesses transient, fluctuating affective states. Subjects are asked to indicate how well 65 adjectives describe how they have been feeling for the past week, including that day, using a 5-point scale. A total score and six subscale scores are calculated. This instrument was completed at entry into the study and at termination of the study.

**Functional Status.** The Sickness Impact Profile (SIP) is a behaviorally based measure of perceived health status. The SIP measures behavioral dysfunction in 12 areas of living, with seven categories that are clustered into physical and psychosocial dimensions. Scores can be calculated for the entire SIP, for the individual categories, and for the physical and psychosocial dimensions. This is a well-established instrument and its reliability and validity were documented in a wide range of patient populations. This instrument was completed at entry into the study and at termination of the study.

**Sensory Examination.** The Semmes-Weinstein pressure aesthesiometer evaluates touch-pressure sensation using nylon monofilament probes (Stoelting; Wood Dale, IL). The monofilaments were applied five times to each of seven sites on the toes, feet, and lower legs. The examiner recorded the force inscribed on the rod at the point at which subjects reported feeling at least three of the five applications. This instrument was completed at entry into the study, at the end of 2 weeks, and at termination of the study.

**Data Analysis**

SPSS for Windows (Version 6) (SPSS, Inc., Chicago, IL) was used for data management and statistical analysis. Since the data had statistically non-normal distributions, the non-parametric Mann-Whitney test was done to compare the study groups with respect to non-nominal variables. The χ² test of association was done to compare groups with respect to nominal variables. A 0.05 significance level was used for all statistical tests, and all statistical tests were two-sided. Means are presented as mean ± standard deviation. Data were obtained for at least 10 subjects per group at weeks 1 and 2, ensuring at least 80% power for detecting a difference between the capsaicin and vehicle groups if the probability that an observation in one group is less than an observation in the other group is 0.86, using a two-sided Mann-Whitney test with a 0.05 significance level. Subjects who dropped out of the study were included in all analyses concerning time points before their exit from the study.

**Results**

Twenty-six subjects (25 men and 1 woman) were enrolled in the study, with a mean age of 40.3 ± 6.0 years. Thirteen (50%) were white, 11 (42%) were black, and 2 (8%) were Hispanic. One (4%) had completed eighth grade, 2 (8%) had completed high school, 17 (65%) had earned an associate’s degree or attended some college, 3 (12%) had completed a bachelor’s degree, and 3 (12%) had obtained advanced degrees. Eight subjects were working part-time (19%) or full time (12%). One subject (4%) was unemployed by choice. Of the remaining subjects, one (4%) was retired, 3 (12%) were unable to find employment, and 13 (50%) were unable to work or disabled. The mean time since HIV diagnosis was 5.8 ± 4.5 years. The mean CD4 count recorded upon enrollment into the trial was 231.1 ± 228.4 (median 180.0).

At entry to the study, current pain and worst pain averaged 4.7 ± 2.6 and 6.6 ± 1.9, respectively on the 0–10 scale. Subjects used many descriptors when asked to characterize their pain, with tingling (96%), aching (88%), numbness (81%), pins and needles (81%), and throbbing (77%) being the most common. Pain intruded upon many aspects of life, as measured by the BPI interference scales at study entry. These scales range from 0 to 10, with high scores indicating greater interference, and consist of walking (6.0 ± 2.9), sleep (5.5 ± 3.2), general activity (5.5 ± 2.8), enjoyment of life (5.5 ± 2.8), mood (5.2 ± 3.2), normal work (5.1 ± 3.0), and relations with other people (3.7 ± 2.9).
Thirteen subjects (50%) had been prescribed no analgesics. Only 8 (31%) had received opioids for their pain, including 2 (8%) receiving morphine, 3 (12%) receiving transdermal fentanyl, and 3 (12%) receiving acetaminophen/codeine admixtures. Eight subjects (31%) were taking nonsteroidal anti-inflammatory drugs prescribed by their physicians. Two subjects (8%) were taking tricyclic antidepressants, and one (4%) received an anticonvulsant. Many subjects used physical measures to relieve their pain, such as massage (65%), rest (50%), heat (42%), elevation (19%), and acupuncture (15%). Walking (85%), standing (42%), resting (15%), climbing stairs (12%), and other activities made pain worse for many subjects.

Dropout was high, with 12 subjects (46%) dropping out before the end of the 4-week period. Subjects randomized to capsaicin were much more likely to drop out than were those randomized to vehicle: 10 (67%) capsaicin subjects and 2 (18%) control subjects dropped out ($P = 0.014$). Five subjects dropped out because of increased pain and burning; all five received capsaicin. One subject became acutely demented due to a central nervous system infection and could not participate; he received the vehicle. Two subjects developed other medical problems and did not obtain sufficient relief to remain in the trial; one received capsaicin and the other received the vehicle. One subject dropped out because he found the documentation too tedious. Three subjects failed to return and were completely lost to follow-up, so their reasons for dropping out are not known. When subjects who did not drop out immediately (before 1 week) were considered, the average number of days in the study was 22.8 ± 6.3 for subjects who received capsaicin and 27.0 ± 6.9 days for subjects who received the vehicle (Mann-Whitney; $P = 0.052$). Subjects who dropped out in less than a week after study entry tended to have lower CD4 counts at entry (15.5 ± 21.6; median 6.0) than did subjects who remained in the study for at least a week (271.5 ± 226.9; median 189.0) (Mann-Whitney; $P = 0.019$). No information regarding clinical symptoms was available, however, the lower CD4 count suggests these patients may have been more ill and unwilling to tolerate the additional pain from capsaicin or the burden associated with participating in a clinical trial.

Fifteen subjects were randomized to receive capsaicin and 11 were randomized to receive the vehicle. Baseline data were obtained at study entry for all of these 26 subjects. After drop out, the sample sizes for the capsaicin and vehicle groups were, respectively, 10 and 11 at week 1, 10 and 10 at week 2, and 6 and 8 at weeks 3 and 4. There were no statistically significant differences at study entry between the capsaicin and vehicle groups with respect to age, education, CD4 count, time since HIV diagnosis, worst pain, current pain, Semmes-Weinstein scores, or the total or subscale scores for the QLI, POMS, or SIP instruments.

Subjects receiving capsaicin tended to report higher current pain scores, $5.50 ± 2.68$, than did subjects receiving the vehicle at the end of week 1, $3.10 ± 2.12$ (Mann-Whitney; $P = 0.042$) (Figure 1). No statistically significant differences were found between the capsaicin and vehicle groups with respect to current pain for any other time period. There were no statistically significant differences at any time period during the study between the capsaicin and vehicle groups with respect to worst pain, pain relief, Semmes-Weinstein scores, or the total or subscale scores for the QOL, POMS, or SIP instruments.

Discussion

The efficacy of topical capsaicin for treating some types of pain has led to the hypothesis that...
capsaicin might be effective in HIV-associated DSPN. This multicenter, randomized, controlled trial of capsaicin 0.075% found no improvement in measures of pain, pain relief, sensory perception, quality of life, mood, or function when patients who received capsaicin were compared to patients who received the vehicle. In fact, subjects who received capsaicin reported statistically significant increases in current pain at 1 week, compared to patients who received the vehicle. This pain was so severe that it caused five patients to drop out of the study. Although the increased pain was expected, and has been reported in other populations, it was not followed by improved pain relief in later weeks.

The reasons for the ineffectiveness of capsaicin for treating DSPN pain are unclear. One possible explanation is that the larger treatment area associated with DSPN, compared to other neuropathic pain syndromes studied, caused a significant increase in pain intensity at the end of week 1. Low and colleagues found no difference in pain relief in a controlled trial of capsaicin in patients with non-HIV associated DSPN (e.g., idiopathic, diabetic, alcoholic, and other causes). More aggressive use of systemic analgesics during the first week might have allowed subjects to tolerate the initial period of increased pain frequently caused by topical capsaicin. Although an initial increase in analgesics would have confounded the findings during the early weeks of the study, a longer trial would allow assessment of any analgesia provided by topical capsaicin during subsequent time points.

Although numerous studies have reported that topical capsaicin is safe and effective, methodological problems limit the certainty with which some of these conclusions can be drawn. Large dropout rates are common, and subjects who drop out cannot be included in the complete analysis. Studies of topical capsaicin are also limited by the fact that the intense burning reported by subjects who receive capsaicin precludes a completely double-masked design, even when a placebo is used. Low and colleagues added methyl nicotinate, a substance that causes erythema and stinging without analgesia, to both active compound and placebo. They found no difference in pain relief in a controlled trial of capsaicin in patients with non-HIV associated DSPN.

Although this study did not find capsaicin to be effective in the treatment of DSPN, other important findings emerged. Few studies have quantified DSPN pain intensity or reported descriptors that patients use to characterize the pain related to HIV-associated DSPN. The subjects in this study reported moderate to severe pain that significantly interfered with many aspects of daily living. Tingling, aching, numbness, and pins and needles were the most commonly reported descriptors, a finding similar to the results of Newshan and Wainapel. This study is also the first report that delineates the techniques used by patients to attempt to relieve HIV-associated DSPN pain and the activities that make DSPN pain worse. In addition, our results suggest that HIV-associated DSPN is undertreated, with only 50% of our subjects prescribed analgesics for pain. This is consistent with numerous reports of inadequate pain treatment in broader groups of persons with HIV. These patients report moderate to severe pain, yet they are rarely prescribed opioids or adjunct analgesics. The low rate of prescribed analgesics in this study may also reflect lack of efficacy, adverse effects, cost concerns, and other factors that led subjects to discontinue these drugs.

There are several limitations to this study. Although the study was controlled, the burning sensation reported by subjects precludes complete double-masking, an inherent problem in most capsaicin studies. In addition, only one subject was female, despite efforts to enroll female subjects. Finally, information related to analgesic drug use was obtained through self-report rather than chart review.

Although topical capsaicin 0.075% may be useful in some patients, the results of this randomized, controlled clinical trial do not support its widespread use in HIV-associated DSPN. Research is needed to identify and evaluate other possible treatments, both pharmacological and nonpharmacological, for pain relief in HIV-associated DSPN. In addition, patients and health-care professionals need to be educated about the severity of DSPN, the negative effect of DSPN on function, and the need to use available opioids and adjunct analgesics.

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