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Topical Capsaicin as a Preventative Treatment for Chemotherapy-Induced Peripheral Neuropathy (CIPN): A Case Series

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a well-known adverse effect of chemotherapy treatment. Despite its prevalence, prevention and treatment of CIPN remain challenging.

Case Report: In this case series, we present the use of topical 0.075% capsaicin as a preventative measure for CIPN in patients with newly-diagnosed stage II breast cancer undergoing chemotherapy. Patients were instructed to use capsaicin cream 3 times daily on hands and feet throughout the course of chemotherapy and for an additional month after chemotherapy concluded.

Conclusions: None of the 5 patients had any symptoms suggestive of CIPN after being followed for 12 months. These findings support further investigation of low-dose capsaicin as a prophylactic measure to prevent CIPN.

Key words: Chemotherapeutic-induced peripheral neuropathy, topical capsaicin, preventative, neuropathy, cancer pain

BACKGROUND

Neuropathy describes nonpurposeful pain signals, which develop as a result of peripheral nerve damage (1). This damage may occur after an injury due to trauma, ischemia, or radiation, exposure to a neurotoxic agent, or secondary to a systemic disease, such as diabetes or herpes (1-3). The nerve damage can have various presentations depending on the type and extent of the nerve damage. Sensory nerves are most commonly affected, although motor or autonomic dysfunction may also result. Exposure to certain classes of medications may cause neurotoxicity, with antibiotics or chemotherapy being the most frequent culprits. Chemotherapy-induced peripheral neuropathy (CIPN) is described as pain, numbness, or tingling in the extremities which develop after exposure to antineoplastic agents. Due to the variety of chemotherapeutic agents, prevention and treatment of CIPN continue to present a challenge since each agent may produce a unique pathophysiology.

The main offenders of CIPN are taxanes, vinca alkaloids, and platinum agents. At the cellular level, taxanes and vinca alkaloids disrupt microtubules which inhibit cell division during mitosis. Taxanes, such as paclitaxel, stabilize tubulin in microtubules which prevents their depolymerization. In contrast, vinca alkaloids—such as vincristine—block microtubule polymerization. This phenomenon not only affects cell division, but also causes axonal transport dysfunction. Platinum agents bind and crosslink DNA in the dorsal root ganglion (DRG) which renders them irreparable and prevents DNA replication (2). When the tumor meets these barriers to replication, it activates apoptosis with subsequent cell death. Similar to how these antineoplastic agents destroy cancer cells, they can also damage neuronal cells resulting in sensory loss and neuropathy. There are no known or approved preventatives for CIPN; duloxetine is the only medication that has been proven to be an effective treatment (3).

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is

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the active component found in hot peppers that produces a spicy, burning sensation (4). This homovanillic acid derivative binds the transient receptor potential channel vanilloid type 1 (TRPV1) nociceptive receptor and has been found to have analgesic, antioxidant, anti-inflammatory, anti-obesity, and anti-cancer properties (4,5). Capsaicin is most commonly employed as a treatment option for neuropathy, especially in patients with post-herpetic and diabetic neuropathy (6). Herein, we present the use of capsaicin in women undergoing chemotherapy as prophylaxis for CIPN.

CASE PRESENTATION

Methods

Patient Selection

Data was obtained via retrospective chart review and approved by the institutional review board (IRB) at the University of Texas Health Science Center at Houston in February 2021. Data from all consecutive patients with newly diagnosed stage II breast cancer followed at the pain clinic from August 2020 to July 2021, who underwent the use of topical over-the-counter (OTC) 0.075% capsaicin for prevention of CIPN, was included. Risks and benefits were discussed with the patient prior to capsaicin usage. A post-treatment chart review was performed to analyze any signs, symptoms, or occurrence of CIPN. There are no conflicts of interest to disclose.

Technique of Capsaicin Use

Patients were instructed to use topical OTC 0.075% capsaicin 3 times a day on both hands and feet starting on the day of the first cycle of chemotherapy and to continue its use until one month after chemotherapy completion, after which it was discontinued. Risks included: allergic reaction, increased pain or numbness, or failure to resolve symptoms. Patients were educated on common symptoms, as well as potential adverse effects—such as burning, itching, dryness, pain, redness, swelling, or soreness at the application site—and agreed to a patient-informed consent. A certified nurse demonstrated the proper technique of applying topical capsaicin on both hands and feet during education and training sessions.

Follow-up Intervals

Patients were followed at 3, 6, 9, and 12 months after the start of chemotherapy. A sensory exam was conducted at each follow-up visit which included:

(1) Testing deep tendon reflexes at the bicep, brachioradialis, patellar and Achilles tendons

(2) Examining strength and assessing tone

(3) Evaluating sensation: 2-point discrimination, vibration sense, proprioception, light touch, and temperature.

Results

Five patients used topical OTC 0.075% capsaicin between August 2020 to July 2021. Each case is presented in detail in Table 1. The 4 patients who declined the use of capsaicin during the same timeframe served as the control group as demonstrated in Table 2.

None of the 5 patients who used topical capsaicin presented with any signs or symptoms of CIPN. In contrast, 2 out of the 4 patients in the control group reported the development of chemotherapy-related neuropathy. All patients in both groups were followed for 12 months. There were no complications associated with the study.

DISCUSSION

We present a case series of 5 patients. Patients in this treatment group who received capsaicin ranged in age from 39 to 55 years old and all underwent chemotherapy with paclitaxel. Except for Patient 5 who only underwent one cycle, all patients received 2 cycles of paclitaxel 175 mg/m^2 intravenously (IV). In addition to paclitaxel, some patients received adjunct cisplatin or carboplatin at 75 mg/m^2 IV or 360 mg/m^2 IV respectively, for a total of one cycle. Each cycle lasted 21 days in duration. All patients had a newly-diagnosed stage II breast cancer and some had pre-existing conditions that required medication use. Two of the 5 patients were taking gabapentin and pregabalin for pre-existing post-herpetic neuralgia (Patient 4 and Patient 5, respectively). Patient one was taking gabapentin and meloxicam for lumbar radiculopathy and Patient 3 was the only patient prescribed opioids for lumbar stenosis due to a history of failed back surgery. All patients were seen at 3, 6, 9, and 12 month intervals after the start of chemotherapy and all patients denied symptoms of CIPN at these follow-up intervals.

The 4 patients who declined the use of capsaicin served as the control group. These patients ranged in age from 38 to 45 years old and all also underwent chemotherapy with paclitaxel 175 mg/m^2 IV, for a total of 2 cycles. Patient B additionally received cisplatin 75

Table 1. Treatment group details.

	Demographics	Past Medical History	Home Medications	Chemotherapy Regimen	Follow-up Intervals
Patient 1	45 year-old African American woman	Obesity, lumbar radiculopathy, and newly-diagnosed stage II breast cancer	Gabapentin 600 mg PO TID + Meloxicam 7.5 mg PO BID PRN	Paclitaxel (175 mg/m2 IV, total of 2 cycles) + cisplatin (75 mg/m2 IV, total of 1 cycle)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN
Patient 2	39 year-old Caucasian woman	Obesity, chronic pelvic pain, coccydynia s/p caudal epidural injection, and newly-diagnosed stage II breast cancer	None	Paclitaxel (175 mg/m2 IV, total of 2 cycles) + carboplatin (360 mg/m2 IV, total of 1 cycle)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN
Patient 3	42 year-old Caucasian woman	Lumbar stenosis c/b radiculopathy, history of failed back surgery, and newly-diagnosed stage II breast cancer	Hydrocodone acetaminophen 5/325 PO BID PRN	Paclitaxel (175 mg/m2 IV, total of 2 cycles)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN
Patient 4	55 year-old Asian woman	Post-herpetic neuralgia and newly-diagnosed stage II breast cancer	Gabapentin 300 mg PO TID	Paclitaxel (175 mg/m2 IV, total of 2 cycles) + carboplatin (360 mg/m2 IV, total of 1 cycle)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN
Patient 5	49 year-old African American woman	Post-herpetic neuralgia and newly-diagnosed stage II breast cancer	Pregabalin 100 mg PO BID	Paclitaxel (175 mg/m2 IV, total of 1 cycles) + carboplatin (360 mg/m2 IV, total of 1 cycle)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN

Each cycle = 21 days

mg/m^2 IV for a total of one cycle. Each cycle lasted 21 days in duration. All patients had newly-diagnosed stage II breast cancer. Patients A and B both had a history of lumbar spondylosis for which they were taking ibuprofen and hydrocodone acetaminophen, respectively. No other medications were taken in concurrence with chemotherapy. Patients A and B were both started on gabapentin at their 3 month follow-up after initiation of chemotherapy for complaints of numbness and tingling in bilateral feet. Patient A had improvement of symptoms at 6 months, so gabapentin was tapered and discontinued at 9 months, with no recurrence of symptoms at 12 months. Patient B endorsed persistent numbness and tingling at 6 months so the gabapentin dose was increased, but still with no improvement of symptoms at 9 months. Patient B was lost to follow-up at the 12 month interval. Patients C and D denied symptoms of CIPN at the 3, 6, 9, and 12 month follow-up intervals.

The clinical presentation of CIPN varies depending on the class of antineoplastic (Table 3). For instance, taxanes—such as paclitaxel—may present with early, acute, reversible pain. The pain later returns as severe numbness and tingling. The pain may not even appear until after chemotherapy treatment has been completed and can be more severe in patients with preexisting neuropathic conditions, such as diabetes (1). Platinum agents also follow a characteristic pattern of an acute cold-inducing sensitivity that evolves into chronic pain with associated numbness and tingling.

CIPN is a dynamic condition that can develop, resolve, and even relapse. Given this variability with symptom onset, there is greater consistency with measuring the overall prevalence rather than the incidence of new cases. All patients in this study received taxane-based chemotherapy with paclitaxel and most breast cancer survivors who receive treatment with taxanes endorse symptoms of CIPN (7). A systematic review and meta-analysis estimated that the prevalence of taxane-induced peripheral neuropathy (TIPN) is 70.8% (95% CI

Table 2. Control group details.

	Demographics	Past Medical History	Home Medications	Chemotherapy Regimen	Follow-up Intervals
Patient A	38 year-old African American woman	Obesity, type 2 diabetes, lumbar spondylosis and newly-diagnosed stage II breast cancer	Ibuprofen 200 mg OTC PRN	Paclitaxel (17 5mg/m2 IV, total of 2 cycles)	- 3 months: started on gabapentin 600 mg PO TID for complaints of numbness and tingling in bilateral feet (decrease in vibratory and pinprick sensation in feet) - 6 months: improvement in symptoms - 9 months: gabapentin stopped; resolution of numbness and tingling in feet -12 months: symptoms unchanged
Patient B	44 year-old African American woman	Obesity, lumbar stenosis, lumbar spondylosis, and newly-diagnosed stage II breast cancer	Hydrocodone acetaminophen 5/325 PO TID PRN	Paclitaxel (175 mg/m2 IV, total of 2 cycles) + cisplatin (75 mg/m2 IV, total of 1 cycle)	- 3 months: started on gabapentin 300 mg PO TID for complaints of numbness and tingling in bilateral feet (decrease in vibratory and pinprick sensation in feet) - 6 months: dose increased to 600 mg PO TID due to lack of improvement in symptoms - 9 month: symptoms unchanged -12 months: no follow-up
Patient C	41 year-old Caucasian woman	Chronic knee pain and newly-diagnosed stage II breast cancer	None	Paclitaxel (175 mg/m2 IV, total of 2 cycles)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN
Patient D	45 year-old Caucasian woman	Sacroiliitis, acid reflux, asthma, and newly-diagnosed stage II breast cancer	None	Paclitaxel (175 mg/m2 IV, total of 2 cycles)	- 3 months: no concern of CIPN - 6 months: no concern of CIPN - 9 months: no concern of CIPN - 12 months: no concern of CIPN

Each cycle = 21 days

Table 3. Clinical manifestations of common CIPN offenders.

Class	Example	Mechanism of Action	Character of CIPN	Clinical Manifestation
Taxanes	Paclitaxel	Stabilizes tubulin in microtubules and prevents depolymerization.	Presents as an early, acute, reversible pain. Pain later returns as a severe numbness and tingling.	Appears after completion of chemotherapy. Can be more severe in patients with preexisting neuropathic conditions, such as diabetes.
Vinca alkaloids	Vincristine	Blocks microtubule polymerization. Prevents cell division and axonal transport dysfunction.	Severe, long lasting irreversible damage.	Develops after the first cycle of chemotherapy.
Platinum agents	Oxaliplatin	Binds and crosslinks DNA to render them irreparable. Ultimately prevents DNA replication.	Begins as an acute cold-inducing sensitivity. Evolves into a chronic pain with associated numbness and tingling.	Creates delays in nerve conduction, then eventual global destruction of fibers.

= 43.5-98.1) during treatment and ranges from 23-80% after completion of therapy (8).

This case series pursues the potential of capsaicin as a preventive therapy for CIPN. Further determining its mechanism of action may promote more targeted treatment and better therapeutic results. Biochemically, capsaicin acts by binding the transient receptor potential channel vanilloid type 1 (TRPV1) nociceptive receptor (5). Once bound, the ion channel opens—leading to an influx of sodium and calcium ions—and causes depolarization and subsequent action potential (6). This activation produces a sensation of burning, stinging, itching, or heat (Fig. 1). Capsaicin distinguishes its effect from a transient, painful environmental stimulus by its activation of TRPV1. The influx of calcium overwhelms intracellular signals and prevents normal cellular and nociceptor function for a sustained period. One proposed mechanism of action is that repeated stimulation or an

increased concentration of capsaicin can paradoxically reduce pain by a system called 'defunctionalization'. This phenomenon describes the failure to achieve an action potential that subsequently blocks the conduction of pain signals and causes sensory deficits. This newly-acquired loss of responsiveness to sensory stimuli proves advantageous when a patient is overstimulated by pain at baseline, such as with CIPN (6).

Historically, capsaicin was thought to exert its effects by its depletion of substance P (5). Substance P levels were significantly reduced after the application of topical capsaicin, which drove the theory towards this mechanism of action. Substance P was traditionally viewed as an important player in the neurotransmission of pain. However, antagonists of substance P proved poor analgesics in clinical trials so its involvement has been proven to be less contributory to pain pathways than initially believed.

Prior studies with capsaicin have been conducted to evaluate its utility in alleviating pain and determining the optimal tolerable dose (6). Capsaicin is available OTC in varying dosages from 0.025% to 0.075% in ointments, gels, and patches. Low doses may require more frequent, repeated applications in order to achieve the desired effect. Since each application may be associated with a burning sensation, patient noncompliance is a common limitation to its value as a treatment option (6). In contrast, high doses such as topical 8% capsaicin patches, will relieve pain for longer durations, but should only be applied under health care supervision to avoid serious reactions (9). Further research is required to determine the optimal dose for neuropathic pain treatment, especially when targeted toward CIPN (6). Topical high-dose capsaicin has been used for the treatment of painful neuropathy, including diabetic neuropathy (6). However, to the best of our knowledge, there is currently no recommendation for treatment or prevention with low-dose formulations (< 1%).

While there are no pharmaceutical agents known to definitively prevent CIPN, natural supplements, such as vitamins and herbs, have been trialed as a preventative with variable success (1). Although duloxetine is the only proven effective treatment, there are multiple alternatives used to manage CIPN. The major players are antidepressants, opioids, and gabapentin or pregabalin (6). Sultana et al (9) suggest that high-dose capsaicin, lidocaine, and tramadol may serve as valuable second-line treatments.

Duloxetine aside, nortriptyline and amitriptyline are commonly used antidepressants in treatment regimens, but have shown limited efficacy. Similarly, neither gabapentin nor pregabalin has shown a substantial benefit. However, one study found that the combination of nortriptyline and gabapentin was additive compared to the efficacy of either one alone (10). Morphine is considered the most effective of the opioids for CIPN, although studies have similarly shown a superior efficacy when it is combined with an additional treatment rather than either medication alone (1). It is important to highlight that while many of these medications have not been proven effective in the treatment regimen for CIPN, they may still be beneficial in other types of neuropathic pain.

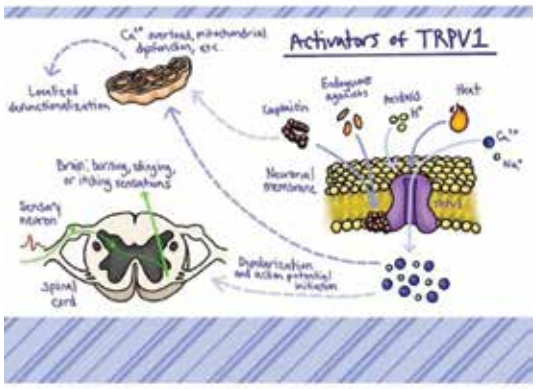

Fig. 1. Activators of TRPV 1.

A meta-analysis by Mason et al (11) compared randomized, controlled trials to determine the efficacy of topical capsaicin for chronic neuropathic or musculoskeletal pain. Out of the initial 38 papers identified, 16 papers were included in this systematic review, amounting to 1,556 patients ranging in age from 20 to 95 years old (11). The primary outcome of the review was set as a 50% reduction in pain, at an 8-week time point for neuropathic conditions. Secondary outcomes were adverse events and subsequent withdrawals from the study. Six hundred and fifty-six patients with neuropathic conditions were identified within 6 double-blind placebo-controlled trials and found that the relative benefit of 0.075% topical capsaicin was 1.4 (95% CI, 1.2 to 1.7) and that the number needed to treat was 5.7 (4.0 to 10.0) when compared to placebo. Therefore, for every 6 patients with neuropathic pain using capsaicin 0.075% for 8 weeks, one additional patient would benefit. Unfortunately, around one-third of patients met the secondary outcome and endorsed local adverse effects with capsaicin as compared to placebo. This re-

view determined that topical capsaicin did not provide good efficacy in the treatment of chronic neuropathic pain, but recognized that capsaicin may be beneficial for patients unresponsive to other treatments (11).

Limitation

The major limitation of our study is due to the nature of a case-series study. We present this data, but do not propose a conclusive causal relationship. Further prospective studies will need to be instituted to establish a cause-and-effect relation.

CONCLUSIONS

This case series presents women with newly-diagnosed stage II breast cancer who underwent chemotherapy while concurrently using OTC topical capsaicin cream and found that none of the patients developed CIPN at any follow-up intervals up to a year after chemotherapy treatment was started. Based on these favorable outcomes, there may be evidence supporting the use of low-dose OTC capsaicin to prevent the development of CIPN. The next step would be to carry out a randomized, prospective study to trial this intervention on a larger scale.

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