

Rational treatment of chemotherapy-induced peripheral neuropathy with capsaicin 8% patch: from pain relief towards disease modification

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Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) with associated chronic pain is a common and disabling condition. Current treatments for neuropathic pain in CIPN are largely ineffective, with unfavorable side-effects. The capsaicin 8% patch (capsaicin 179 mg patch) is approved for the treatment of neuropathic pain: a single topical cutaneous application can produce effective pain relief for up to 12 weeks. We assessed the therapeutic potential of capsaicin 8% patch in patients with painful CIPN, and its mechanism of action.

Patients and methods: 16 patients with chronic painful CIPN (mean duration 2.5 years), in remission for cancer and not receiving chemotherapy, were treated with 30 min application of capsaicin 8% patch to the feet. Symptoms were monitored using the 11-point numerical pain rating scale (NPRS), and questionnaires. Investigations were performed at baseline and three months after patch application, including skin biopsies with a range of markers, and quantitative sensory testing (QST).

Results: Patients reported significant reduction in spontaneous pain (mean NPRS: -1.27; 95% CI 0.2409 to 2.301; $p=0.02$), touch-evoked pain (-1.823; $p=0.03$) and cold-evoked pain (-1.456; $p=0.03$). Short-Form McGill questionnaire showed a reduction in neuropathic ($p=0.0007$), continuous ($p=0.01$) and overall pain ($p=0.004$); Patient Global Impression of Change showed improvement ($p=0.001$). Baseline skin biopsies showed loss of intra-epidermal nerve fibers (IENF), and also of sub-epidermal nerve fibers quantified by image analysis. Post-patch application skin biopsies showed a significant increase towards normalization of intra-epidermal and sub-epidermal nerve fibers (for IENF: structural marker PGP9.5, $p=0.009$; heat receptor TRPV1, $p=0.027$; regenerating nerve marker GAP43, $p=0.04$). Epidermal levels of Nerve Growth Factor (NGF), Neurotrophin-3 (NT-3), and Langerhans cells were also normalized. QST remained unchanged and there were no systemic side-effects, as in previous studies.

Conclusion: Capsaicin 8% patch provides significant pain relief in CIPN, and may lead to regeneration and restoration of sensory nerve fibers ie, disease modification.

Keywords: capsaicin, neuropathic pain, chemotherapy, skin biopsy

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and often disabling adverse effect of common cancer treatments,¹⁻³ which may persist for years, and affect the quality of life.⁴⁻⁷ CIPN is a cause of dose-reduction or discontinuation of chemotherapy treatment, with consequences for prognosis.⁸⁻¹⁰ Despite the prevalence and impact of CIPN, there is no treatment for its prevention or cure.

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More than 30% of patients treated with neurotoxic chemotherapy agents develop peripheral neuropathy.¹¹ The risk is higher with cisplatin, paclitaxel, docetaxel, vincristine, oxaliplatin, and bortezomib.^{12,13} The platinum-based¹⁴ and other drugs^{15–18} may lead to the “coasting” phenomenon ie, an increase in the severity of symptoms after cessation of chemotherapy treatment.

Chemotherapy agents exert effects on peripheral nerve fibers,¹⁹ with reduced amplitude of the sensory action potentials, and the involvement of small sensory fibers leading to the development of pain.²⁰ The diverse underlying cellular and molecular mechanisms include loss of intra-epidermal nerve fibers (IENF),²¹ mitochondrial changes,²² neuronal viability,²³ sodium channels,²⁴ potassium channels,²⁵ transient receptor potential vanilloid receptors (TRPV),²⁶ Langerhans cells,²⁷ oxidative stress,²⁸ mitogen activated protein kinase (MAPK),²⁹ N-methyl-d-aspartate (NMDA) receptors,³⁰ neuropeptide Y,³¹ nitric oxide,³² 5-HT_{2A},³³ protein kinase C,³⁴ calpains and caspases,³⁵ and phosphoglycerate dehydrogenase (3PGDH).³⁶ The involvement of small sensory fibers in CIPN has been well documented.^{37–41}

Randomized clinical trials have been conducted with drugs currently used for neuropathic pain in CIPN, such as Gabapentin,⁴² Lamotrigine,⁴³ Nortriptyline,⁴⁴ Amitriptyline,⁴⁵ and Duloxetine.^{46,47} Two studies have evaluated the effectiveness of topical agents incorporating Amitriptyline, Ketamine, and Baclofen.^{48,49} One study was conducted to determine the effect of an oromucosal cannabis-based spray.⁵⁰ The results of these trials have been largely disappointing,⁵¹ and only Duloxetine showed a small statistical effect on pain outcome measures.

Topical capsaicin formulations are widely used to manage pain. Low-concentration creams for daily skin application over weeks have been available for decades. Application of the high-dose capsaicin 8% patch (also known as capsaicin 179 mg patch, Qutenza) reduces neuropathic pain after a single 30 to 60 min application,^{52–62} with pain relief maintained up to 12 weeks.^{63–65} Capsaicin is an agonist which acts on TRPV1, the heat and capsaicin receptor, and recent advances in the understanding of its mechanism and site of action have been reviewed.⁶⁶ Our recent study showed its effect and mechanisms in amputation stump pain and phantom limb syndrome.⁶⁷

Our aim in this study was to assess the effect of capsaicin 8% patch in patients with painful CIPN in relation to its underlying mechanism of action, using a range of pathophysiological markers in skin biopsies, and

neurophysiological tests. The skin biopsy markers included nociceptor subsets, and their target-derived neurotrophic factors, which maintain nociceptors, regulate their phenotype, and induce nerve regeneration. The neurophysiological tests included standard neurophysiological techniques and quantitative sensory testing (QST).

Our hypothesis was that the capsaicin 8% patch may relieve pain but also induce nerve regeneration and/or restoration of the nerve fiber phenotype, by “pruning” the abnormal nerve fibers. The capsaicin 8% patch causes a reversible “cutaneous nerve terminal axotomy” ie, nerve terminal degeneration followed by regeneration. As the patients were in remission and now not receiving chemotherapy, which adversely affects both their nerves and target skin cells, hence their nerve fibers may now regenerate more “normally” following capsaicin 8% patch treatment.

Materials and methods

Study design

This was a single center, open-label, longitudinal study with capsaicin 8% patch treatment as licensed, conducted in patients who attended the Peripheral Neuropathy Unit, Imperial College London, based at Hammersmith Hospital, Imperial College Healthcare NHS Trust. The study was approved by the London Fulham Research Ethics Committee (Ethics reference number: 12/LO/0895). The study involved hospital visits and telephone calls, as shown in [Figure 1](#). Patients attended the hospital unit for study visits 1 to 3, and the application of the capsaicin 8% patches was carried out in the hospital as previously described in detail, with illustrations.⁶⁷ The capsaicin 8% patches covered the feet and distal calf, including the region of the pretreatment baseline skin biopsies, after they had fully healed. All patients had a total number of 4 patches, 2 for each foot.

Participants

All participants provided written informed consent, and this study was conducted in accordance with the Declaration of Helsinki.

Patients with painful CIPN for at least 3 months prior to enrollment, and aged between 18–80 years, were eligible for inclusion in the study. 16 patients with different types of cancer, who had received chemotherapy (mainly platinum, taxane, and proteasome inhibitor compounds) and developed symptoms of CIPN, were enrolled. Patients Demographic and characteristics are outlined in [Table 1](#). All patients fulfilled the criteria for neuropathy

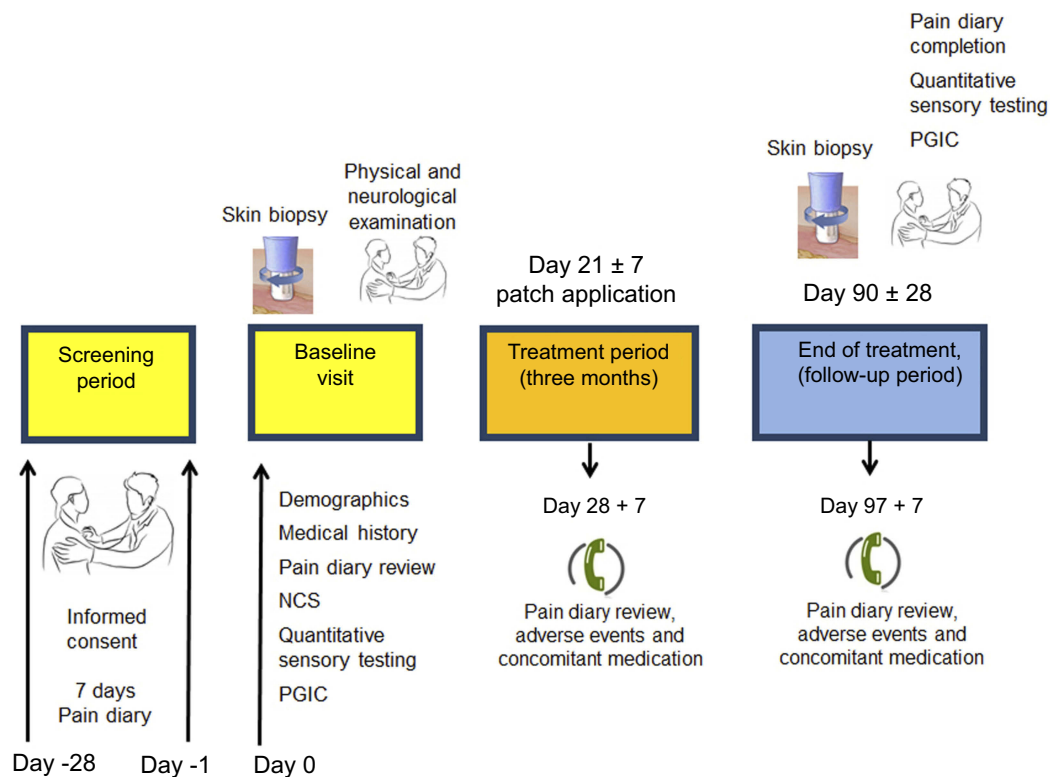


Figure 1 Study flow diagram.

Abbreviations: NCS, nerve conduction study, PGIC, patient global impression of change.

outlined by the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC), including pain and hypersensitivity. Patients were considered suitable for the study if their symptoms had been stable on their prescribed medical treatment for 8 weeks prior to enrollment. Patients described symptoms in their lower limbs, most commonly numbness, pins, and needles, tingling and burning pain or discomfort. All patients reported pain in their feet; most were taking treatment for pain at the start of the study (gabapentin, pregabalin, amitriptyline, duloxetine, tramadol, oxycodone, or a combination of these).

Clinical symptoms and pain assessment scales

Patients were given a study diary to complete starting on the day of screening and continuing for the next 7 days. The diary collected numerical pain rating scores (NPRS) twice daily. An 11-point numerical rating scale (NRPS), with the 0 point being “no pain” and the 10 point being “pain as bad as you can imagine,” was used to describe “pain on average in the last 24 hrs” for spontaneous and evoked pain. After 7 days of completing this diary, a member of the study team contacted the patients by telephone and averaged the

result of their NPRS to determine their eligibility for the study. Only patients with average pain intensity equal or greater than 4/10 on the NPRS for spontaneous pain were eligible to participate further in the study and were advised to continue with the study diary until the end-of-study follow up visit. Symptoms were also assessed using the Short Form McGill Pain Questionnaire (SF-MPQ-2).⁶⁸ The standard Patient Global Impression of Change (PGIC) was recorded.

Clinical examination and assessment of neuropathy

Clinical examination and tests were performed to confirm that patients had a predominantly sensory, length-dependent neuropathy. The Neuropathy Impairment Score Lower Limbs (NIS-LL)⁶⁹ was recorded.

Nerve conduction studies were performed once at the start of the study for all patients. Nerve conduction studies of the common peroneal (including F wave studies) and sural nerves in the right leg were performed in a standardized manner by the same examiner on a Medtronic Keypoint electromyogram (Medtronic, Minneapolis, MN, USA). Sural antidromic sensory action potentials of <5 μ V amplitude and 40 m/s conduction velocity were considered abnormal, and common

Table 1 Patients' demographics and clinical characteristics

Patients demographics	
Age (years, range)	64 (45–79)
Number of patients	16
Number of male patients (%)	8 (50)
Ethnic origin, %	
Asian or Asian British	25.0
Caucasian	68.0
Other	7.0
Clinical characteristics	
Duration of CIPN (years, range)	2.5 (5 month–8 years)
Pain level at baseline (NPRS, mean [SEM])	6.6 (0.43)
Number of patients taking pain medications at baseline	12 (75%)
Acetaminophen (Paracetamol)	2
Gabapentinoids (Pregabalin and Gabapentin)	4
Tricyclic anti-depressants/SNRIs	1
Opioids	4
Other analgesic combinations	1
Patient cancer types:	
Colon cancer	7
Multiple myeloma	6
Lung cancer	1
Ovary cancer	2
Patient chemotherapy types:	
Bortezomib	6
Platinum/taxane or both	10

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; SEM, standard error of the mean; SD, standard deviation; NPRS, numerical pain rating scale; SNRIs, serotonin and norepinephrine reuptake inhibitors.

peroneal nerve (compound muscle action potential from extensor digitorum brevis) values <3 mV amplitude, and 40 m/s conduction velocity were considered abnormal.⁷⁰ An F-wave latency >60 ms was considered abnormal.

Most patients (66%) had at least one abnormality on the nerve conduction study, 11% had both motor and sensory abnormality. F-waves were absent in 1 patient. The mean \pm SEM (range) for the peroneal motor action potential was 3.8 ± 0.5 (1.2–6.3) μ V and for the peroneal conduction velocity was 46 ± 1.4 (40–56.8) m/s. The mean \pm SEM (range) for the sural sensory action potential was 6.8 ± 1.4 (0.0–16) μ V, and for the sural nerve velocity was 44.1 ± 6.3 (0.0–67) m/s.

Quantitative sensory testing (QST)

For quantitative sensory testing (QST), thresholds for light touch were measured using Semmes–Weinstein hairs

(made by A. Ainsworth, University College London, UK), No. 1 (0.0174 g) to No 20 (263.0 g). The number of the hair with the lowest force reliably detected by the patient on the dorsum of the toe was recorded. Values > No. 3 monofilament (0.0479 g) were considered abnormal.⁷⁰ Vibration perception thresholds were measured using a biothesiometer (Biomedical Instrument Company, Newbury, OH, USA) placed on the metatarsophalangeal joint of the big toe. Three ascending and three descending trials were carried out, and the mean value obtained. Values >12 V were considered abnormal.⁷¹

Thermal perception thresholds were performed as described in previous publications^{72,73} using the TSA II–NeuroSensory Analyzer (Medoc, Ramat Yishai, Israel). A 30 mm x 30 mm thermode was used and thermal thresholds determined in the soles of the feet (under the instep), right lateral calf and palms of the hands (thenar eminence) for warm perception, cool perception, heat pain and cold pain from a baseline temperature of 32 °C, with a change in temperature of 1°C/s. The mean of three consecutive tests for each modality was recorded. Values >6.4 °C for warm sensation, >2.3 °C for cool sensation and >10.4 °C for heat pain, were considered abnormal.^{70,72,73}

Calf skin biopsy and immunohistochemistry

Two 3.5-mm diameter skin punch biopsies were collected under local anesthesia from the distal lateral calf of 16 patients with CIPN on visit 1 before capsaicin 8% patch application, and repeated 3 months after patch application. Skin biopsies collected from age and gender-matched 12 healthy volunteers were analyzed alongside the CIPN patient biopsies, as controls. The immunohistochemical methods and antibodies used here had been reported previously.^{74–76} One of the two skin biopsies was snap frozen and stored at –70 °C, and the other immersed in fixative (modified Zamboni's fluid – 2% formalin; 0.01 M phosphate buffer; 15% saturated picric acid (pH 7.2), then washed in phosphate buffered saline (PBS; 0.1 M phosphate; 0.9% w/v saline; pH 7.3) containing 15% w/v sucrose for an hour, before snap freezing in optimum cutting tissue embedding medium (Tissue-Tek OCT, RA Lamb Ltd, Eastbourne, U.K.). Frozen sections (15 μ m thickness) were collected onto poly-L-lysine (Sigma, Poole, UK) coated glass slides and post-fixed in freshly prepared, 4% w/v paraformaldehyde in 0.15M phosphate buffered saline (PBS) for

30 min. Sections of pre-fixed tissue were collected in the same way and allowed to air dry for markers. Endogenous peroxidase was blocked by incubation in methanol containing 0.3% w/v hydrogen peroxide for 30 mins for both post- and pre- (Zamboni) fixed sections. After rehydration, appropriately processed sections were incubated overnight with primary antibodies (n=16 biopsies, unless stated otherwise, as tissue was not enough to study all markers in some biopsies). The antibodies were to the structural nerve marker PGP 9.5 (Rabbit, RA95/06, 1:40,000; Ultraclone, Isle of Wight, UK), the heat and capsaicin receptor transient receptor potential vanilloid 1 TRPV1 (Rabbit, C22, 1:10,000; GlaxoSmithKline, Harlow, UK), the human sensory neuron-specific receptor SNSR, marker of IB-4 nociceptor subset (Rabbit, 1:15,000; gift from Astra Zeneca, Montreal, Canada) nerve regeneration marker, growth associated protein GAP-43 (G9264, Mouse, 7B10, 1:80,000; Sigma, Poole, UK), recombinant human Nerve Growth Factor (Genentech Inc, San Francisco, USA, Rabbit, 12,756/71, 1:2000), NT3 (Rabbit, C/845 No 883, 1:50,000, Amgen, Thousand Oaks, USA) epidermal Langerhans cells marker S-100 (Rabbit, Z311, 1:40,000, Dakocytomation, Dako UK, Ltd, Cambridge, UK). Sites of primary antibody attachment were revealed using nickel-enhanced, avidin-biotin peroxidase (ABC - Vector Laboratories, Peterborough, UK) as previously described.⁷⁴⁻⁷⁶ Sections were counterstained for nuclei in 0.1% w/v aqueous neutral red, air dried and mounted in xylene-based mountant (DPX; BDH/Merck, Poole, UK), prior to analysis. Negative controls included omission of primary antibodies or their replacement with pre-immune serum.

Nerve fibers were counted along the length of four nonconsecutive sections. The length of epithelium in each counted section was measured using computerized microscopy software (Olympus ANALYSIS 5.0 Soft, Olympus UK, Southend, Essex, UK) and results expressed as fibers/mm length of the section. Sub-epidermal nerve immune-reactivity obtained as a percentage (% area) measured by image analysis where digital photomicrographs were captured via video link to an Olympus BX50 microscope. The grey-shade detection threshold was set at a constant level to allow detection of positive immuno-staining and the area of highlighted immuno-reactivity was expressed as a percentage (% area) of the field scanned. Images were captured (x40 objective magnification) along the entire length, and the mean values were used for

statistical analysis. Quantification was performed by two independent blinded observers, and there was no significant difference between observers. Validation of these methods, including vs PGP9.5 IENF in 50µm thickness sections, have been published previously.

Statistical analysis

Data were analyzed using GraphPad Prism version 5.0 for Windows (GraphPad Prism Software, San Diego, CA, USA). The statistical test used was the paired two-tailed Mann-Whitney test. Values were compared before and after the treatment with capsaicin 8% patch. For all statistical tests, *p*-values <0.05 were considered significant.

Results

Neuropathy Impairment Score Lower Limbs (NIS-LL) showed a significant improvement after treatment with the capsaicin 8% patch (*p*=0.01), with a reduction of the mean score ± SEM of 1.875±0.40 (Table 2).

Pain scores and questionnaires

There was a significant reduction in the average (±SEM) daily NPRS for spontaneous pain, -1.271 (±0.077), *p*=0.02, three months after capsaicin 8% patch application (baseline week vs week 12 after patch application). There was also a significant reduction in scores for pain evoked by touch -1.823 (±0.07), *p*=0.03, and cold -1.456 (±0.06), *p*=0.03 (Table 2).

Short-Form McGill Pain Questionnaire (SF-MPQ-2) showed a significant reduction in the continuous (-13.0 ±0.66, *p*=0.001) and neuropathic (-11.7±0.72, *p*=0.0007) pain scores. There was no significant difference in the intermittent and affective pain scores.

Patient Global Impression of Change (PGIC) showed significant improvement, *p*=0.0029 (Table 2).

Quantitative sensory testing

All patients showed abnormalities on QST pre-treatment compared to normal values reported previously,⁷⁷ in accord with other laboratories. There was no significant change after treatment (*p*>0.05, Table 2).

Immunohistochemistry

Skin biopsies at baseline showed fewer PGP9.5-immunoreactive intra-epidermal nerve fibers (IENF) counts than controls; the latter were in accord with our previously published normative data, for all the skin biopsy markers used in this study.^{70,76-78,84} There was a significant increase in PGP9.5

Table 2 Results before and after capsaicin 8% patch: spontaneous pain (NPRS), short form McGill pain questionnaire, patient global impression of change, quantitative sensory testing, and contact heat evoked potentials

Numerical Pain Rating Scale (NPRS), mean \pm SEM			
	Pre patch application	Post patch application	p-value
Spontaneous pain	6.6 \pm 0.4	5.3 \pm 0.5	0.01
Light touch evoked pain	4.8 \pm 0.8	2.6 \pm 0.7	0.02
Cold evoked pain	4.0 \pm 0.8	2.6 \pm 0.8	0.03
Short Form McGill pain Questionnaire (SFMPQ), mean \pm SEM			
	Pre patch application	Post patch application	p-value
Continuous pain	27.9 \pm 3.6	14.9 \pm 2.9	0.001
Intermittent pain	21.2 \pm 3.8	14.0 \pm 3.1	ns
Affective pain	9.5 \pm 2.8	9.4 \pm 2.4	ns
Neuropathic pain	30.5 \pm 3.3	19.5 \pm 2.6	0.0007
Overall pain	83.6 \pm 12.3	53.5 \pm 8.7	0.003
Patient Global Impression of Change (PGIC), mean \pm SEM			
	Pre patch application	Post patch application	p-value
PGIC score	4.2 \pm 0.2	2.8 \pm 0.3	0.003
Quantitative Sensory Testing (QST), mean \pm SEM			
	Pre patch application	Post patch application	p-value
Cool Threshold ($^{\circ}$ C)	20.4 \pm 2.1	20.7 \pm 1.7	ns
Warm Threshold ($^{\circ}$ C)	44.3 \pm 1.2	43.9 \pm 0.9	ns
Cold Pain Threshold ($^{\circ}$ C)	9.6 \pm 2.1	10.4 \pm 2.4	ns
Heat Pain Threshold ($^{\circ}$ C)	47.9 \pm 0.7	48.2 \pm 0.6	ns
Vibration Threshold (V)	33.6 \pm 3.4	28.7 \pm 3.0	ns
Monofilament Threshold (gm)	34.9 \pm 22.2	2.3 \pm 1.4	ns
Neuropathy Impairment Score Lower Limbs (NIS-LL), mean \pm SEM			
	Pre patch application	Post patch application	p-value
NIS-LL Score	10.5 \pm 1.2	8.6 \pm 0.8	0.01

Abbreviations: SEM, standard error of the mean; NPRS, numerical pain rating scale; ns, not significant; PGIC, patient global impression of change; QST, quantitative sensory testing; NIS-LL, neuropathy impairment score lower limbs; $^{\circ}$ C, Celsius degree; V, Volt; gm, gram.

IENF fibers after capsaicin 8% patch treatment patients ($p=0.009$, Figure 2), and in subepithelial nerve fibers (SENF), ($p=0.0056$). There was also a significant increase in TRPV1 IENF fibers ($p=0.027$, Figure 3), and in TRPV1 SENF ($p=0.001$). There were no significant differences between Sensory Neuron-specific Receptors (SNSR) IENF and SNSR SENF ($p=0.7$ and 0.18 respectively; Figure 4). GAP-43 immunoreactive IENF were significantly more abundant after capsaicin 8% patch treatment $p=0.04$, and also GAP-43 SENF ($p=0.004$), Figure 5).

NGF antibodies labeled basal keratinocytes which express NGF which normally helps maintain the IENF^{73,78–80} (Figure 6). In this study, there was a decrease of NGF in basal keratinocytes compared to controls at baseline ($p=0.012$), but an increase towards normal values after treatment with capsaicin 8% patch ($p=0.0035$, Figure 6); further,

this reversal appeared to restore levels towards normal values compared to controls ($p=0.44$, Figure 6). In both control and CIPN subjects, Neurotrophin 3 (NT3) antibodies labeled suprabasal keratinocytes (Figure 7). There was a significant increase in NT3 levels in CIPN patients before treatment compared to control subjects ($p=0.0348$ (Figure 7), which was abolished after treatment with capsaicin 8% patch ($p=0.1778$, Figure 7); this decrease of NT3 was significant ($p=0.009$, Figure 7). S100 antibody labeled Langerhans cells (LCs) (Figure 8). These were decreased, towards normal levels, after capsaicin 8% patch treatment ($p=0.002$, Figure 8).

Discussion

Chemotherapy-induced peripheral neuropathy with associated chronic pain has a major impact on the quality of life of cancer patients, including those in remission from cancer.

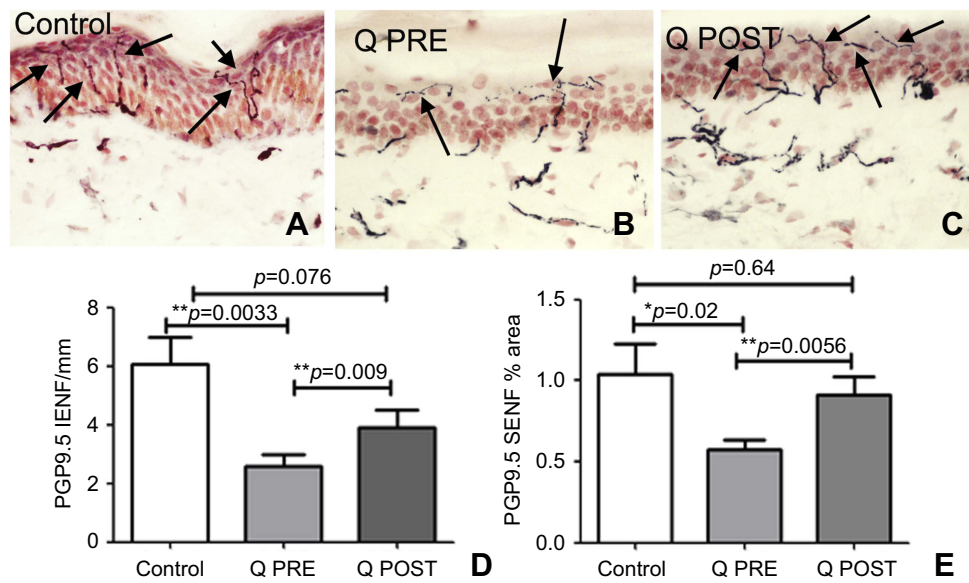


Figure 2 Immunohistochemistry in skin biopsies for PGP9.5, before and after capsaicin 8% patch treatment. Intra-epidermal nerve fibers (arrowed) and sub-epidermal nerve fibers from (A) control subjects, at the baseline visit (B, Q PRE) and, after capsaicin 8% patch treatment (C, Q POST), magnification x40. (D) Bar chart of intra-epidermal nerve fibers for PGP 9.5 counts, (E) bar chart of sub-epidermal (SENF) analysis (% area).

Notes: *Significant; **very significant.

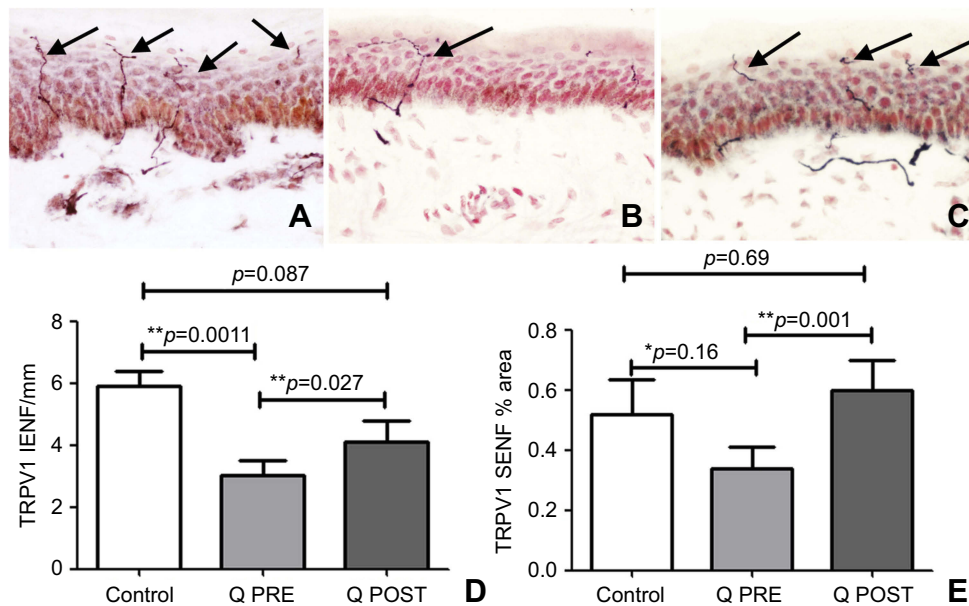


Figure 3 Immunohistochemistry in skin biopsies for TRPV1, before and after capsaicin 8% patch treatment. Intra-epidermal nerve fibers (arrowed) and sub-epidermal nerve fibers from (A) control subjects, at the baseline visit (B, Q PRE) and, after capsaicin 8% patch treatment (C, Q POST), magnification x40. (D) Bar chart of intra-epidermal nerve fibers for TRPV1 (IENF) counts; (E) bar chart of sub-epidermal (SENF) analysis (% area) for TRPV1.

Notes: *Significant; **very significant.

Current symptomatic treatments used for neuropathic pain have limited efficacy with significant side-effects, and there are no preventive measures for development of CIPN, or amelioration of established painful CIPN.

In this study, CIPN patients reported significant pain reduction following a single 30 min treatment with the

capsaicin 8% patch - in spontaneous pain, touch-evoked pain and cold-evoked pain. Their Short-Form McGill questionnaire showed a reduction in neuropathic, continuous and overall pain scores; Patient Global Impression of Change also showed improvement. The effect-size on pain relief by capsaicin 8% patch was similar to that for chronic

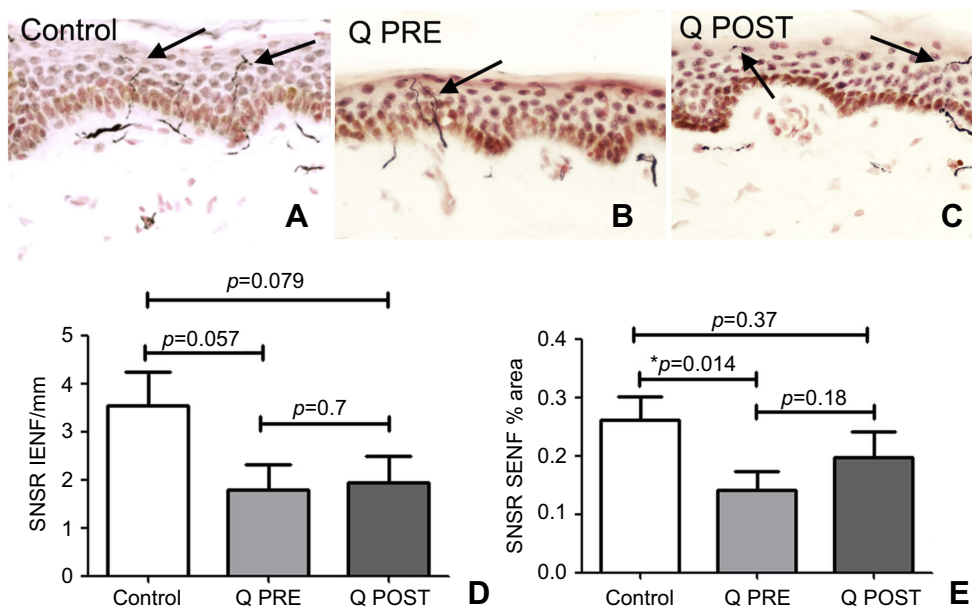


Figure 4 Immunohistochemistry in skin biopsies for SNSR, before and after capsaicin 8% patch treatment. Intra-epidermal nerve fibers (arrowed) and sub-epidermal nerve fibers from (A) control subjects, at the baseline visit (B, Q PRE) and, after capsaicin 8% patch treatment (C, Q POST), magnification x40. (D) Bar chart of intra-epidermal nerve fibers for SNSR (IENF) counts; (E) bar chart of sub-epidermal (SENF) analysis (% area) for SNSR.

Note: *Significant.

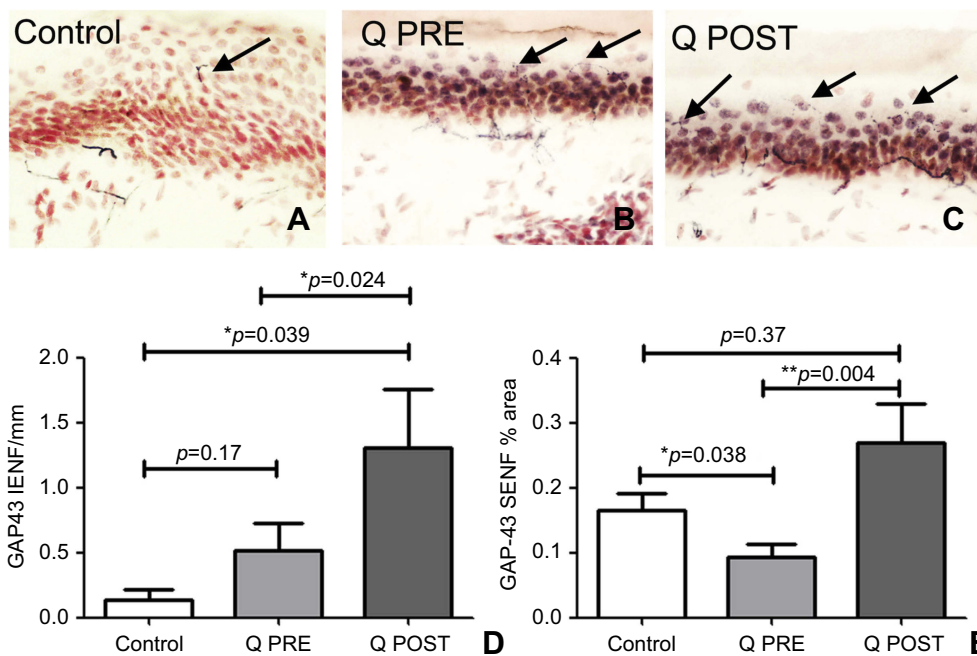


Figure 5 Immunohistochemistry in skin biopsies for GAP43, before and after capsaicin 8% patch treatment. Representative image of intra-epidermal nerve fibers (arrowed) and sub-epidermal nerve fibers from (A) control subjects, at the baseline visit (B, Q PRE) and, after capsaicin 8% patch treatment (C, Q POST), magnification x40. (D) Bar chart of intra-epidermal nerve fibers for GAP43 (IENF) counts; (E) bar charts of sub-epidermal (SENF) analysis (% area) for GAP43.

Notes: *Significant; **very significant.

neuropathic pain caused by other conditions, and as reported recently in two open label treatment studies for painful CIPN.^{81,82} QST remained unchanged, and there were no systemic side-effects, as in previous clinical trials.

The novel findings in the study were the changes observed in skin biopsy markers. The baseline skin biopsies showed loss of intra-epidermal nerve fibers (IENF), as in painful small fiber neuropathy caused by several other

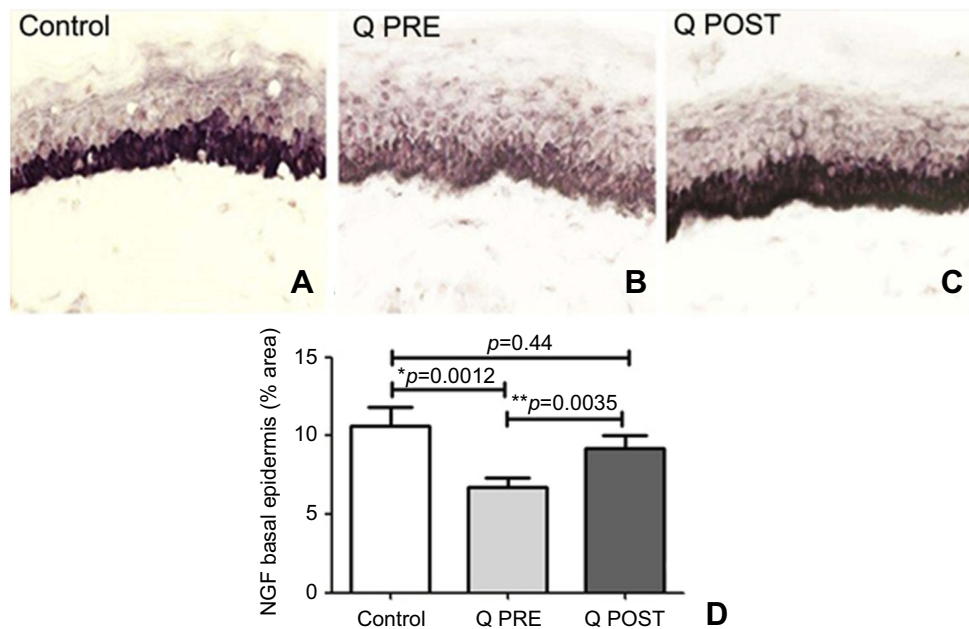


Figure 6 Immunohistochemistry in skin biopsies for NGF, before and after capsaicin 8% patch treatment. NGF immunostaining of basal epidermis in calf skin obtained from (A) control subjects, and CIPN patients before (B, Q PRE) and after capsaicin 8% patch treatment (C, Q POST), magnification x40. (D) Bar chart showing the basal cell NGF image analysis (% area).

Notes: *Significant; **very significant.

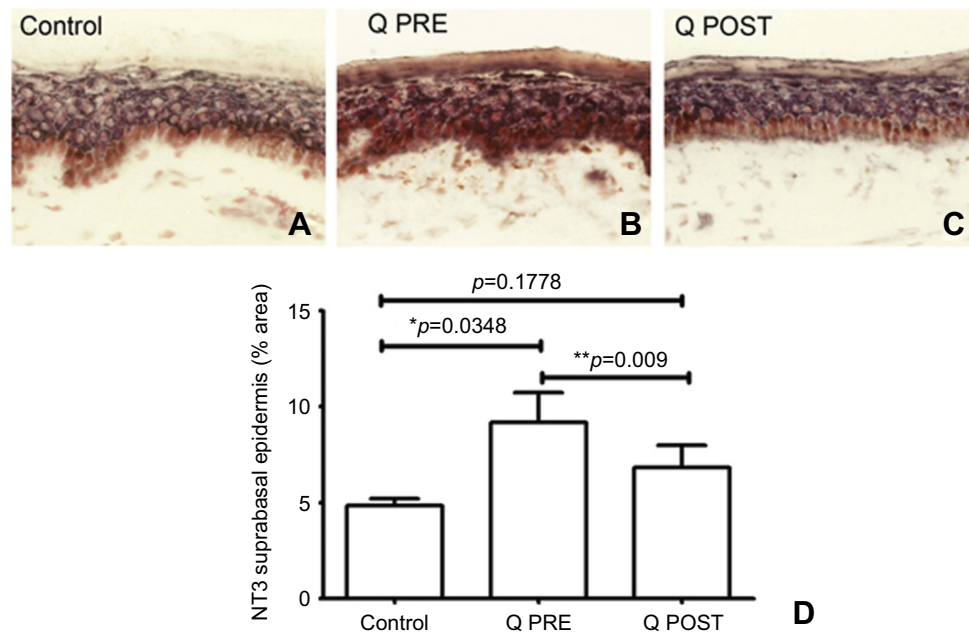


Figure 7 Immunohistochemistry in skin biopsies for NT3, before and after capsaicin 8% patch treatment. NT3 immunostaining from (A) control subjects, and CIPN patients before (B, Q PRE) and after capsaicin 8% patch treatment (C, Q POST). (D) Bar chart showing NT3 suprabasal image analysis (% area).

Notes: *Significant; **very significant.

conditions. Post-patch application skin biopsies showed a significant increase towards normalization of intra-epidermal and sub-epidermal nerve fibers for the pain-neuronal structural marker PGP9.5, capsaicin and heat receptor

TRPV1, and regenerating nerve fibers with the selective marker GAP43. Epidermal Nerve Growth Factor (NGF), Neurotrophin-3 (NT-3), and Langerhans cells were also changed towards normalization post-patch application.

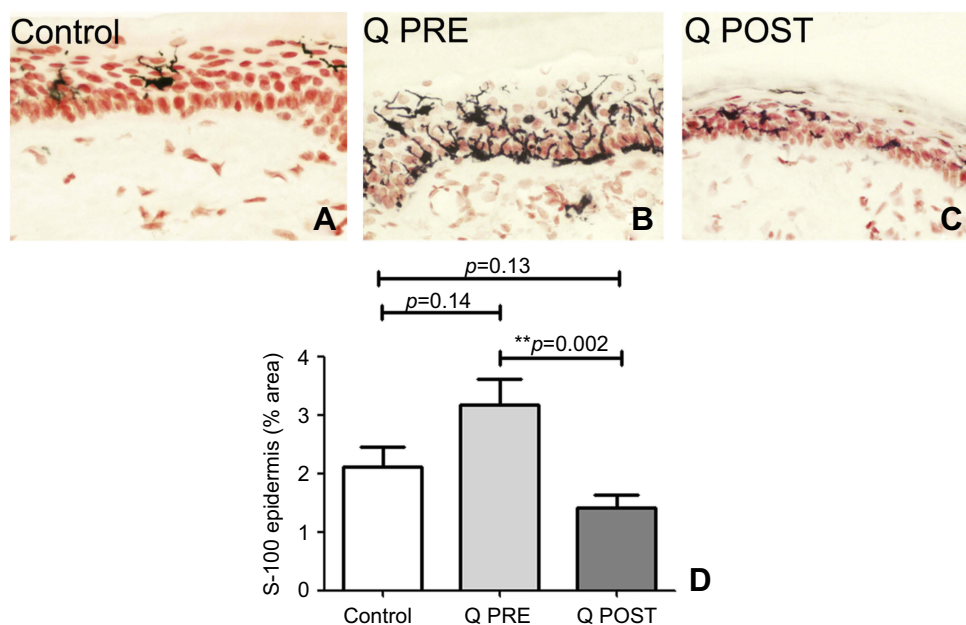


Figure 8 Immunohistochemistry in skin biopsies for Langerhans cells (LCs), before and after capsaicin 8% patch treatment. LCs immunostaining in the epidermis of calf skin from (A) control subjects, and CIPN patients before (B, Q PRE) and after capsaicin 8% patch treatment (C, Q POST), magnification $\times 40$. (D) Bar chart showing LCs image analysis (% area).

Note: **Very significant.

Capsaicin 8% patch is a topical formulation for the treatment of peripheral neuropathic pain; we have reviewed its mechanism of action in detail.⁶⁶ In brief, capsaicin is the pungent “hot” ingredient in chili peppers, a natural selective agonist of the vanilloid receptor TRPV1. It is released rapidly from the capsaicin 8% patch and leads to an overstimulation of skin nociceptors - they are “defunctionalized” acutely, and are no longer able to respond as previously to the range of stimuli that may cause pain in patients with peripheral neuropathy.⁶⁶ The defunctionalization occurs in nociceptor cutaneous terminals, as the patch has an effect on their mitochondrial function to the dermis, with a concentration gradient. A single application of capsaicin 8% patch can provide pain relief for up to 3 months or more – however, the effect of the patch is reversible, and nerve fiber terminals usually regenerate, hence some patients require 3 monthly patch applications for pain relief.

For this study, our hypothesis was that a single application of capsaicin 8% patch, by “pruning” the abnormal nerve fibers, may induce nerve regeneration and restoration of the nerve fiber phenotype in skin biopsies, as the patients were now not receiving chemotherapy which adversely affects both nerves and target skin cells. The milieu in the absence of chemotherapy agents may enable more healthy interactions between the regenerating sensory nerve fibers and their target organs,

leading to restoration of nociceptor phenotype and expression of neurotrophic factors by the target organ.^{66,73,79} The sensory neuropeptides eg, calcitonin gene-related peptide CGRP when released by nerve terminals enhances keratinocyte proliferation and their expression of NGF.^{73,79} The results of this study are in accord with our hypothesis. Thus, the capsaicin 8% patch provides significant pain relief in CIPN, and may also lead to regeneration and restoration of sensory nerve fibers ie, disease modification.

The potential roles of the key epidermal neurotrophins in painful peripheral neuropathies, and the inverse correlation between NGF and NT-3 levels observed before and after treatment with capsaicin 8% patch, is in agreement with our previous publications and reviews.^{73,79,83,84} Decreased epidermal expression and levels of NGF, eg, induced by cancer chemotherapy which is toxic to epidermal keratinocytes expressing NGF, may lead to reduced IENF. The increased level of NT-3 observed at baseline in this study has been reported previously in association with epidermal denervation in small fiber painful peripheral neuropathy, and attributed to a possible compensatory mechanism.⁸⁴ The persistence of these neurotrophic factor changes and their dependent innervation following cessation of chemotherapy observed at baseline in our study deserve further investigation, particularly long-term epigenetic mechanisms.

The potential role of Langerhans cells in painful CIPN has been described,²⁷ their changes following treatment with capsaicin 8% patch towards normalization in our study suggests a contribution in pain relief, or a secondary effect. The interaction between neuro-inflammatory, neuro-degenerative and neuro-regenerative mechanisms at different stages of painful neuropathies are complex, and also deserve further studies in CIPN.

Future studies should include randomized clinical trials in a greater numbers of participants, in comparison with placebo and also other treatments for neuropathic pain. These will address some of the limitations of this initial study, including spontaneous improvements in pain and skin biopsy markers – we regard the latter as unlikely, as the patients all had persistent neuropathic pain over months to years, and on assessments showed features of chronic CIPN. To our knowledge, repeat skin biopsies have not been analyzed previously in patients with CIPN, without or following treatments. We have reported a decline of nerve fiber markers in skin biopsies repeated after 6 months in a natural history study of patients with chronic diabetic sensory polyneuropathy.⁷⁷

Conclusion

Capsaicin 8% patch provides significant pain relief in CIPN, and may lead to nerve regeneration and restoration of sensory nerve fibers ie, disease modification. These mechanistic changes following capsaicin 8% patch treatment in painful CIPN are promising, and deserve further study for pain relief and disease modification.

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Author contributions

The study was conceived by PA, clinical assessments were conducted by EE, RP, KN, PM and PA, tissue studies and review were performed by YY, PD and PA, statistical analysis was by EE, YY and RP, the patients were recruited with HG, HW, LK, and AR, who reviewed clinical data. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

PA has received speaker fees for symposia and meetings organized by Astellas UK, but no remuneration for this investigator-led study. PA also reports grants from Astellas, during the conduct of the study. HG reports is jointly employed by Imperial College and Astra Zeneca and received personal fees from Sensorkinesis. HG is also the Chief Scientific Officer and patent holder for Papyrus Therapeutics, during the conduct of the study. The authors report no other conflicts of interest in this work.

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