Phase II trial of the electrocutaneous nerve stimulation device, MC5-A Calmare® In patients with refractory chemotherapy induced peripheral neuropathy

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Abstract

Purpose: Chemotherapy induced peripheral neuropathy (CIPN) is a major dose-limiting and persistent consequence of numerous classes of antineoplastic agents affecting 30-40% of patients. To date, there is no effective prevention or therapy. An evolving hypothesis for reducing CIPN pain involves direct nerve stimulation to reduce the pain impulse.

Patients and Methods: We evaluated the impact on CIPN associated with the MC5-A Calmare® therapy device. The device is designed to generate a patient-specific cutaneous electro-stimulation to reduce the abnormal pain intensity. Sixteen patients from one center received 1-hour interventions daily over 10 working days.

Results: Of 18 patients, 16 were evaluable. The pts had a mean age of 58.6 years; 4 men, 14 women; the duration of CIPN was 3 months to 8 years. The most common drugs were taxanes, platinums, and bortezimib. At the end of the study (Day 10) a 20% reduction in numeric pain scores was achieved in 15 of 16 patients. The pain score fell 59% from 5.81±1.11 before treatment to 2.38±1.82 at the end of 10 days (paired t test, <0.0001). A daily treatment benefit was seen with a strong statistically significant difference between the pre and post daily pain scores (p-value < 0.001). Four patients had their CIPN reduced to 0. A repeated measures analysis using the scores from all 10 days confirmed these results. No toxicity was seen. Some responses have been durable without maintenance.

Conclusions: Patient-specific cutaneous electro-stimulation with the MC5-A Calmare® device appears to dramatically reduce pain in refractory CIPN patients with no toxicity. Further studies are underway to define the benefit, mechanisms of action, and optimal schedule.

Introduction

• 30-40% of cancer patients suffer CIPN from taxanes, bortezomib, thalidomide/lenalomide, the platinums, and many new drugs.
•This has become a dose limiting toxicity -- and the cause of much permanent suffering.
•To date there has been no proven effective therapy, and many drugs have proven ineffective.
•An evolving hypothesis is that direct nerve stimulation may help, similar to spinal cord stimulation, by allowing the damaged nerve to remodel or repair, or by changing the pain threshold.

Objectives

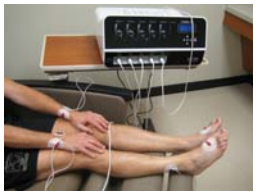
1. To determine if MC5-A Calmare therapy would improve CIPN pain scores.
2. To determine the magnitude of pain relief, toxicity, and effect on pain medication use.

Eligibility and Participant Characteristics

Inclusion criteria:
•CIPN pain > 3 months, stable for 2 weeks.
•Pain > 5 on 0-10 scale.
•No recent changes in medications; no chemo in 3 months.
Exclusion criteria:
•Seizures.
•Metal stents.

The study was approved by the Massey Cancer Center Protocol Review and Monitoring System, and the VCU Investigational Review Board, and registered at clinicaltrials.gov (MCV-MCC-12110, NCT00952848). We thank Dr. Charles Loprinzi for help in study design.

The MC5-A Calmare (Scrambler) Therapy Device



• Delivers "non-pain" information across the pain dermatomes to block the effect of pain information.
•Multiprocessor simulates 5 artificial neurons with 16 different types of synthetic nerve action potentials in sequence via algorithms.
•Feels like rapidly alternating bee sting, pressure, other hard to describe sensations; increased to tolerance for 45 minutes daily.
•Approved by the Food and Drug Administration February 2009.
•Applied to the skin with gel patches as shown in Figure 1.

Data collection and analysis

• CIPN pain scores ("Pain now" from BPI) collected before and after each session, then every 2 weeks for 3 months.
•QOL, pain drugs, symptom assessment done on schedule.

Study Participants were typical for CIPN

Table 2: Patient characteristics

UPN	Age, Sex	Disease	CIPN Drugs	Duration (mo.)	Prior treatments for CIPN
1	59, F	Lung	Carboplatin, paclitaxel	3	Opioids, duloxitene
2*	42, F	Breast	Docetaxol	12	ADs, others
3*	76, F	Lymphoma	Cyclophosphamide, procarbazine	24	Gabapentin
4	54, F	Breast	Paclitaxel, docetaxol	78	Gabapentin, opioids, pregabalin, others
5	46, M	Myeloma	Thalidomide	48	Opiods, Ads
6	56, M	Colon	Oxaliplatin, fluorouracil, leucovorin	9	Magnesium, opoids, ADs
7	60, F	Breast	Adriamycin, paclitaxol	30	Opioids, ADs, pregabalin
8	76, F	Lymphoma	Flavopiradol, bortezomib	6	Opioids, ADs
9	67, F	Colon	Oxaliplatin	24	Opioids, ADs, pregabalin, gabapentin
10	56, F	Breast	Taxanes	48	Opioids, ADs, gabapentin
11	60, F	Breast	Taxanes	96	Opioids, carbamazepine
12	53, M	Colon	FOLFOX + bevacizumab	30	Opioids, gabapentin, carbamazepine, duloxitene
13	52, F	Hodgkins	MOPP	5	Opioids, duloxitene, tegretol
14	62, F	Myeloma	Bortezomib + flavopiradol	48	Opioids, gabapentin, tegretol, duloxetine
15	63, F	Breast	Docetaxol	5	Gabapentin
16	75, F	Breast	Paclitaxel	4	Gabapentin
17	40, M	Colon	FOLFOX	3	ADs; tramadol, venlafaxine
18	59, F	Breast	Paclitaxel	24	Gabapentin

UPN=unique patient number; FOLFOX=fluorouracil, oxaliplatin, leucovorin; MOPP=mechlorethamine, vincristine, prednisone, procarbazine; AD=anti-depressants. *Not Evaluable Patients.Patient #2 was never treated due to rapidly progressive disease immediately after enrollment. Patient #3 only completed 2 treatments due to transportation problems.

Minimal Side Effects

• No side effects were reported, as observed in the prior trials of over 300 patients.
•Therapy was well tolerated, requiring less than an hour a day.
•2 patients stopped due to transportation problems or recurrent cancer requiring treatment.

Findings: CIPN was rapidly and significantly relieved.

Table 2: Effect of Electrocutaneous stimulation with MC5-A Calmare® therapy on Pain Scores

	Before	After	P value
Reduction in pain by 20%	0	15 of 16 (94%)	<0.0001*
CIPN pain score	5.81±1.11	2.38±1.82 -59%	<0.0001 **
Adjusted pain scores	4.9±0.4	1.8±0.4 -64%	< 0.0001***
Daily reduction in pain scores	3.74± 0.38	2.72± 0.38 -1.02, -27%	< 0.001***

*Fischer's exact test; **paired t test; ***repeated measures analysis

Figure 2: Unadjusted CIPN pain scores

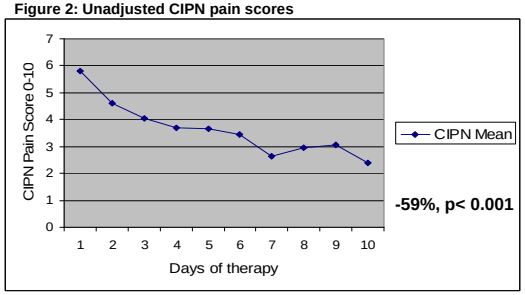
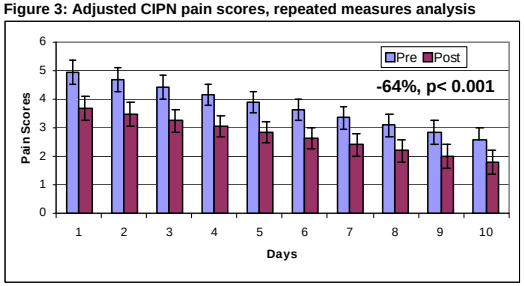


Figure 3: Adjusted CIPN pain scores, repeated measures analysis



Conclusions

• MC5-A Calmare therapy relieved refractory CIPN pain quickly and significantly, with minimal side effects.
•Some pain relief is durable for months but some requires retreatment and maintenance.
•4 of 16 had complete disappearance of pain.
•Some patients had return of complete or partial normal sensation, and relief of numbness, as well as relief of pain.
•Randomized blinded trials are difficult due to the need to adjust the electrodes and dose until relief is obtained, the characteristic MC5-A sensation, and lack of alternative effective controls.
•Further prospective trials are ongoing.

References

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