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Authors

Miaskowski, Christine
Paul, Steven M
Mastick, Judy
et al.

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CONTRIBUTION OF LOSS OF LARGE FIBER FUNCTION TO PAIN IN TWO SAMPLES OF ONCOLOGY PATIENTS

Christine Miaskowski, RN, PhD[1], **Steven M. Paul, PhD**[1], **Judy Mastick, RN, MN**[1], **Gary Abrams, MD**[2], **Kimberly Topp, PT, PhD**[2], **Betty Smoot, PT, DPTSc**[2], **Kord M. Kober, PhD**[1], **Margaret Chesney, PhD**[2], **Mark Schumacher, MD, PhD**[2], **Yvette P. Conley, PhD**[3], **Marilyn Hammer, RN, PhD**[4], **Steven Cheung, MD**[2], **David Borsook, MD, PhD**[5,6], and **Jon D. Levine, MD, PhD**[2,7]

[1]School of Nursing.

[2]School of Medicine.

[3]School of Nursing, University of Pittsburgh, Pittsburgh, PA.

[4]Department of Nursing, Mount Sinai Hospital, New York, NY.

[5]Boston Children's Hospital.

[6]Harvard Medical School, Boston, MA.

[7]School of Dentistry, University of California, San Francisco, CA.

Abstract

Numbness associated with neuropathic pain suggests the loss of function in myelinated, large diameter sensory neurons. The purpose of this study was to examine the relationships between pain severity and subjective (i.e., severity of numbness) and objective (i.e., loss of light touch sensations, vibration thresholds) measures of loss of large fiber function in adult survivors with chemotherapy-induced peripheral neuropathy (CIN, n=426) and breast cancer patients with persistent post-surgical pain (n=80). For both samples, average pain and numbness were evaluated using a 0 to 10 numeric rating scale (NRS). Loss of light touch sensations in the hands and feet of patients with CIN and in the upper arm of patients at 5 and 6 months following breast cancer surgery were assessed using Semmes Weinstein monofilaments. Loss of vibration in the hands and feet of patients with CIN was assessed using a biothesiometer. Pearson Product Moment correlation coefficients were calculated between average pain and the number or percentage of sites with loss of light touch sensations, mean vibration thresholds, and the severity of numbness. For both pain conditions, average pain scores were significantly correlated with objective measures of large fiber function (r = 0.12 to 0.34; all, p<.05) and numbness (r = 0.22 to 0.52; all, p<.008). Our findings, in two independent samples of oncology patients, suggest that loss of function of myelinated, large diameter fibers contributes to the severity of neuropathic pain.

Address correspondence to: Christine Miaskowski, RN, PhD, Professor, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 415-476-9407 (phone), 415-476-8899 (fax), chris.miaskowski@ucsf.edu.

Keywords

large myelinated fibers; neuropathic pain; chemotherapy-induced peripheral neuropathy; post-surgical pain; numbness; vibration; breast cancer

INTRODUCTION

Peripheral neuropathy is the most common adverse effect associated with cancer chemotherapy (CTX).[1,2] CTX-induced peripheral neuropathy (CIN) is a dose-dependent neuropathy characterized by the "dying back" of peripheral axons. Some patients with CIN describe a variety of sensations (e.g., numbness) in the upper and lower extremities that are compatible with involvement of large diameter myelinated sensory afferents.[1–3] Findings from animal studies suggest that multiple mechanisms are involved in the development of CIN associated with the administration of platinum and taxane compounds, the two most commonly used neurotoxic drugs.[4,5] While, both preclinical[6–8] and clinical[9–11] studies suggest that these two groups of neurotoxic drugs damage both small (pain) and large (touch, vibration) myelinated sensory fibers, little is known about the impact of loss of large fiber function on pain intensity.

Recent work from our group found that numbness, a sensation associated with loss of large fiber function, was the most common quality reported by cancer survivors with CIN and had the highest severity rating.[12] In the initial description of the Gate Control Theory of Pain,[13] Melzack and Wall hypothesized that activity in myelinated, large diameter fibers (e.g., produced by rubbing a distal extremity) would "close the gate" in the dorsal horn and decrease pain intensity. This hypothesis led to the development of transcutaneous nerve stimulation (TENS) of large diameter fibers[14] which has been used to treat neuropathic pain.[15] Based on this literature, we hypothesized that if neurotoxic CTX damaged large diameter sensory fibers, associations would be found between subjective and objective measures of loss of large fiber function (i.e., increased numbness, loss of light touch sensation, increased vibration threshold) and pain intensity.

Another very common chronic pain in oncology patients, particularly following breast cancer surgery, is persistent postsurgical pain.[16] Following breast conserving surgery or mastectomy surgery,[17–20] some women with persistent pain describe numbness and sensory loss in the affected breast and arm. Factors that may contribute to this loss of large fiber function include the surgery itself, as well as radiation therapy[18,21] and/or CTX.[22] Similar to CIN, it is plausible that the loss of large fiber function in women who report these symptoms would be associated with increased pain.

In this study, we explored the impact of loss of large fiber function on these two cancer-related pain syndromes in two well characterized patient samples (i.e., adult cancer survivors with CIN and breast cancer patients with persistent postsurgical pain). The purpose of this secondary analysis was to examine the relationships between pain severity and subjective (i.e., severity of numbness) and objective (i.e., loss of light touch sensations, vibration) measures of loss of large fiber function.

METHODS

CIN Study

Cancer Survivors and Settings—The methods for this cross-sectional study are described in detail elsewhere.[12] In brief, survivors were recruited from throughout the San Francisco Bay area and met pre-specified inclusion and exclusion criteria. Of the 1450 survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires and the study visit.

Subjective Measures—A demographic questionnaire obtained information on age, marital status, education, ethnicity, employment status, living situation, and financial status. The Karnofsky Performance Status (KPS) scale was used to evaluate functional status.[23] The Self-Administered Comorbidity Questionnaire (SCQ) was used to measure comorbidity.[24,25]

Prior to the study visit, survivors completed separate questionnaires that evaluated pain characteristics in their upper and lower extremities. Average pain intensity over the past week was assessed using a 0 (no pain) to 10 (worst imaginable pain) numeric rating scale (NRS). The severity of numbness (0 = not numb to 10 = the most numb sensation imaginable) was assessed using the Pain Quality Assessment Scale (PQAS).[26,27]

Objective Measures of Large Fiber Function—Semmes-Weinstein monofilaments (SWM; North Coast Medical, Inc., Morgan Hill, CA) were used to test light touch sensation in the upper and lower extremities. Each upper extremity was evaluated at 7 locations: the pad of the thumb, thumb webspace, tip of the index finger, tip of the little finger, midway up the base of the palm, one third up the anterior surface of the arm, and two thirds up the anterior surface of the arm. Each lower extremity was evaluated at 9 locations: pad of the great, 3rd, and 5th toes; base of the heel; dorsal surface of the metacarpophalangeal (MP) joint of the great, 3rd, and 5th toes; midway along the anterior surface of the tibia, and the patella. These locations were tested in random order.

SWM sizes used for the upper extremities were: 3.61 (0.4 grams (g)), 4.31 (2 g), 4.56 (4 g), 5.07 (10 g), and 6.65 (300 g). SWM used for the lower extremities were: 4.31, 4.56, 5.07, and 6.65. Before testing began, survivors were familiarized with the filament being used and the expected sensation was demonstrated. Then with the survivors' eyes closed, starting with the smallest, filaments were applied in ascending order at each site. The filaments were applied perpendicular to the skin and pressed until the filament bowed for 1.5 seconds. The survivor was asked to respond to the stimulus by stating the location of the light touch sensation. In contrast to Bell-Krotoski's recommendation, two correct responses out of three rather than one out of three at each location were considered a positive response, as the survivor could make one correct response by guessing.[28] At each location, once a positive response was identified, the next location was tested in random order. SWM measurements have good inter-and intra-rater reliability and validity when calibrated and applied correctly. [29–31] For each location, the smallest SWM that the survivor sensed was used in the statistical analyses.

Vibration threshold was tested using a biothesiometer (Bio-Medical Instrument Company; Newbury, OH). After familiarizing survivors with the sensation, vibration thresholds were tested at four sites in the upper extremities (i.e., dorsal interphalangeal (IP) joint of the thumb and index finger, ulnar prominence of the wrist, lateral epicondyle) and three sites in the lower extremities (i.e., dorsal IP joint of the great toe, medial malleolus, patella). Following the manufacturer's instructions, the biothesiometer was placed on the skin over the bone at each location. Beginning at zero, the amplitude of the vibration was increased until the survivor reported feeling vibration (i.e., vibration perception threshold). Then the amplitude was turned down to zero and the procedure was repeated, increasing the intensity more slowly as the initial value was approached. The survivor reported the perception of the sensation of vibration by saying, "NOW." Each site was tested three times and a mean score was calculated.

Study Procedures—This study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF). Research nurses screened and consented the survivors over the phone; sent and asked them to complete the self-report questionnaires prior to their study visit; and scheduled the in person assessment. At this assessment, written informed consent was obtained, questionnaires were reviewed for completeness, and objective measurements were done. Inter-rater reliability among the research nurses for each of the objective measures, evaluated every six months, exceeded 0.80.

Breast Symptoms Study

Patients and Settings—The methods for this longitudinal study are described in detail elsewhere.[18] In brief, adult women who were scheduled for unilateral breast cancer surgery, without distant metastasis; were able to complete the questionnaires; and gave written informed consent were eligible to participate. Patients were recruited from seven sites in Northern California.

Subjective Measures—A demographic questionnaire obtained information on age, marital status, education, ethnicity, employment status, living situation, and financial status. The KPS scale was used to evaluate functional status.[23] The SCQ was used to measure comorbidity.[24,25]

At 5 and 6 months after surgery, average pain intensity over the past week in the arm/shoulder was assessed using a 0 (no pain) to 10 (worst imaginable pain) NRS. The severity of numbness (0 to 10 NRS) was assessed as part of the Pain Quality Assessment Scale (PQAS).[26,27]

Objective Measure of Large Fiber Function—Sensation in the upper inner arm was tested at 4 to 8 sites along the surgical incision, using a 5.07 gram SWM and compared to the corresponding area on the unaffected side. For each site tested, patients reported whether it was "much less sensitive than the opposite side", "same as the opposite side", or "much more sensitive than the opposite side". The percentages for the total number of sites classified as "much less," "same," and "much more" were calculated.

Study Procedures—This study was approved by the Committee on Human Research at UCSF and by the Institutional Review Boards at each of the study sites. A research nurse had the patients complete the study questionnaires and obtained the objective measures either in the patients' home or in the Clinical Research Center. Over the course of the study, medical records were reviewed for disease and treatment information. Inter-rater reliability among the research nurses for each of the objective measures, evaluated every six months, exceeded 0.80.

Data Analysis—Descriptive statistics were generated using SPSS version 23 (IBM Corporation, Armonk, NY). For the CIN Study, for the upper and lower extremities, Pearson Product Moment correlation coefficients were calculated between average pain at the site and the number of sites with loss of protective sensation, mean vibration threshold across the number of sites tested, and the severity of numbness. For the Breast Symptoms Study, Pearson Product Moment correlation coefficients were calculated between average pain ratings at 5 and 6 months and the percentage of sites in the affected arm with decreased sensation and the severity of numbness. A p-value of <.05 was considered statistically significant.

RESULTS

Sample Characteristics for the CIN Study

As shown in Table 1, the 426 survivors with CIN were 60.9 (SD=10.5) years of age; had on average two years of college education; and were predominantly female (86.6%), White (77.2%) and married/partnered (60.9%). The majority of the survivors was diagnosed with breast cancer (54.9%) and most had received a taxane as the neurotoxic CTX (46.9%).

Sample Characteristics for the Breast Symptoms Study

As shown in Table 2, the 80 patients with arm pain at the 5-month assessment were 52.7 (SD=10.3) years of age; had an average of two years of college education; were predominantly White (58.2%), and had gone through menopause (62.3%). The majority of these patients had breast conservation surgery (75.0%), a sentinel lymph node biopsy (81.3%), an axillary lymph node dissection (57.5%), and had received radiation therapy in the six months following surgery (52.5%). Approximately one third of the women had received neoadjuvant CTX (33.8%), adjuvant CTX in the six months following surgery (41.3%), and had a re-excision or mastectomy in the six months following the initial surgery (31.3%).

Correlation Analyses

As shown in Table 3, for both chronic pain conditions, average pain scores were positively correlated with objective measures of large fiber function (r = 0.12 to r = 0.34, all p<.05). Average pain scores were positively correlated with the severity of numbness (r = 0.22 to 0.52, all p .008; see Supplementary Figures 1, 2, and 3, Supplemental Digital Content 1, 2 and 3, http://links.lww.com/CJP/A527, http://links.lww.com/CJP/A528, http://links.lww.com/CJP/A529).

DISCUSSION

Consistent with our a priori hypothesis, this study is the first to demonstrate relationships with both subjective and objective measures of loss of large diameter myelinated fiber function and higher pain severity scores in two independent samples of individuals who were experiencing neuropathic pain following receipt of neurotoxic CTX or breast cancer surgery. While the findings from a small number of pilot studies suggest that the use of TENS-like treatments results in decreases in neuropathic symptoms in patients with CIN[32,33] and post-mastectomy pain,[34] in another pilot randomized controlled trial,[35] TENS had no effect on the pain associated with CIN. In addition, the authors of a recent Cochrane review concluded that definitive conclusions regarding the efficacy of TENS for various types of neuropathic pain could not be determined because the quality of the evidence was very low.[15] Given our findings on the associations between our measures of loss of large fiber function and increased pain, it is reasonable to suggest that the lack of efficacy of TENS for neuropathic pain conditions may be partially explained by the loss of large fiber function. Additional evidence to support for this hypothesis comes from an analysis of our CIN study data. A small subset of our survivors provided information on the efficacy of massage (rated on a 0 = not at all effective to 10 = completely effective NRS) for their foot and hand pain. The negative associations between the objective measure of loss of large fiber function (i.e., SWM testing) and the efficacy of massage for the feet ($r = -0.19$, $p = .056$, $n = 108$) and hands ($r = -0.20$, $p = .113$, $n = 65$) approached statistical significance.

In terms of CIN, controversy exists regarding the complex etiology of this heterogeneous type of neuropathic pain. Both preclinical[6–8] and clinical[9–11] studies suggest that platinum and taxane compounds damage both small and large myelinated sensory fibers. At the two ends of this controversy are the use of TENS to treat neuropathic pain[15] and evidence that suggests that large fiber activity contributes to allodynia.[36–38] Findings from the current study and our recent report on the same sample,[12] as well as work by Ventzel and colleagues,[39] suggest that cancer patients who receive platinum and/or taxane compounds report symptoms and objective findings that are congruent with loss of large fiber function and associated increases in pain severity.

Persistent postsurgical pain following breast cancer surgery has an equally complex etiology. While most studies have attributed the persistent pain to the effects of surgery,[40–42] additional treatments, that are administered prior to or following the surgical procedure, may contribute to this neuropathic pain condition. For example, in our sample of breast cancer patients, 52.5% of the women had received radiation therapy in the six months following surgery. Radiation can have acute and delayed effects on peripheral nerves. Acute effects include transient electrophysiological and biochemical changes, as well as alterations in the vascular network. Delayed effects include axonal injury demyelination, extensive fibrosis within and surrounding nerve trunks, and ischemia.[43] In addition, 41.3% of our patients received neoadjuvant CTX and 41.3% had adjuvant CTX in the six months following surgery. Given that many of these women will receive a neurotoxic drug as part of their CTX regimen,[44] the positive associations between persistent shoulder pain and numbness as well as a higher percentage of sites with decreased light touch sensation on the affected side compared to the contralateral side may be the result of the neurotoxic effects of the CTX,

and/or the surgical procedure. Given our relatively small sample size, it is not possible to examine these relationships in the current study.

A number of limitations warrant consideration. For both studies, we chose to use objective measures of large fiber function that clinicians can use in clinical practice (e.g., SWM). In future studies, more detailed characterization of nerve fibers using quantitative sensory testing may provide additional insights into the association between large fiber loss and small fiber injury and increased pain. The number of patients with persistent postsurgical pain at 5 and 6 months was relatively small. Studies with larger samples are needed to determine the relative contributions of surgery, CTX, and radiation therapy to changes in large fiber function in women following breast cancer surgery. Despite these limitations, our findings from two independent samples of oncology patients suggest that loss of function in myelinated, large diameter fibers contributes to increases in neuropathic pain. These findings strengthen one of the original tenets in Melzack and Wall's Gate Control Theory of Pain.[13]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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Table 1 –

Characteristics of the Survivors with Chemotherapy-Induced Neuropathy (n=426)

Characteristics	Mean (SD)
Age (years)	60.9 (10.5)
Education (years)	16.4 (2.8)
Body mass index (kilograms/meter squared)	26.6 (5.5)
Karnofsky Performance Status score	83.2 (10.2)
Self-Administered Comorbidity Questionnaire	4.2 (3.4)
Time since cancer diagnosis (years)	4.8 (4.8)
Number of years with CIN in the lower extremities	3.9 (4.2)
Number of years with CIN in the upper extremities	3.6 (4.2)
Total dose of platinum compound (milligrams/meter squared)[a]	704.9 (491.2)
Total dose of taxane compound (milligrams/meter squared)[b]	759.6 (668.5)
For survivors who received both a platinum and a taxane compound	
Total dose of platinum compound (milligrams/meter squared)	1787.3 (791.5)
Total dose of taxane compound (milligrams/meter squared)	895.0 (460.7)
	% (n)
Female	86.6 (368)
Married/partnered	60.9 (252)
Living alone	29.2 (122)
Currently employed	42.1 (179)
Ethnicity	
White	77.2 (329)
Asian/Pacific Islander	7.0 (30)
Black	5.2 (22)
Hispanic/Mixed/Other	10.6 (45)
Cancer diagnosis	
Breast	54.9 (234)
Colon	9.6 (41)
Lung	1.9 (8)
Ovarian	10.6 (45)
Other	23.0 (98)

Characteristics	Mean (SD)
Chemotherapy regimen	
Only platinum	22.3 (95)
Only taxane	46.9 (200)
Both platinum and taxane	30.8 (131)
Location of CIN	
Only upper extremities	4.9 (21)
Only lower extremities	27.0 (115)
Both upper and lower extremities	68.1 (290)
	Mean (SD)
Average pain in the lower extremities	4.0 (2.1)
Severity of numbness in the lower extremities	5.4 (3.0)
Number of sites in the lower extremity with loss of protective sensation	2.1 (2.4)
Vibration threshold in the lower extremity sites	24.7 (11.7)
Average pain in the upper extremities	3.1 (2.1)
Severity of numbness in the upper extremities	3.9 (2.9)
Number of sites in the upper extremity with loss of protective sensation	0.2 (0.8)
Vibration threshold in the upper extremity sites	8.4 (4.1)

[a]Survivors who received only a platinum compound

[b]Survivors who received only a taxane compound

Abbreviation: CIN = chemotherapy-induced neuropathy, SD = standard deviation

Table 2 –

Characteristics of the Patients with Breast Cancer (n=80)

Characteristics	Mean (SD)
Age (years)	52.7 (10.3)
Education (years)	15.7 (2.6)
Body mass index (kilograms/meter squared)	27.9 (6.9)
Karnofsky Performance Status score	89.0 (12.0)
Self-Administered Comorbidity Questionnaire	4.5 (3.0)
	% (n)
Female	100.0 (80)
Married/partnered	41.3 (33)
Living alone	21.3 (17)
Currently employed	43.0 (34)
Ethnicity	
White	58.2 (46)
Asian/Pacific Islander	11.4 (9)
Black	10.1 (8)
Hispanic/Mixed/Other	20.3 (16)
Gone through menopause	62.3 (48)
Had neoadjuvant chemotherapy	33.8 (27)
Stage of disease	
Stage 0	12.5 (10)
Stage I	40.0 (32)
Stage IIA and IIB	37.5 (30)
Stage IIIA, IIIB, IIIC, and IV	10.0 (8)
Type of surgery	
Breast conservation	75.0 (60)
Mastectomy	25.0 (20)
Had a sentinel lymph node biopsy	81.3 (65)
Had an axillary lymph node dissection	57.5 (46)
Had radiation therapy in the past 6 months	52.5 (42)
Had adjuvant chemotherapy in the past 6 months	41.3 (33)

Characteristics	Mean (SD)
Had reconstruction in the past 6 months	5.0 (4)
Had a re-excision or mastectomy in the past 6 months	31.3 (25)
	Mean (SD)
Average pain in the arm at 5 months	3.1 (1.8)
Severity of numbness in the arm at 5 months	2.4 (2.9)
Percentage of sites in the arm with decreased sensation at 5 months	15.5 (28.9)
Average pain in the arm at 6 months	3.2 (1.9)
Severity of numbness in the arm at 6 months	2.6 (3.1)
Percentage of sites in the arm with decreased sensation at 6 months	14.0 (27.8)

Abbreviation: SD = standard deviation

Table 3 –

Correlations between average pain intensity and measures of large fiber loss

Chemotherapy-Induced Neuropathy			
Site	Number of sites with loss of protective sensation	Vibration threshold	Severity of numbness
	r, p-value	r, p-value	r, p-value
Average pain in upper extremities	0.12, p<.032	0.22, p<.001	0.52, p<.001
Average pain in lower extremities	0.20, p<.001	0.15, p=.003	0.37, p<.001

Arm Pain following Breast Cancer Surgery			
Time post-surgery	Percentage of sites in the arm with decreased sensation	Vibration threshold	Severity of numbness
Average pain in the arm 5 months after surgery	0.34, p=.005	n/a	0.30, p=.008
Average pain in the arm 6 months after surgery	0.28, p=.034	n/a	0.46, p<.001

Abbreviation: n/a = not assessed