Ultrasound Acupuncture for Oxaliplatin-induced Peripheral Neuropathy in Colorectal Cancer Patients: a randomized controlled study

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Abstract:
Background: Oxaliplatin used to treat colorectal cancer, induces peripheral neuropathy. We hypothesized that ultrasound on acupuncture points might help control Oxaliplatin-induce Peripheral Neuropathy (OIPN).

Methods: Sixty patients with OIPN, Individuals aged 20 to 70 were randomly allocated to two groups via an opaque sealed envelope: Group A was administered pulsed therapeutic ultrasound (1 MHz) at the bilateral acupuncture sites PC6, PC7, BL60, and KI1, Group B received placebo therapeutic ultrasound, and both groups received the traditional physical therapy program. Pain Pressure Threshold (PPT), Neuropathic Pain Scale (NPS), and the Common Toxicity Criteria of the National Cancer Institute (NCICTC) were used to assess patients before and after 4 weeks of therapy (3 times/week) and 6 weeks of follow-up.

Results: Significant decreases in NPS mean ± SD (2.93 ± 1.11) and follow-up (2.55 ± 1.04) compared to pretreatment (5.87 ± 1.52) and increases in PPT (6.38 ± 1.17) and follow-up (6.71 ± 1.18) compared to pretreatment (4.14 ± 1.31). A decrease in NCICTC median (1(1-1)) compared to pretreatment (3(3-2)).

Conclusions: Ultrasound acupuncture reduced neuropathic symptoms from oxaliplatin-based chemotherapies.

Key words: ultrasound acupuncture, neuropathy, oxaliplatin, colorectal cancer.

Introduction

A popular platinum-based cytotoxic drug, oxaliplatin, is a top therapy for colorectal cancer. [19]
Acute sensory neuropathy develops quickly in oxaliplatin-induced peripheral neuropathy (OIPN), and after many treatment cycles, a late-onset cumulative sensory neuropathy develops, which has a substantial impact on health-related quality of life. [18]

Therapeutic ultrasonography modifies peripheral nerve function to reduce pain and hasten the healing of damaged nerves. [16]
There are several possible uses for it in the treatment of neuropathic pain. [3]
Therapeutic ultrasonography has analgesic benefits on cold allodynia and opioid-induced mechanical hyperalgesia in a rat model. [10]

An important part of eastern medicine, acupuncture provides alternative and complementary therapies in a number of therapeutic areas. Acupuncture treatments are based on the idea that activating certain "acupoints" alters the activities of related target regions or organs, however methods might differ. [24]
'Meridians,' the pathways in the body that acupuncture needles are spread along, are where these acupoints are situated. [20]

Specific sensations that might be characterized by adjectives like tingling, numbness, heaviness, and fullness are evoked by acupuncture treatment. Deqi feelings are different from fundamental tactile sensations or intense pain. It has been proposed that ultrasound acupuncture is a good substitute for conventional needle acupuncture because it stimulates acupuncture sites locally with heat and mechanical stimulation to produce the deqi feeling. [23]

Sample size:
Before the experiment started, the sample size was estimated. Using quality of life information obtained from [7], G*POWER The sample size was calculated using statistical software (version 3.1), with an effect size of 0.74, a power of 80%, and an α-level of 0.05. Each set of 30 people was needed for the investigation.

Randomization:
Participants were divided into two groups at random using a computer-generated randomization block. Four was chosen as the block size in order to reduce bias and preserve group balance. To ensure the anonymity of the allocations, randomization codes were sequentially numbered and placed within opaque sealed envelopes.

Ethical approval:
The study pertaining to human usage has been approved by Cairo University's Faculty of Physical Therapy's study Ethics Committee (RCE/012/005416), complies with all relevant national laws and institutional rules, and follows the Declaration of Helsinki's tenets.

Subjects and methods
Study design and participants:
This pre-post randomized controlled trial was single-blinded (assessor) and took place at Ismailia University's physical therapy outpatient clinic between July 2023 and August 2024. Four weeks of therapy were given to each participant, and then there was a six-week follow-up. The participants were sent to the outpatient physical therapy clinic after receiving an oncologist's diagnosis of OIPN. Male and female participants with neuropathy who were between the ages of 20 and 40 and who had neuropathy that was grade I, II, or III according to NCICTC were included. In order to ensure the accuracy of quantitative sensory testing findings, patients with (1) additional cancer or (2) severe or unstable cardiorespiratory or musculoskeletal disorders were eliminated. Treatment was given to the patients three times a week for four weeks. PPT, NPS, and NCICTC were used to assess patients before, during, and after therapy, as well as during a six-week follow-up period.

Interventions:
In Group A (the experimental group), bilateral acupuncture sites PC6, PC7, BL60, and KI1 were treated with pulsed therapeutic ultrasound (1 MHz), while Group B (control) received placebo therapeutic ultrasound at the same points. Both groups participated in a traditional physical therapy program, which included strengthening exercises, balance training, stretching exercises, and a home exercise program, over a duration of 4 weeks (3 times/ week). Patients were assessed both before and after the intervention period, and then again six weeks later.

Ultrasound Acupuncture
The patients were treated while lying comfortably in a supine posture. Using the Gymna Uniphy us 401 device, which has a treatment head that is 1.1 cm in diameter, pulsed therapeutic ultrasound (1 MHz, 50% duty cycle) was applied at the acupuncture sites. Anatomical identification of acupuncture sites was done using a ruler and marker. The upper extremity acupuncture points PC6 (Neiguan) and PC7 (Daling) as well as the lower extremity acupuncture sites BL60 (Kunlun) and KI1 (Yongquan) were the focus of this investigation. Both the lower and upper extremities received bilateral therapy. [4]

To create a deqi sensation—which is characterized by tingling, numbness, or soreness—at the acupuncture points, the ultrasound output intensity was progressively increased. After that, ultrasonography was performed three times a week for 12 sessions, lasting five minutes each point.

Traditional physical therapy program for both groups :
Stretching and strengthen exercises:
wrist extensor stretching, finger spread stretching, thumb touch, hamstring stretch, calf stretch, and finger pinch were Repeat 2-3 times on each side, holding for 10-30 seconds each time.

In a supine posture, the patient underwent workouts for foot and leg muscles, wrist flexor and extensor strengthening, and grip training using low resistance bands. Using a light dumbbell, 10 repetitions of each wrist flexion and extension exercise were performed. To increase the power of their finger pinch, the patient was advised to squeeze a soft ball or sponge that was placed between their fingers and thumb. [15]

Balance exercises:
One-legged and tandem balancing exercises lasted 30 seconds each, with increasing levels of difficulty added over time. [6]

Home exercise program and education:
Every patient got conventional treatment, which included self-care techniques, a home exercise regimen, and information on chemotherapy-induced peripheral neuropathy (CIPN). This included tandem and one-legged balancing exercises, as well as activities like ball squeezing, finger abduction and extension, toe flexion and extension, ankle dorsiflexion, and plantar flexion.Over the course of the research, the intervention progressed from one set of ten repetitions to three sets of ten. [1]

Outcome measures:
A 4-week intervention phase (three sessions per week) and a later 6-week follow-up period were both preceded and followed by patient evaluations. The results were assessed using PowerPoint, which was authorized by [17] Patients were evaluated both before and after a 4-week intervention phase that included three sessions per week. Assessments were also performed during a 6-week follow-up period.

Data analysis:
Subject characteristics were compared between the groups using an unpaired t-test. The distributions of diabetes, cancer stage, and sex were compared using a chi-square test. To determine if the data had a normal distribution, the Shapiro-Wilk test was used. To evaluate if the variances in each group were equal, Levene's test for homogeneity of variances was used. The effect of therapy on NPS and PPT was investigated using a mixed MANOVA. To compare NCICTC throughout time periods within each group, the Friedman test was used. For pairwise comparisons, the Wilcoxon Signed Ranks test was then used. The NCICTC was compared between groups using the Mann-Whitney test. All statistical tests have a significance threshold set at $p < 0.05$. IBM SPSS, Chicago, IL, USA's Statistical Package for the Social Sciences (SPSS) version 25 for Windows was used to conduct the statistical analysis

RESULTS
- Subject characteristics:
This research comprised sixty individuals with oxaliplatin-induced peripheral neuropathy. In Table 1, the research and control groups' characteristics are shown. Regarding age, treatment duration, sex, cancer stage, and diabetes distribution, there were no discernible variations between the groups ($p > 0.05$).

Table 1: Essential characteristics of the participants.

	Study group	Control group	MD	t- value	p-value
	Mean ± SD	Mean ± SD			
Age (years)	51.33 ± 11.47	52.03 ± 8.79	-0.7	-0.27	0.79
Duration of treatment (months)	**19.47 ± 14.19**	**18.67 ± 13.43**	0.8	0.22	0.82
Sex, n (%)					
Females	16 (53%)	17 (57%)		$\chi^2 = \mathbf{0}.07$	**0**.79
Males	14 (47%)	13 (43%)			
Stage of cancer, n (%)					
Stage II	8 (27%)	6 (20%)			

Stage III	16 (53%)	19 (63%)		$\chi^2 = \mathbf{0}.63$	**0**.73
Stage IV	6 (20%)	5 (17%)			
Diabetes, n (%)					
Diabetic	22 (73%)	24 (80%)		$\chi^2 = 0.37$	0.54
Nondiabetic	8 (27%)	6 (20%)			

SD, standard deviation; χ2: Chi squared value; p-value, probability value

Treatment's impact on PPT and NPS:

The results of a mixed MANOVA showed that therapy and time had a significant interaction effect (F = 74.91, p = 0.001, partial eta squared = 0.85). There was a noteworthy main impact of the therapy (F = 9.08, p = 0.001, partial eta squared = 0.24). There was a noteworthy main impact of time (F = 173.56, p = 0.001, partial eta squared = 0.93). Comparing groups inside one another

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At follow-up, the study group's NPS and PPT significantly decreased and increased, respectively, when compared to pre-treatment and post-treatment ($p < 0.001$). Furthermore, a noteworthy improvement was seen towards the end of therapy as opposed to the beginning ($p < 0.001$). Table 2. At follow-up, the control group's NPS significantly decreased when compared to both pre-treatment and post-treatment ($p < 0.001$), and it significantly decreased when compared to pre-treatment ($p < 0.001$). In contrast to pre-treatment, the control group's PPT increased significantly at follow-up and post-treatment ($p < 0.01$), whereas there was no discernible change between follow-up and post-treatment ($p > 0.05$). Table 2.

Between group comparison:

Before treatment, there was no discernible difference between the groups ($p > 0.05$). At post-treatment and follow-up, the study group showed a substantial rise in PPT and a significant reduction in NPS when compared to the control group ($p < 0.001$). Table 2.

Table 2. Mean NPS and PPT for the research and control groups before, during, and after treatment:

	Study group	Control group		
	mean ± SD	mean ± SD	MD	p-value
NPS				
Pretreatment	5.87 ± 1.52	5.72 ± 1.55	0.15	0.71
Post treatment	2.93 ± 1.11 [a]	5.05 ± 1.43 [a]	-2.12	0.**00**1
Follow up	2.55 ± 1.04 [a, b]	4.82 ± 1.45 [a, b]	-2.27	0.001
	p = 0.001	*p = 0.001*		
PPT (kg)				
Pretreatment	4.14 ± 1.31	4.32 ± 1.34	-0.18	0.61
Post treatment	6.38 ± 1.17 [a]	4.57 ± 1.25 [a]	1.81	0.**00**1
Follow up	6.71 ± 1.18 [a, b]	4.62 ± 1.26 [a]	2.09	0.001
	p = 0.001	*p = 0.001*		

SD, standard deviation; MD, mean difference; p-value, probability value; a significant difference with pretreatment; b significant difference with post treatment.

The impact of treatment on NCICTC.

Prior to, during, and after treatment, the study and control groups' mean NPS and PPT .

The study group's NCICTC was significantly lower at follow-up and after therapy than it was before ($p < 0.001$). The study group's NCICTC did not significantly alter between post-treatment and follow-up ($p > 0.05$). According to Table 3, there was no discernible difference in the control group ($p > 0.05$).

Table 2. The research and control groups' median NCICTC before, during, and after treatment:

NCICTC	Study group	Control group		
	Median (IQR)	Median (IQR)	U-value	p-value
Pretreatment	3 (3-2)	3 (3-2)	428	0.70
Post treatment	1 (1-1) [a]	(3-2)	45	0.**001**
Follow up	1 (1-1) [a]	(3-2)	45	0.001
χ^2 value	56	3		
	p = 0.001	*p = 0.22*		

IQR, Interquartile range; p values: Probability values, a significant difference with pretreatment

Discussions:

The purpose of this research was to assess how well ultrasound acupuncture relieved OIPN symptoms.

All patients underwent evaluation prior to treatment, following 12 sessions of ultrasound acupuncture (3 sessions per week), and after a 6-week follow-up. The severity of peripheral neuropathy was assessed using NPS, PPT, and NCICTC metrics.

Results indicated a significant reduction in NPS mean ± SD posttreatment (2.93 ± 1.11) and follow-up (2.55 ± 1.04) compared to pretreatment (5.87 ± 1.52). Additionally, there was a significant increase in PPT mean ± SD posttreatment (6.38 ± 1.17) and follow-up (6.71 ± 1.18) relative to pretreatment (4.14 ± 1.31). Furthermore, a significant decrease in NCICTC median was observed at follow-up (1(1-1)) and posttreatment (1(1-1)) compared to pretreatment (3(3-2)).

The therapeutic effects of stimulating acupuncture sites with needles, electric current, or lasers for peripheral neuropathy brought on by several chemotherapy drugs, such as carboplatin, paclitaxel, oxaliplatin, and thalidomide/bortezomib, are well documented in the literature. [10], For peripheral neuropathy caused by many chemotherapy medications, including carboplatin, paclitaxel, oxaliplatin, and thalidomide/bortezomib, the therapeutic benefits of stimulating acupuncture sites with needles, electric current, or lasers are well-established in the literature. Needle-free acupuncture has been suggested to provide advantages for both patients and clinicians, particularly for those on anticoagulant therapy. [2] which supports our consideration of the efficacy of ultrasound acupuncture as a non-invasive technique.

[10] In a model of rats, therapeutic ultrasound has shown analgesic benefits on cold allodynia and mechanical hyperalgesia brought on by oxaliplatin. The findings show that repeated oxaliplatin treatment may reduce mechanical and cold hyperresponsive behaviours with therapeutic ultrasonography. Together, the data showed that TUS improved cold allodynia and mechanical hyperalgesia brought on by oxaliplatin, confirming our hypothesis that ultrasound may improve OIPN.

Furthermore, ultrasonic acupuncture has been proposed as a potential substitute for conventional needle acupuncture because it applies targeted mechanical and thermal stimulation to acupuncture sites to create deqi feeling. [23] Our application strategy was supported by this research, which showed that ultrasonic acupuncture is effective in producing the deqi feeling at acupuncture locations.

It was acknowledged that only a limited number of acupuncture sites may be included in interventional trials for practical and safety reasons in order to maintain overall research uniformity and reduce bias when evaluating therapeutic effects. The acupuncture sites PC6 (Neiguan), PC7 (Daling), BL60 (Kunlun), and KI1 (Yongquan) were chosen for ultrasonic stimulation in this investigation based on a review of the literature, clinical experience, and previous research results. These acupuncture locations may be appropriate, as shown by the significant improvement in neuropathic pain and

paraesthesia in the limbs seen in the present investigation. Additionally, future studies may use these results as a foundation to examine other acupuncture locations. [4] The efficiency of ultrasonic acupuncture on points PC6, PC7, BL60, and KI1 in reducing OIPN symptoms in patients with colorectal cancer was validated by the research using the same acupoints.

[1] shown that a home exercise program and therapeutic ultrasonography are viable therapies for individuals with colorectal cancer who are suffering pain and related neuropathic symptoms. The research design and intervention techniques are viable, as shown by the 100% completion rates for both the intervention and the study. According to outcome measures, administering all of the tests and questionnaires was simple, and the average time spent on both objective testing and questionnaire completion was between 10 and 15 minutes each session. Objective evaluations of warmth, numbness, and pain perception revealed baseline deficiencies and showed quantifiable improvements after the intervention.

[4] Therapeutic ultrasonography was used to certain acupuncture sites in a short, single-group pilot research (N = 17) to treat OIPN symptoms in patients with colorectal cancer. According to the findings, applying ultrasound to both acupuncture sites for five minutes reduced pain and the intensity of CIPN, which is similar to our research.

Focused ultrasound (FUS) can be applied at depths greater than 5 cm below the skin. This is especially useful for stimulating acupoints deep within the body (greater than 2 cm, specifically up to 5 cm). FUS acupuncture's non-invasive nature and ability to control stimulation depth support its clinical applications. [9] This research showed that the sites PC6, PC7, BL60, and KI1 are successfully stimulated by ultrasonic acupuncture.

[11] This research looked at how self-acupressure affected the quality of life, daily life disruptions, and peripheral neuropathy symptoms in breast cancer patients receiving chemotherapy. The results showed that self-acupressure greatly improved overall quality of life, reduced the influence on day-to-day functioning, and lessened the severity of chemotherapy-induced peripheral neuropathy symptoms. According to data consistent with our results, the control group's improvement was probably caused by the effects of acupressure on PC6, PC7, BL60, and KI1 sites.

It was acknowledged that while the present research emphasises the therapeutic advantages of ultrasonic acupuncture, other clinical investigations indicate that acupuncture and comparable stimulatory therapies may predominantly have a large placebo effect. [13]

Furthermore, a number of meta-analyses have concluded that there is not enough strong evidence to support the clinical effectiveness of acupuncture in pain management, often concluding that treatment is no more beneficial than sham controls. [5]

[8] One important consideration in assessing the effectiveness of acupuncture therapy is the precision of the acupuncture sites. Acupuncture points such as CV4 (Guanyuan) and CV6 (Qihai) in the lower trunk; ST36 (Zusanli), ST34 (Liangqiu), and SP6 (Sanyinjiao) in the legs; LV3 (Taichong), EX-LE8 (Neihuaijian), EX-LE10 (Bafeng), EX-LE12 (Qiduan), and GB42 (Diwuhui) in the feet; LI11 (Quchi) in the arms; EX-UE9 (Baxie), SI3 (Houxi), and LI4 (Hegu) in the hands; and Du20 (Baihui) in the head have all been used in the treatment of chemotherapy-induced neuropathic pain and paraesthesia in the extremities. The points used in the present research, which include PC6, PC7, BL60, and KI1, are different from these.

Based on the findings of the study and prior research on the effectiveness of ultrasonic acupuncture on OIPN, it can be said that ultrasound acupuncture is a useful technique for enhancing OINP in patients with colorectal cancer.

Limitations:

This research, which looked at how ultrasonic acupuncture affected OIPN treatment, had a number of drawbacks. Nonpharmacological therapies may be less effective depending on the degree of neuropathy and the chemotherapy combo regimen. Six weeks after the end of ultrasound acupuncture, the study's last follow-up visit revealed that the ultrasound acupuncture group's pain intensity had significantly improved as evaluated by NPS; however, the PPT improvement was not maintained. Ultrasound acupuncture application time and dose may have an impact on how symptoms of chronic OIPN are modulated.

Conclusions:

An efficient way to improve oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer is to apply a 4-week pulsed therapeutic ultrasound (1 MHz, 50% duty cycle) three times a week at bilateral acupuncture sites PC6, PC7, BL60, and KI1.

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The writers say they have no competing interests.

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