Acupuncture for chemotherapy-induced peripheral neuropathy: a randomised controlled pilot study

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) can cause loss of independence and poor quality of life (QoL) due to severe disabilities, but in spite of its importance there is still a lack of data for the management of CIPN. Acupuncture has showed promising results and may be a cost-effective option for the treatment.

Objectives To evaluate the effect of acupuncture treatment on neurological symptoms of CIPN and QoL of oncological patients.

Methods We performed a clinical, single-centre, randomised and controlled pilot study that involved 33 adult patients with cancer and CIPN randomised into two groups (control and acupuncture treated with 10 sessions, two times per week). Both groups were subjected to a complete physical examination and clinical assessment with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Scale V.2.0, FIM Scale, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) Scale and Visual Analogue Scale for pain before and 5 weeks after treatment.

Results There were no adverse events, and we found statistical differences in groups in physical (p=0.03) and function (p=0.04) domains of EORTC QLQ-C30 when comparing control and acupuncture groups. About NCI CTCAE Scale and neuropathy sensory symptoms, we found better results in acupuncture group, comparing pretreatment and post-treatment analyses (p=0.01). In control group, we have no differences after 5 weeks (p=0.11).

Conclusion Although these results suggest an interesting effect of acupuncture on this patient population, the clinical significance has remained unclear. Given the tendency towards benefit and the lack of adverse effects, the authors recommend a follow-up acupuncture trial using higher follow-up time and better sample size.

Trial registration number NCT02309164.

INTRODUCTION

One of the most common side effects related to cancer treatment is neurotoxicity.[1] Neurotoxicity induced by antineoplastic drugs may occur both in the peripheral nervous system and the central nervous system. Symptoms range from purely motor to purely sensory or even major autonomic dysfunctions. A broad spectrum of symptoms can be found, from mild discomfort to complete sensory and motor dysfunction of the limb. The clinical features are highly dependent on the type of drug and their toxicity.[2] Many patients develop burning sensation, tingling sensation and functional disabilities.[3] As a result, neurotoxicity can cause high risk of falls and fractures, an inability to walk freely, loss of independence and a poorer quality of life (QoL) and ability to work.[4] So, maximising physical function is one of the primary goals for the management of chemotherapy-induced peripheral neuropathy (CIPN).[1]

There is no established intervention for the prevention of CIPN in patients undergoing treatment with neurotoxic agents like platinum drugs, taxanes, vinca alkaloids and bortezomib. In patients with existing CIPN, duloxetine is the only medication with partial evidence of benefit mainly by reducing the symptoms of neuropathic pain after CIPN.[5] According to the American Society of Clinical Oncology Clinical Practice Guidelines, no recommendations can be made on the use of acetyl-L-carnitine, tricyclic antidepressants, gabapentin and a topical gel containing baclofen, amitriptyline and ketamine for CIPN[5] to minimise pain symptoms nor to ameliorate neurological symptoms from the CIPN.

On the other hand, in 1997, the National Institute of Health, the government agency of the Department of Health and Human Services of the USA, published a consensus on acupuncture that concluded that the technique was promising for oncological patients, especially for pain and nausea after chemotherapy.[6] Acupuncture is a medical technique based on stimulation of certain points on the surface of the body for therapeutic purposes. Despite some evidence of previous practice, the first unequivocal record about acupuncture use comes from China and dates back to 100 BC.

Although robust studies are lacking, some studies investigating the use of acupuncture for CIPN[4 6–9] has shown promising results in controlling its neurological symptoms. The literature has suggested that acupuncture may be a promising technique in the management of sensory and motor symptoms after CIPN.

In fact, most of the disabilities and loss of QoL occurring after CIPN are related to sensory and motor loss, rather than painful symptoms. Hence, the development of therapies that reduce sensory and motor deficiencies is the focus of increasing number of researches. While initial studies suggest that acupuncture reduces these deficiencies, larger, confirmatory data are needed. So, in this sense, this study is one of the first studies evaluating acupuncture treatment for CIPN sensory symptoms—not just pain symptoms—correlating the results with QoL data.

OBJECTIVE

With all of this in mind, this study aims to evaluate the effect of acupuncture treatment for reducing the neurological symptoms of CIPN. The primary aim of this study was to evaluate whether acupuncture treatment improves sensory symptoms of CIPN as evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Scale. Secondary outcomes included functionality and QoL on the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) Scale. We hypothesised that acupuncture is effective for reducing sensory symptoms while improving both functionality and QoL.

METHODS

The trial is a clinical, single-centre, open randomised controlled trial study that involves 33 adult patients with cancer and peripheral neuropathy induced by chemotherapy treatment. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice.

Randomization and blinding

An online software generator was used to generate randomisation plan (http://www.randomization.com). The software produced a numbered randomisation list. The patients were allocated to each of the control or acupuncture groups according to the order in which they were referred to the study and evaluated by the initial assessment protocol, following the order determined by the randomisation list. Both patients and examiners were blind to randomization. As the author did not perform a sham acupuncture group, both patients and the acupuncturist physician were not blinded to allocation. Only the examiners who performed the final evaluation after therapy were blinded.

Participants

A total of 33 patients with CIPN were recruited from the oncology and rehabilitation departments of our institute. Of these 33 patients, 29 patients presented inclusion criteria and 4 patients presented non-inclusion criteria (two patients with diabetes mellitus, one alcohol user in treatment against addition and one patient with neuropathy of another aetiology prior to oncological treatment). So, 29 patients were enrolled in the study to perform clinical assessment and randomisation (see figure 1).

Inclusion criteria

The inclusion criteria for the patients in this study were adults over 18 years of age with clinical diagnosis of CIPN, regardless of whether these patients were already using medical treatment for CIPN, and accepted and signed informed consent form (ICF) standardised by the ethics committee of our university.

Non-inclusion criteria

The non-inclusion criteria for the patients in this study were presence of other comorbidities that caused peripheral neuropathy such as diabetes mellitus or alcoholism, patients suffering from neuropathy due to other aetiologies or other neurological disorders. Patients who received acupuncture treatment within the past 90 days for other indications were not included in the study.

Exclusion criteria

Patients who changed peripheral neuropathy medications during this protocol or patients who presented with any adverse effects associated with acupuncture were excluded from the final analysis.

Trial procedure

Evaluation

Study subjects were recruited at the outpatient medical setting. Different researchers were involved in conducting the trial. Three physicians were involved in the evaluation and treatment regimen: the researcher who conducted the initial assessment, an oncologist physician, the acupuncturist physician responsible for treatment and the researcher who conducted the final assessment. We chose to have different examiners conducting the initial pretreatment assessment

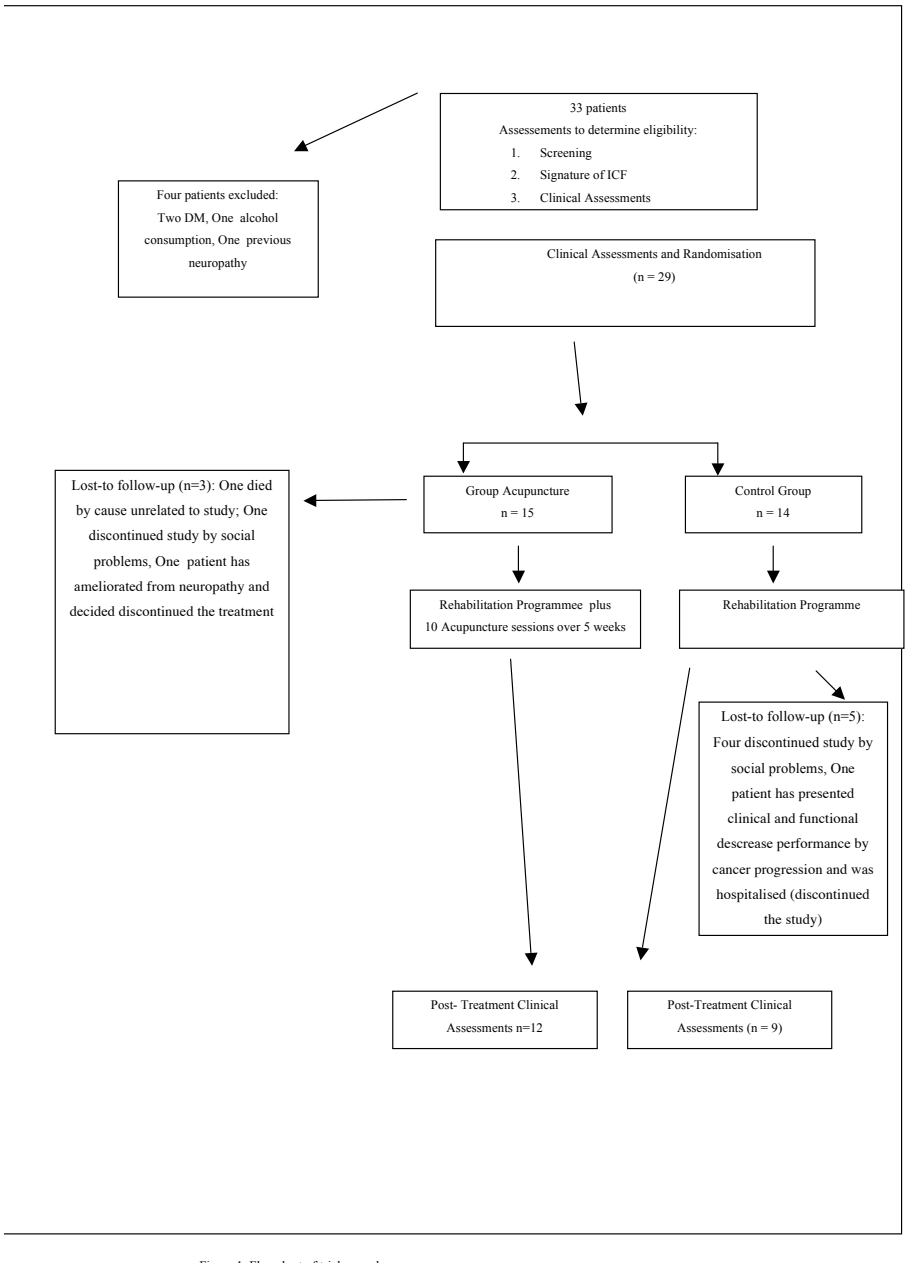

Figure 1 Flow chart of trial procedures. ICF, informed consent form; DM, Diabetes Mellitus

and performing the final post-treatment evaluation to maintain the final examiner's post-treatment blinding. The initial examiner was not blind to the allocation of the patient but it was possible to maintain the blinding of the final examiner post-treatment. Both of them belonged to the oncology department of the hospital school where the study took place. The three researchers have a specialisation in oncology, and the last two also have specialisation in acupuncture. One of them has the PhD grade and the other two have a MSc grade. The whole team involved in the study, both the medical initial and final evaluators and the acupuncturist have training in oncology. All diagnostic and therapeutic procedures were in agreement with the the National Comprehensive Cancer Network (NCCN) guidelines. We have decided not to perform or to test the inter-rater reliability prestudy between researchers because all of the examiners are previously trained in the use of the methodology. Since they work in clinical practice in oncology, they are routinely trained and retrained in the use of the evaluation methodologies used in the study.

Initial evaluation

The first evaluation applied was the clinical evaluation in order to identify the presence or absence of peripheral neuropathy and to determine if the patient met the eligibility criteria of the study. The diagnosis of peripheral neuropathy was made clinically according to the criteria previously described in the literature by

NCCN.[10 11] Due to the characteristic clinical picture and the direct correlation with the administration of chemotherapy, the diagnosis of CIPN was established using a complete anamnesis and physical examination, and no complementary tests were used. A previous evaluation of patients was done to identify other causes of pre-existing sensory neuropathy, such as diabetic neuropathy. The correlation between the onset and progression of neuropathic symptoms, and the timing of chemotherapy administration also facilitated the identification of these patients. At this time, the subjects were counselled about the study protocol and signed the ICF. Following that, they underwent a complete physical examination and clinical assessment:

1. NCI CTCAE scale V.2.0.[10 11]
2. Functional Independence Measure (FIM) Scale.[12]
3. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core Scale (EORTC QLQ-C30).[13]
4. Visual Analogue Scale (VAS) for pain.

After the initial evaluation, patients were randomised into two groups (acupuncture treatment group and control group).

Intervention

Control group

Patients underwent rehabilitation programme for peripheral neuropathy that included: management guidelines for foot/hand care, sensory desensitisation, risk prevention guidelines, proper ergonomics and orthosis when necessary.

Acupuncture treatment group

Additionally, to the rehabilitation programme for peripheral neuropathy described above, patients at this group also received an acupuncture treatment. Based on previous studies of the literature,[7] we have chosen a protocol of 10 acupuncture sessions of 30 min duration each during 5 weeks, two times per week. The points were defined according to the clinical indication and each patient's symptoms. These points were occasionally minimally modified during the treatment according to the medical evaluation. For all patients, however, a minimum set of basic points was used: yuan points of the hands and feet (LR3, SP3, KI3, HT7, PC7, LU9) plus SP9 and wrist-ankle technique (areas 1–3) based on previous studies published.[8 14–17]

The selection of these acupoints was due to the hypothesis that the loss of sensation is caused by diminished Chi circulation in the affected channels. Thus, the yuan (source) acupoints would be capable of restoring the channels' levels of Chi.[18]

The SP9 point was selected because the sensation of obstruction commonly described by patients could also be interpreted as dampness retention in the lower limbs according to the Traditional Chinese Medicine.[18]

Contraindications for the acupuncture sessions

1. Platelet count below 20 x 10^9/L or below
2. Neutrophil count below 1000 per µL.
3. Anticoagulated patients.
4. Pregnancy.

Locations where the punctures were avoided

1. Upper or lower extremities that underwent lymph node dissection, even with no perimeter increase or clinical lymphoedema.
2. Regions with column instability (postsurgery, metastases, multiple spinal injuries) or cranial trepanation.
3. Regions of the body with ulcers, surgical wounds, tumours, metastases, prostheses or nodules.

Final evaluation

Following the completion of the treatments groups (a maximum of 15 days after the final treatment), all patients were subjected to the same initial clinical assessments.

Data analysis

Initially, data were analysed in order to assess the demographic distribution. The means and SD were reported. Moreover, we used Student's t-test, assuming a normal distribution. Paired-group t-tests between groups were used to analyse and compare NCI CTCAE Scale V.2.0, FIM Scale, EORTC Scale and VAS Scale measures at baseline and after follow-up period (5 weeks of acupuncture treatment weeks). The primary endpoint is analysing the change of sensory components of NCI CTCAE Scale from baseline to 5 weeks.

In addition, it is also expected to find a modification and amelioration in the functionality and QoL of the patients undergoing acupuncture as measured by the EORTC QLQ-C30. For all tests, two-tailed error α=5% was used.

RESULTS

Thirty-three patients with CIPN were screened and 29 patients who met the eligibility criteria and agreed to participate were enrolled in the study (see figure 1). Eight patients discontinued the study before 5 weeks of treatment (five patients discontinued the treatment due to social transportation/mobility causes; one patient reported clinical and functional decrease in performance from cancer progression and was hospitalised; one patient ameliorated from neuropathy and decided to discontinue the study; one patient died due to causes unrelated to the study). Twenty-one patients (72.41%) completed all study follow-ups. Trial schema is summarised in figure 1.

Patients characteristics are summarised in figure 2.

There were no adverse events associated with the acupuncture treatment.

At baseline, the majority of patients (n=28, 96.5%) had sensory deficits. Just 16 patients had baseline motor deficits (n=16, 55.17%). Fifteen patients had both sensory and motor deficits (51.72%) and one patient had only motor deficits (3.44%).

	Minimum (years)	Maximum (years)	Mean (years)
Age	41	82	57.68
Gender	Female	Male	
	58.62% (17)	41.37% (12)	
Diagnosis	Breast	37.93% n (11)	
	GIT	48.27% n (14)	
	GUT	10.34% n (3)	
	Haematologic	3.4% n (1)	
	Minimum (weeks)	Maximum (weeks)	Mean (weeks)
Time from initial chemotherapy	2	19	5.3

Figure 2 Patients characteristics; GIT, gastrointestinal tract; GUT, genitourinary tract.

On the NCI CTCAE sensory scale, there was no statistical difference on the baseline grade of neuropathy comparing the two groups (p=0.30). At the acupuncture group, patients presented a decrease in values with statistical difference (p=0.01). At the control group, patients presented a decrease of the mean NCI CTCAE Scale sensory symptoms score with no statistical difference (p=0.11) (see table 1A,B).

Regarding the EORTC QLQ-C30 total score, there was no difference in the baseline score of EORTC QLQ-C30 between the groups (p=0.53), and there was no statistical difference between pretreatment and post-treatment values in both groups (see table 2).

On the physical domain of the EORTC QLQ-C30 score, there was no difference between the groups in the baseline score (p=0.30). At the acupuncture group mean changed from baseline to post-treatment values with statistical difference (p=0.03), and there was no statistical difference between pretreatment and post-treatment values in the control group (see table 3).

On the functional domain of the EORTC QLQ-C30 score, there was no difference between the groups in the baseline score (p=0.97). In the acupuncture group, mean changed from baseline to post-treatment values with statistical difference (p=0.04), and there was no statistical difference between pretreatment and post-treatment values in the control group (see table 4).

There was no statistical difference comparing pretreatment and post-treatment scores of both groups for all of the other EORTC QLQ-C30 domains and FIM scores (see table 5).

There was no difference in the baseline FIM scores between the groups (p=0.60).

As for the Spearman correlation, we did not find a strong statistical correlation between the pretreatment and post-treatment variation of VAS and physical or functional domains of the EORTC (r=0.24 and r=0.34, respectively).

Ten patients (34.48%) presented no painful symptoms (VAS=0) at baseline and 19 patients (65.51%) presented painful symptoms at baseline. Regarding the VAS score of the patients with pain, mean changed from pretreatment and post-treatment values with no statistical difference in both groups (see table 6). There was no difference in the baseline score of VAS between the groups (p=0.96).

Table 1 Mean and SD of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) sensory symptoms scale values pretreatment and after treatment and follow-up period

	Baseline		After follow-up		
	Mean	SD	Mean	SD	P value
Control group	2.5	0.85	1.9	0.87	0.11
Acupuncture group	2.8	0.87	2.0	0.77	0.01*

NCI CTCAE sensory symptoms scale grade	Patients (%)
Grade 1	10.34
Grade 2	20.68
Grade 3	62.06
Grade 4	6.89

*Statistical difference.

DISCUSSION

This study evaluated a group of 29 randomised patients with CIPN treated with acupuncture+rehabilitation (acupuncture group) or just rehabilitation (control group) and found statistical differences between groups in physical and function domains of EORTC QLQ-C30 and NCI CTCAE Scale.

Table 2 Mean and SD of European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core Scale total score values pretreatment and after treatment and follow-up period

	Baseline		After follow-up		
	Mean	SD	Mean	SD	P value
Control group	55.85	15.69	53.11	11.63	0.63
Acupuncture group	52.53	12.12	49.08	11.48	0.45

Table 3 Mean and SD of physical domain of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core Scale (EORTC QLQ-C30) score values pretreatment and after treatment and follow-up period

Physical domain of the EORTC QLQ-C30 score	Baseline		After follow-up		
	Mean	SD	Mean	SD	P value
Control group	10.8	5.01	8.75	4.86	0.35
Acupuncture group	8.86	5.04	5.83	0.93	0.03*

*Statistical difference.

We found statistical difference in the change of mean values of the NCI CTCAE Scale of the patients submitted to the acupuncture treatment but only 58.33% of the patients of the acupuncture group showed changes on the rating value of the NCI CTCAE Scale classification after the follow-up period. Otherwise, in the control group, 55.55% of the patients showed changes in the rating value of the NCI CTCAE Scale classification after the follow-up period, similar to the result found in treatment group patients. So, we can deduce that although there is a tendency of modification of the NCI CTCAE Scale after the use of acupuncture, this modification could not be demonstrated by this clinical scale assessment. In fact, previous studies discuss about the NCI CTCAE Scale sensibility. Despite the easy of use, this assessment technique suffers from inter-observer disagreement.[14] Although older studies have suggested that the NCI CTCAE has good intrarater/inter-rater scores and good validity, some recent studies were inadequately powered to detect significant differences in the grade of neuropathy among studied groups. It is clear in the literature that the assessment of CIPN with NCI CTCAE is suboptimal, and there is no consensus on which is the best assessment method for CIPN. The NCI-CTCAE has been criticised for not having unambiguously defined grades, and the literature suggests that the NCI Common Toxicity Criteria assessment for neuropathy may overestimate the presence of motor neuropathy and misdiagnose CIPN. It is also not definitely determined how large of a difference in the NCI CTCAE Scale is required to demonstrate a clinically meaningful improvement in symptoms. Additionally, early trials have often relied on clinician assessment of neuropathy with methods such as the NCI CTCAE criteria which have been shown to be less sensitive than the patient-reported outcomes.[14] In this sense, this classification could not translate subtle changes in the variation of neuropathy and failed to show slight modifications in the neuropathy grade in studies with low sample size.

Table 4 Mean and SD of functional domain of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core Scale score values pretreatment and after treatment and follow-up period

	Baseline		After follow-up		
	Mean	SD	Mean	SD	P value
Control group	5.35	2.06	4.44	2.0	0.3
Acupuncture group	5.33	1.87	3.81	1.77	0.04*

*Statistical difference.

Table 5 Mean and SD of Functional Independence Measure (FIM) score values pretreatment and after treatment and follow-up period

FIM scores	Baseline		After follow-up		
	Mean	SD	Mean	SD	P value
Control group	114.78	17.44	119.78	8.15	0.44
Acupuncture group	117.66	10.82	120.7	6.44	0.38

It is important to highlight that cancer survivors are at high risk for diminished health and well-being from cancer and from cancer treatment. Persistent effects include physical and psychological symptoms, comorbidities illness, functional limitations, difficulties with returning to work and barriers to quality healthcare. So, cancer functionality is one of the main interests of WHO research.

In this sense, this study also evaluated QoL and functionality.

As previous studies, CIPN may also seriously compromise patients' QoL. Therefore, it is important to be able to assess QoL of patients with CIPN in a valid and reliable manner. The two most widely used cancer-specific QoL questionnaires are the EORTC QLQ-C30 Scale and the Functional Assessment of Cancer Therapy. Unfortunately, we did not find significant changes in total score of EORTC.

Although the EORTC QLQ-C30 measurement system does not yet have a CIPN module, several of the existing EORTC questionnaires, as EORTC CIPN 20 scale, include a few items regarding CIPN (eg, pain, paraesthesias).[15] In spite of this, we chose to use the EORTC QLQ-C30 scale because it is validated in the cultural context of the patients studied; so, although it is designed to assess a core set of QoL issues, it is intended to be supplemented by additional evaluations. This could explain why in this study the total score of EORTC did not show differences between the groups. Likewise, because many of the symptoms of CIPN are subjective in nature, it is logical that the assessment of CIPN is based, at least in part, on patient self-report data. In this way, other instruments are being studied.

Table 6 Mean and SD of Visual Analogue Scale (VAS) score values of the patients with pain pretreatment and after treatment and follow-up period

VAS score of the patients with pain	Baseline		After follow-up		
	Mean	SD	Mean	SD	P value
Control group	5.71	2.28	4.6	2.0	0.4
Acupuncture group	5.66	2.26	4.0	3.2	0.33

In addition to this, the functional and physical domains of EORTC presented better outcome results in the acupuncture group than the control group. CIPN is predominantly a sensory phenomenon, with symptoms arising in a cumulative dose-dependent manner and occurring in a stocking-glove distribution. So, it is expected that functional and physical domains of EORTC change more than areas such as humour or cognitive symptoms. Other interesting studies have also found improvement in functional and quality aspects of life of these patients after the use of acupuncture.[14 16 17 19] These results reinforce the idea that the grade of neuropathy could be changed in the acupuncture group, although the NCI CTCAE Scale failed to show this improvement and also suggests that acupuncture is an effective treatment for the control of sensory functional symptoms after CIPN.

Different from previously published studies,[19 20] we did not find significant improvement in the assessment of pain by VAS. No statistically significant differences were observed in pain score. Although pain is known to have a negative impact on QoL and functionality, we did not find a statistical correlation between the values of VAS and physical or functional domains of EORTC. This result suggests that the changes found in the EORTC could not be a consequence of pain modification but an acupuncture effect on sensory symptoms of CIPN, corroborating to the idea that acupuncture is an effective treatment for the control of sensory symptoms in patients with CIPN.

In fact, the magnitude of the benefit from acupuncture for pain in this study was modest, and appeared to be more prominent for patients with more recent neuropathy symptoms. It is also important that there is considerable heterogeneity among the various forms of neuropathy and its response to pharmacological treatment.[21–23] Treatments that are effective for painful neuropathy from alcohol, such as tricyclic antidepressants and gabapentin, do not provide benefit in painful CIPN.[21–23] Understanding this difference suggests that it is important to separate CIPN from other types of neuropathy. Moreover, an enhanced understanding of the natural history of CIPN can improve clinical practice, predict better outcomes and manage patient QoL. Besides, it is important to note that the chosen acupoints of this study are not typically used with analgesic purposes, and it is not the main goal of this study to achieve analgesic effects. The primary endpoint was the change of functional symptoms as measured by the EORTC QLQ-C30 and NCI CTCAE Scale from baseline to 5 weeks. The chosen acupoints group was designed for this purpose based on previous published studies.[8 14 16 17 19]

Finally, there were no adverse events associated with the acupuncture treatment. Parallel to its effectiveness, strong evidence for the safety of acupuncture comes from a systematic review published in 2006 suggesting that acupuncture performed by trained practitioners using standardised clean needle technique is a safe procedure.[24] Since 2008, the medical literature also indicates that acupuncture may be used successfully on patients with cancer for symptom management due to the low risks associated with its use.[25] Besides this, cost-effectiveness of acupuncture in the treatment of pain has been evaluated in several recent studies. Compared with the high cost associated with imaging, surgical procedures or traditional medications for pain conditions, acupuncture seems to be extremely cost-effective for pain treatment.[26–28] Unfortunately, there are no studies comparing the costs of using traditional therapeutics or acupuncture for neurological symptoms related to CIPN but given the fact that studies suggest that acupuncture costs less in treating pain than traditional medications, it becomes urgent to test and compare not only the effectiveness but also the costs of these two therapeutic options. This study starts from this premise and it walks in this direction.

This study is one of the first studies evaluating acupuncture treatment for CIPN sensory symptoms—not just pain symptoms—correlating the results with QoL data. However, we recognise some methodological limitations of the study. It was expected that this sample size would not detect significant differences between the groups which made it difficult to consider these results to be applicable to the general population. Moreover, the epidemiological, cultural and social characteristics of this sample that might have interfered in these results were not raised here. A trial with a larger sample may provide a more accurate assessment of the results. Based on these results, new future studies need to include a power calculation for the sample size and a longer follow-up time after discharge to detect significant differences between the groups. In addition, it would be very interesting if a new trial with a third group (a sham acupuncture group) and also a double-blinded study are initiated. Although we have managed to maintain the final evaluator's blinding, which is a positive point of this study, unfortunately, we could not perform a group with sham acupuncture, neither could we blind the patients and the initial examiner. We also had more than 25% patient withdrawal and treatment non-compliance. Although this is a significant number, the major cause was social and mobility to get to the hospital. In general, other studies with patients with disabilities show a similar dropout rate due to mobility difficulties. So, we consider that this rate is within the expected limit. In future trials, authors should take steps to address mobility issues, such as arranging transportation to the hospital or promoting home visits. The short follow-up time is also a limitation of this study. Since this is a pilot study, we chose to implement the final evaluation 15 days after the end of treatment without a long-term follow-up. Naturally, a longer follow-up may bring new information about the permanence of these results found. In our

opinion, the small sample size is also a major limitation of this study. Finally, we chose not to perform or test the inter-rater reliability prestudy between researchers because all of the examiners were previously trained in the use of the methodology. Since they work in clinical practice in oncology, they are routinely trained and retrained in the use of the evaluation methodologies used in the study but this is also a limitation and a risk of bias in the study.

Nevertheless, given the tendency towards benefit and the lack of adverse effects, the authors recommend a follow-up acupuncture trial using higher follow-up time and better sample size. This study suggests that acupuncture is an effective treatment for the control of sensory symptoms after CIPN. Moreover, acupuncture is a low-cost, easy-to-implement technique, even in large populations or public health services.

CONCLUSION

This study suggests that acupuncture is an effective treatment for the control of sensory symptoms after CIPN. Although these results suggest an interesting effect of acupuncture in this patient population, the clinical significance has remained unclear. The results reinforce the idea that the grade of neuropathy could be changed by acupuncture treatment, although the NCI CTCAE Scale has failed to show this improvement. Given the tendency towards benefit and the lack of adverse effects, the authors recommend a follow-up acupuncture trial using higher follow-up time and a bigger sample size.

Contributors All authors have contributed to all stages of this study, from conception, idea, protocol development, collection of data, analysis of results and writing of the article. All authors have substantial contributions to the study. ED'A and DRN have substantial contributions to conception and design of the work; to acquisition, analysis and the interpretation of data; and to draft the work and revising it critically for the version published. CMMdB and EPA have substantial contributions to conception and design of the work; to analysis and the interpretation of data; and to draft the work and revising it critically for the version published. LRB and RBC have substantial contributions to conception and design of the work; to the interpretation of data; and to draft the work and revising it critically for the version published.

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