

Effectiveness and safety of acupuncture to treat sleep difficulties in women on hormone replacement therapy for the treatment of breast cancer: a randomized controlled trial

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Abstract

Sleep difficulties are commonly reported by cancer patients as consequences of cancer or its treatments. Aim of this study was to measure the effectiveness and safety of acupuncture to treat sleep difficulties in breast cancer women **on hormone replacement therapy**.

Methods: 58 breast cancer women were randomized to once weekly acupuncture session for 8 weeks (acupuncture group) or to a standard care session once a week, for 8 weeks (control group). The primary endpoint was change in sleep difficulties and insomnia, as measured by the Insomnia Severity Index (ISI), administered at baseline and 8 weeks later.

Results: Random assignment produced equivalent groups regarding demographic and clinical characteristics at baseline. After 8 weeks, the changes in sleep quality and quantity were significantly different in the two groups. In the acupuncture group 43.33% go into complete remission (absence of insomnia), but none in the control group, and the mean ISI score decreased from 15.87 (standard deviation, SD= 3.95) to 9.80 (SD= 6.22), in the acupuncture group *versus* 17.46 to 15.39. No patient reported any problems or discomfort associated with acupuncture.

Conclusion: A weekly session of acupuncture may have beneficial effects on quality and quantity of sleep among breast cancer women on **hormone replacement therapy**, after 8 weeks. The results could have important implications for Public Health to prioritize promotion of healthy sleep and acupuncture may be considered as alternative intervention in healthcare setting to ameliorate cancer patients' sleep and quality of life.

Introduction

The management of oncological pathology is complex and requires multifocal attention that brings together different disciplines capable of offering care and support to the patient. While the introduction of new targeted therapies is definitely improving the survival of many patients, on the other hand, many aspects related to the side effects of the treatments still remain to be resolved [1–4].

Among the common side-effects of many cancer treatments there are disturbances in the quality and quantity of sleep [5–7]. Insomnia, one of the sleep problems, is an important source of discomfort, and especially if chronic, is accompanied by a series of consequences and comorbidities that can have important repercussions in various areas of the person's life. As described in DSM-5 [8], insomnia involves a broad spectrum of disorders with one common denominator being dissatisfaction with the quality, continuity and duration of sleep. There may be difficulty falling asleep, nocturnal awakenings with difficulty falling back asleep, and early awakening, with wide variability in combinations and variations from day to day. In all cases, sleep is subjectively described as insufficient and non-restorative regardless of objective polysomnographic confirmation.

Prevalence of insomnia and sleep difficulties in cancer

Cases of insomnia among cancer patients are widespread and higher than those found in the general population as some side effects of the treatments and of the disease itself affect the quantity and quality of sleep [7, 9, 10]. The prevalence of sleep difficulties in cancer patients is generally estimated to be between 30% and 50% [11], and in a recent study, sleep difficulty was linked in 40% of cases to problems with early awakening, in 45% to the maintenance of sleep, and in 32% to difficulty falling asleep, with overlaps between the different difficulties [12]. The prevalence of insomnia was 8.21%, among 30.400 cancer patients, and varied according to cancer type (7.8%, among 3.120 breast cancer) [13], in a sample in which insomnia was identified on the basis of cases diagnosed with ICD-10 or prescription of sleeping pills; otherwise, in studies in which patients themselves were required to report sleep difficulties, using validated tools as the Insomnia Severity Index, ISI [14], the prevalence of insomnia was much higher: 42.80% among 213 cancer patients [7], 43.66% among breast cancer women [12].

The variability among different studies depends to many factors including the definition of sleep difficulties and insomnia and how these were assessed.

Treatments for insomnia

Treatment of insomnia involves improving the quality and / or quantity of sleep, and daytime functioning in terms of fatigue and efficiency. Generally, the treatments are pharmacological (sedative hypnotics) although in recent years studies on the effects of alternative treatments have increased. Cancer patients may have difficulty taking medication (polypharmaceutical toxicity) and because the use of hypnotic drugs is associated with different risks, including addiction, it seems desirable to treat sleep difficulties in cancer patients using non-drug treatments [11].

Acupuncture to treat insomnia

Acupuncture is an alternative to drug treatment and it can be used in treating insomnia - is one of the top 10 indications among patients visiting an acupuncture clinic [15].

Acupuncture is a branch of what is known as traditional Chinese medicine, and in Europe has been known thanks to the work and cultural influence of some people such as the Jesuit Father Matteo Ricci, and the French sinologist George Soullié de Morant. The first country in Europe to develop acupuncture and to integrate it into its clinical practice is France.

The mechanisms of action of acupuncture have not all been clarified but it is known with certainty that it exerts effects on the cytokine system and therefore on inflammation, on endorphins, on different areas of the CNS and on the ortho / parasympathetic balancing system. These actions are solicited through the insertion of needles, generally bimetallic, on a combination of acupuncture points located along the path of 12 meridians, divided into 6 groups, each with its functional correspondences and all these systems are in a relationship of mutual control with each other.

The NIH Consensus Statement on Acupuncture [16] found that the incidence of adverse effects is substantially lower than that of many drugs or other accepted procedures for the same conditions.

Systematic reviews and surveys have clarified that acupuncture is safe when performed by appropriately trained practitioners, with infrequent minor side effects, such as feeling relaxed, elated, tired, or having sensation or itching at the point of insertion. Safe use of acupuncture has also been established in pediatrics and for women who are pregnant [17].

Two meta-analyses showed that acupuncture appeared to have beneficial effect in treatment of insomnia. The first study has been conducted on 46 randomized clinical trials (RCTs) involving 3811 patients [18], and the second, has been an update of the first, conducted on 73 RCTs involving 5533 patients [19]. The Authors concluded that acupuncture might result in improvement than no treatment and appears safe “However, the quality of the evidence is varied from very low to low due to the potential risk of bias and inconsistency among included trials. Further large sample size and rigorously designed RCTs are still needed” [19].

Another recent meta-analysis showed the efficacy of acupuncture compared to that of placebo in treating insomnia, underlining that the differences in acupuncture therapies and control groups may underestimate the efficacy of acupuncture in different ways [20].

Acupuncture control group

Randomized controlled trials (RCTs) have provided the best evidence in assessing the efficacy of any medical intervention. The evaluation of the acupuncture presents a number of methodological problems.

Several difficulties are inherent in the design of valid blinded RCTs of acupuncture, due an appropriate placebo for the acupuncture control group is difficult to determine given the invasive nature of inserting needles into the skin. A 'blind' or reproducibility study is also difficult given the heterogeneity of application of the needles. Various studies have used the placement of needles placed at non-meridian sites, called “sham” acupuncture, to model acupuncture in control group patients. However, “sham” presents a unique problem as a placebo. The well-outlined energy channels of the acupuncture meridian systems cover the entire body, linking wei-qi (defense qi), rong-qi (growth and development qi), and yuan-qi (the original qi inherited at birth). As the meridian systems affect the entire body, the sham acupuncture does still provide some acupuncture effect, and therefore cannot be considered to produce a true placebo effect [21].

As pointed out by Lundeberg et al [22] in the evaluation of an acupuncture treatment the choice of the comparator treatment is not so obvious. As mentioned, although the control with sham acupuncture procedures were considered inert, the clinical and experimental results have shown that sham acupuncture also induces a physiological response with a significant effect compared to that obtained with a placebo drug or through the use of waiting list checks. The lower proportion of patient with beneficial effects was for those in waiting list compared to those exposed to minimal/sham acupuncture or standard care or routine care [22]. These results and the consideration of making the two groups comparable with respect to the number of visits with a doctor, led us to compare the effects of acupuncture with those of a routine care where the scheduling of the meetings was the same.

The aim of this study was to measure the effectiveness and safety of acupuncture in the treatment of sleep difficulties in cancer patients. First of all, we defined a homogeneous sample, that of women with breast cancer on hormone replacement therapy; then we identified the sleep difficulties to be measured and the tools to detect them. Finally, we accurately described the acupuncture method applied by qualified professionals of the same training, choosing to compare the acupuncture group with a control group in which ordinary treatments were offered with the same temporal-spatial cadence, in accord with [21, 22], who argues that sham acupuncture produces the same effects as acupuncture.

Materials And Methods

This study was a randomized controlled trial, conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the hospital (13/CE/15, n.437/1), in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines for designing and reporting controlled trials [23,24]. All participants signed the informed consent form before participation in the study.

Inclusion/Exclusion criteria

- Inclusion criteria for the study were the following: female subjects; age more or equal 18 years; diagnosis of non-metastatic breast cancer; in treatment with hormone replacement therapy; ECOG Performance Status [25] equal to "0-1"; sleep difficulties arising after the start of breast cancer treatment; onset of sleep difficulties in the 3 months before; absence of restless legs syndrome; absence of sleep apnea; availability for 1 weekly meeting for 8 consecutive weeks; if being treated for insomnia, the sleep therapy must have been stable for at least 30 days; willingness not to change therapies and dosages of treatments for sleep disorders and / or hot flashes for the duration of the study, unless otherwise indicated by the doctor; adherence to the study by signing the Informed Consent Form (ICF).

- Exclusion criteria were: previous acupuncture treatment in the last 12 months; presence of lymphedema; thrombocytopenia (<50000); neutrophils <1000; presence of relevant comorbidity; history of other neoplasms in the last 10 years; presence of important psychiatric syndromes or cognitive disorders; bleeding tendency; participation in other studies of the oncology division.

Definition of insomnia. We have divided insomnia into 4 macro-areas. A first form, initial insomnia, related to the difficulty of falling asleep. A second is median insomnia which occurs in both the non-REM and REM phases. A third, terminal insomnia, linked to an early morning awakening. Finally, insomnia due to light and unstable sleep. The proposed definition is dictated by the need to combine the personalization of the intervention (multiplicity) with the replicability of the study (simplification). The resulting groups are sufficiently homogeneous within them, but differentiated with respect to the specific problem of the patient.

- *The Initial Insomnia.* In our hypothesis, the initial insomnia is linked, according to the schemes of traditional Chinese medicine, to different imbalances. The first consists of a deficit Yang Ming, in

particular of the meridian of the large intestine which is responsible, among its various functional correspondences, for the functioning of the intestinal transit and the secretion of serotonin through which it partly controls the mood and the initial phase of sleep through an effect on Tsue Yin (Meridians of Pericardium and Liver, responsible for the ortho-sympathetic tone) and the Shao Yang (Meridians of Triple Burner and Gallbladder, responsible for the parasympathetic tone). A deficit of the meridian of the large intestine, reducing the secretion of serotonin, would induce an increase in the ortho-sympathetic tone and reduce the parasympathetic tone, preventing the normal relaxation of the striated muscles that accompanies the first phases of sleep. A second type of Initial Insomnia is always linked to a deficit of the meridian of the large intestine, but also to an excess of the liver meridian, the latter would in turn induce an excess of the heart meridian with a mental hyperactivation and an inability to abandon oneself to rest. Often the two conditions coexist. The third type of initial insomnia is due to a primary excess of the Shao Yang which induces motor restlessness and is reflected secondarily, given its action on the heart meridian in a mental Hyperactivity.

- *The Median Insomnia.* We have 2 types of median insomnia, that is, linked to awakening after a first phase of deep sleep. The first is linked to an awakening that takes place in a non-REM phase of sleep and is always linked to a dysfunction of the meridian of the large intestine but whose prevailing effects are those of overstressing the Shao Yang inducing an anxious awakening, also characterized by a state of mental confusion. The second is linked to an awakening that occurs in a REM sleep phase and is always linked to a primitive or secondary excess of the Shao Yin group and in particular of its heart meridian that causes an awakening in a clear mental state.

- *The Terminal Insomnia.* It is what we define as an early awakening compared to the patient's previous habits and which does not allow the achievement of an adequate satisfaction of the individual needs for sleep. From the point of view of traditional Chinese medicine this is mainly due to a hyperactivity of the Tai Yin energy group which suppresses the activity of the Shao Yin energy group (Kidney and Heart meridians), responsible among other things, in our interpretation, for the synthesis of a neuromodulator important in maintaining the sleep, the Gamma-Aminobutyric acid.

- *The Light and Unstable Sleep.* In the complex relationship of energetic groups of meridians, this form of insomnia is related to an imbalance of three groups: the Tai Yang responsible of a insufficient GABA synthesis that enhances the central sympathetic tone due to Shao Yang (Heart meridian) and suppress the synthesis of serotonin, controlled by the Yang Ming (Large intestine meridian).

Enrollment. The study was presented to Oncology DH patients who met the inclusion criteria. If a patient agreed to participate, a researcher checked for eligibility criteria. All confirmed patients underwent a first diagnostic visit by a medical doctor acupuncturist for an anamnestic examination of the energy imbalances that can be configured in a different way in relation to the constitutional type according to traditional acupuncture diagnosis (Tai Yin, Yang Ming, Shao Yin, tai Yang, shao Yang and tsue Yin) and according to the sleep disorder presented (i.e.: initial calm and agitated insomnia, median insomnia with lucid awakening, median insomnia with confused awakening). For each patient the acupuncturist (F.J.)

sets an energy diagnosis, according to the ethical-professional principles of the Italian Acupuncture Association, based on what emerged during an in-depth individual interview. Once the energy diagnosis was made, patient signed the ICF, and agreed a weekly schedule of appointments for a duration of 8 weeks. During the same visit, the patient filled in the questionnaires for the detection of the variables under study.

After ICF and baseline assessment the patients were randomized to either acupuncture group (AG) or control group (CG) using a block allocation of four. The randomization was performed using a computer-generated list of random numbers, with a block size of four provided by an investigator not involved in the trial. The sealed envelopes numbered in ascending sequence contained the allocation for each patient.

Intervention

Acupuncture group (AG)

At each meeting, the medical doctor acupuncturist, before placing the needles, visited the patient by detecting the radial pulse and examining the tongue (for traditional Chinese medicine they are an integral part of the diagnosis, together with the medical history). Patients will have been applied 8-20 disposable needles. The patients were treated with acupuncture in relation to the energy picture presented. The positioning of the needles was done according to the evaluation of the type of insomnia according to the following scheme:

- 1- Initial Insomnia, first type, was treated with: LI11, St25, St36, St43, St44, REN12, P6, GB34, GB38.
- 2- Initial Insomnia, second type, was treated with: H3, H7, P6, REN 17, Ki6, Bl60, Li11, ST36, ST43.
- 3- Initial Insomnia, third type, was treated in two steps. 1st: Ren5, HE3, Ki3, TB5, Gb38, Bl59, Bl60 and 2nd: Gb34, Gb38, He3, Ki3, Gv3, Gv5.
- 4-Median Insomnia, with Awakening in non-REM phase: P1, P7, Ren17, Gb34, Gb38, Gb43, Li11, St25, St36, St 43, St44, Ren12
- 5- Median Insomnia, with Awakening in REM phase: He3, He7, Ki6, Bl60, Lv3 Ren5.
- 6- Terminal Insomnia: Ki6, Ren5, St36, St44, Lu2, Lu5, He3, He5.
- 7- Light and Unstable Sleep: Bl59, Bl60, Ren17, Ren3, He3, He5.

All the points mentioned are bilateral except for the points marked with the initials DU and REN which are respectively on the posterior and anterior midline of the trunk. The details on the anatomical location of these points are reported in Table 1.

Table 1. Description of acupuncture pressure points

Needling point	Location
Great Stream, Ki 3	On the medial aspect of the foot, posterior to the medial malleolus, in the depression between the tip of the medial malleolus and tendo calcaneus.
Shining Sea, Ki6	On the medial aspect of the foot, in the depression below the tip of the medial malleolus.
Pool at the Crook, Li11	With the elbow flexed, the point is on the lateral end of the transverse cubital crease, at midpoint between LU 5 and the lateral epicondyle of the humerus.
Middle Epigastrium, Ren12	On the anterior median line of the upper abdomen, 4.0 cun above the umbilicus.
Chest Center, Ren17	On the anterior median line of the chest, at the level of the 4th intercostal space, at the midpoint between the two nipples.
Inner Gate, P6	On the palmar aspect of the forearm, 2 cun above the transverse crease of the wrist, on the line connecting PC 3 and PC 7, between the tendons of m. palmaris longus and m. flexor carpi radialis.
Hill Spring, Gb34	On the lateral aspect of the lower leg, in the depression anterior and inferior to the head of the fibula.
Yang Aid, Gb38	On the lateral aspect of the lower leg, 4 cun above the tip of the external malleolus, slightly anterior to the anterior border of the fibula.
Celestial Pivot, St25	On the middle of the abdomen, 2 cun lateral to the umbilicus.
Leg Three Miles, St36	On the anterior aspect of the lower leg, 3 cun below ST 35, one finger-breadth (middle finger) from the anterior crest of the tibia.
Sunken Valley, St43	On the dorsum of the foot, in the depression distal to the junction of the second and third metatarsal bones.
Inner Courtyard, St44	On the dorsum of the foot, proximal to the web margin between the second and third metatarsal toes, at the junction of the red and white skin.
Lesser Sea, He3	When the elbow is flexed, the point is at the midpoint of the line connecting the medial end of the transverse cubital crease and the medial epicondyle of the humerus.
Connecting Interior, He5	On the palmar aspect of the forearm, the point is on the radial side of the tendon m. flexor carpi ulnaris, 1.0 cun above the transverse crease of the wrist.
Spirit Gate, He7	On the wrist, at the ulnar end of the transverse crease of the wrists, in the depression on the radial side of the tendon m. flexor carpi ulnaris.
Instep Yang, Bl59	On the posterior aspect of the lower leg, behind the external malleolus, 3 cun directly above UB 60.

Kunlun Mountains, Bl60	On the foot, behind the external malleolus, in the depression between the tip of the external malleolus and tendo calcaneus.
Lumbar Yang Gate, Du3	On the lumbar region, on the posterior median line, in the depression below the spinous process of the 4th lumbar vertebra.
Suspended Pivot, Du5	On the lumbar region, on the posterior median line, in the depression below the spinous process of the 1st lumbar vertebra.
Great Surge, Lv3	On the dorsum of the foot, in the depression proximal to the 1st metatarsal space.

The acupuncture was performed for 8 sessions during a 8-week period (once weekly).

Sterilized disposable bimetallic needles (copper handle and steel blade) (Hwato brand, in compliance with all European and Italian regulations) measuring 40mm x 0.32mm were inserted, forming a 90-degree angle with the skin surface and rotated anti-clockwise.

The acupuncture points were identified and chosen after the interpretation of the energy imbalances present in the patient.

Acupuncture is a safety form of healthcare with a low relative risk. Since it is not an entirely risk-free medical procedure, it should be administered by practitioners with the proper training who follow accepted guidelines of practice. To mitigate the “acupuncturist effect” we had established the rotation of acupuncturists in the treatment of the same patient.

The acupuncture treatment will be carried out exclusively by 3 medical doctors qualified by the Italian Association of Acupuncture (F.J., M.C., P. C.) with more than 15-year of acupuncture experience, who participate in the study on a voluntary basis.

Before the start of the study, 6 in-depth and comparison meetings were held between the 3 acupuncturists to guarantee the uniformity of the application of the treatment. Before each session, the acupuncturists confronted each other to decide on a shared treatment. Every week, on Wednesday afternoon, meetings were held between the whole team to monitor the progress of the treatment.

Control group (CG)

Patients assigned to the control group were received once a week, for 8 weeks, by an oncologist. Received individually in an outpatient room and interviewed about the state of health and the undesirable effects of the therapies.

Outcome measure

The main study outcome was the severity of insomnia measured by ISI.

-The Insomnia Severity Index (ISI) [14,26] is a brief self-report questionnaire to measure the patient's perception of severity insomnia. The questionnaire measures characteristics and consequences of insomnia in the last 2 weeks. The items' content corresponds in part to the diagnostic criteria of the insomnia in DSM-5. The ISI is composed of seven items that evaluate (1) the severity of sleep-onset, (2) difficulties in sleep maintenance, (3) early morning awakening problems, (4) dissatisfaction with current sleep pattern, (5) interference with daily functioning, (6) noticeability of impairment attributed to the sleep problem, and (7) level of distress caused by the sleep problem. Each of these items is rated on a 0-4 scale and the total score ranges from 0 to 28. ISI has frequently been used as measure of outcome.

The severity of insomnia is assessed on the basis of the reported score, as below:

0- 7 = absence of clinically significant insomnia;

8-14 = insomnia below the clinical threshold;

15-21 = clinical insomnia of moderate severity;

22-28 = severe clinical insomnia.

Patients that reported ISI score >14 are probable cases affected by clinical insomnia. In this study, the internal consistency of the scale was $\alpha = 0.77$.

Secondary outcomes

- The Sleep Disturbance Questionnaire (SDQ) [27,28] is a 12-item questionnaire to measure subjective experiences of usual sleep habits and sleep difficulties. The items are grouped into four factors which reflect physiological, cognitive and behavioral aspects. Each item is answered on a 5-point scale ("1=never true," "2=seldom true," "3=sometimes true," "4=often true," "5=very often true"). It is possible to obtain 4 distinct scores: (1) a measure of restlessness/agitation or "Physical tension", (2) a measure of "Inadequate sleep pattern", (3) a measure of "Cognitive vigilance" or difficulty in falling asleep, and (4) a measure of "Effort to sleep". A measure of "Mental overactivity" derives from the sum of the scores in "Difficulty in falling asleep" and "Effort to sleep". Subjects are asked to rate items in relation to typical nights when they do not sleep well, and to specify if each problem happened at least three nights per week for at least 3 months. In this study, the internal consistency of the scale was $\alpha = 0.70$.

The questionnaires were filled out for both groups at baseline and 8 weeks later.

Sociodemographic and clinical information, as the presence of as specific symptoms (i.e.: repetitive leg movements), were also collected.

Sample Size

The sample size calculation was based on the results of a pilot study on sleep quality (mean score in "absence of chronic insomnia" = 9.52; standard deviation = 3.16; mean score in "presence of chronic

insomnia" = 12.05; standard deviation = 2.03). Intending to compare the differences between post-treatment mean and mean at baseline (change method), to calculate the number of subjects to be allocated to each group, setting alpha = 0.05 (two-sided) and power = 90%, 56 patients were examined and equally assigned to each group. Considering a 30% exclusion, 72 patients will be invited to participate in the study.

Statistical Analysis

Data were presented as mean and standard deviation (SD) or frequency (n) and percentage (%), to describe demographic and clinical characteristics of the whole sample and separately for acupuncture and control group.

The difference in the baseline characteristics between the acupuncture and control groups was determined with the t-test or Chi-square test. Differences between baseline and follow up measures for variables in study used mean, 95% confidence intervals (CIs). The change between baseline and follow up was calculated as the difference between the two measures (delta).

For the purpose of analysis, we divided into two categories the SDQ domain scores at the median value (0=less than or equal median value; 1= higher than median value); delta scores (0=no improvement if delta score <1; 1=improvement, delta score >0).

Multivariate logistic regression models were built to assess the association between improvement in insomnia (compared to stability/deterioration) and all variables resulted associates at the univariate analyses, while simultaneously adjusting for possible confounding factors as age, previous use of CAM (0= no; 1= yes), years of school (0= less than 13 vs 1= 13 or more).

The internal consistency of the scales was estimated with a Cronbach alpha coefficient by the item-total correlations.

All statistical analyses have been performed using STATA, version 11.0 (StataCorp, College Station, Tex).

Sample

Seventy-two breast cancer females aged 26-81 years (mean = 53.59; standard deviation, SD = 11.06) volunteered for this study by responding to an invitation to participate if the inclusion criteria were met.

After a preliminary visit with two medical doctor acupuncturists, to assess the characteristics of the sleep difficulties, 14 women were excluded. Seven for important comorbidities no-cancer related, 4 for the minor difficulties in sleep, 3 for not being available for a weekly treatment in the month after.

Fifty-eight breast cancer women with ascertained sleep difficulties were randomized into two groups (AG and CG).

Results

Baseline

The demographic and clinical characteristics at baseline are reported in Table 2, separately for the acupuncture and control group. No significant differences were observed on age, years of study, marital status, surgery type, lymphectomy, chemotherapy, radiotherapy, psychoactive drug use, herbal medicine use, and changes in quality and quantity of sleep, and mood (compared to those before the hormone replacement therapy). For the whole sample there was a pejorative variation in the quality and quantity of sleep compared to before treatment for breast cancer. For 21 patients in each of the two groups there was a worsening of mood (70% vs 75%, p-value 0.670).

At baseline, among 58 patients, 38 (65.52%) reported an ISI score > 14 and were classified as probable cases of clinical insomnia. Of these, 30 (51.72%) had a moderate insomnia, with ISI score between 15 and 21, and 8 (13.79%) had a severe insomnia, with ISI score ranging 22–28. Twenty participants (34.48%) had a subthreshold insomnia (ISI score 8–14). No differences emerged by group.

At baseline, no differences emerged in sleep difficulties as measured by ISI (see Table 3) and SDQ-domain median score (physical tension, inadequate sleep pattern, overactivity, cognitive vigilance, effort to sleep; see Table 4), between acupuncture and control group.

At follow up, after 8 weeks, the ISI mean score differed significantly between acupuncture and control group (p-value = 0.001), with a mean change (delta) of 6.07 in the acupuncture group and of 2.07 in the control group (p-value = 0.037).

No significant changes emerged in the SDQ-domain scores. Although there are improvements, not statistically significant, in all SDQ domain scores for the acupuncture group, unlike the control group where scores remain stable or worsen between baseline and follow-up measures (see Table 5)

Follow up

At follow up, 21 (36.2%) reported ISI scores compatible with clinical insomnia; of these, 14 (24.14%) had a moderate insomnia, and 7 (12.07%) a severe insomnia; for 24 (41.38%) there were a subclinical insomnia and for 13 (22.41%) there were absence of insomnia, with significant differences between acupuncture and control group (p-value < 0.001), as shown in Table 6.

In the acupuncture group for 13 patients (43.33%) there was a complete remission of sleep difficulties. Seven (23.33%) had an improvement with a reduction in severity. For 9 (30.00%) patients there was change in sleep difficulties. In particular, of the 10 patients with subclinical insomnia at baseline, 3 showed no change at follow-up and 7 improved (absence of insomnia);

of the 18 with moderate insomnia, 6 showed no changes and 11 improved (5 with subclinical insomnia and 6 absence of insomnia); the 2 patients with severe insomnia both improved (1 with subclinical

insomnia and 1 moderate insomnia).

In the control group, no patients had complete remission (absence of insomnia) and for 17 (60.71%) their status did not change (9 with subclinical insomnia, 5 moderate and 3 severe). For 7 patients (25.0%) there was an improvement, while 4 (14.29%) worsened.

No legs movements were reported and no patient complained of problems or discomfort due to the insertion of the needles.

In the multivariate logistic regression final analysis, the improvement in insomnia was strongly and independently associated with acupuncture treatment (OR 13.02; 95%CI 2.87–59.13; p-value = 0.001) and low cognitive vigilance (OR 5.23; 95%CI 1.17–23.32; p-value = 0.030), and BMI-normal weight (OR 5.57; 95%CI 1.40-22.22; p-value = 0.015) after adjustment for previous use of CAM as a choice of care, age and years of school.

Discussion

Sleep is essential to animal health and well-being like the proper nutrition and physical exercise.

But shorter sleep duration, increased wakefulness and changes in the sleep cycle are very common in the general population and even more so among patients [7, 10]. Sleep difficulties can have a variety of causes and even in chronic cases show a certain variability over time. Furthermore, their severity is largely attributable to the perception that the subject who suffers from them has. In the case of cancer patients, in addition to the shock of the diagnosis, sleep problems are attributable to the psychological state of the patient, the disease itself and the side effects of drug treatments. In spite of individual variability significantly sleep difficulties reduce quality of life for many.

In this study we wanted to focus on the quality and quantity characteristics of sleep typical of insomnia. We have chosen to use a measurement tool widely used in research, the self-completed ISI questionnaire, which traces the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [29]. As well as on the clinical evaluation of what was reported by patients in the dedicated medical examination. As treatment, we wanted to measure the effectiveness of acupuncture not only to improve the quality and quantity of sleep, but also the daytime functioning, and the patient's well-being. The "strength" of acupuncture is its nature as a complementary medicine treatment, especially when addressed to a population of patients already in multi-drug treatment.

The results of this study made it possible to highlight the effectiveness of acupuncture in reducing sleep difficulties and insomnia in this sample and how simply "taking care and dedicating time" to the patients in the control group is not enough to mitigate the discomfort of sleeping in an unsatisfactory and non-restful way.

The most important finding is that in the acupuncture group 43.33% go into complete remission (absence of insomnia), but none in the control group. Although the percentage of improvement after 8 weeks, for

both groups is around 25%, it should be noted that in the control group 14% undergoes a worsening and the percentage of situations that do not vary is double compared to those who have acupuncture (60% vs 30%).

As shown by the multivariate logistic analysis, the patients who showed an improvement in insomnia were those who underwent 8 cycles of acupuncture (compared to 8 meetings with the oncologist) and with a physiological hyper-excitation lower than the median value (compared to above) as the cause of difficulty falling asleep. With this treatment scheme - once a week for a total of 8 - patients with very high hyperexcitation find less benefit than those with less elevated hyperexcitation. Our hypothesis is that the response to acupuncture is to be considered generated by a multiplicity of factors where a non-specific role is played by the human variable: the supplier of the work and the user. The touch of the skin and the exposure of the nakedness of the body offered for the treatment of acupuncture places the patient in a position of trusting / trusting the other and in some way could emphasize the perception of attention / care received favoring the psychological reorientation.

No problems with needle insertion have been observed or reported and the safety of acupuncture is established.

Effectiveness and safety of acupuncture in the management of gastrointestinal disorder, neuropathy, arthralgia, joint symptoms, and cognitive impairment as side effects in breast cancer patients was recently showed by Chan and colleagues' meta-analysis [30].

Some limitations can be noted in this study. Although we filtered patients who had sleep difficulties only after the cancer diagnosis and treatment (to add credence to a causal relationship), we cannot consider it completely truthful as these problems are those reported solely by the patient. We could not completely overcome this limitation. The reliability and validity of diagnosis or assessment of signs / symptoms is not as qualified as that in designed prospective longitudinal studies. As the information reported is largely influenced by the individual expectations of the patient and physician. Our results supported the acupuncture's acceptability by patients and its effectiveness, but for patients who volunteered in this study. Although in our protocol we had established the rotation of acupuncturists in the treatment of the same patient, future research should serve to distinguish the effect due to the relational skills of the acupuncturist from that of needles.

A further element that remains to be considered is the outcome measure. In this study we have used the ISI, a measure frequently used as measure of outcome, but which, like all Patient-reported outcome measures [31], is affected by the patient's expectations and his personal judgment yardstick. On the one hand, future research will have to combine these self-report questionnaires with more objective measures, although in the case of sleep the difficulties are largely subjective. Randomized controlled trials with different and more numerous samples are needed to further evaluate the results

Finally, sleep is influenced by several factors. From age, from evolutionary changes, from medical pathologies, from drugs, from lifestyles, from environmental factors, but also from stress and emotional

suffering, the latter elements, frequent in breast cancer patients. Our study took place over a limited period of time, a couple of months, and it was possible to detect all the changes that the patients reported. However, in a study like this, the subjectivity of the perception of the quality and quantity of sleep and restful sleep remains, which can be overcome only through equipment such as the polysomnography.

Conclusion

An element arising from the results, which must guide future research, is the importance of offering the patient psychoeducational interventions that on the one hand help the patient to recognize the different forms of sleep difficulties, the phases, the continuity and the architecture, as well as to evaluate "without judgment" the periods of sleep / absence of sleep, to get to distinguish acute insomnia from mild and transient sleep difficulties and on the other, orient him to ask for targeted help and to learn ways of sleep hygiene and relaxation.

Given the prevalence of the problem investigated, an important indication for the healthcare team is to regularly inquire about sleep habits and symptoms and about sleep-wake circadian rhythm disturbances, as they well know an inadequate amount of poor sleep affects the immune system.

Declarations

Competing interests

Authors declared that they have no competing interests.

Authors' contributions

EM conceived the project, led the design and co-ordination of the trial, and analyzed data and wrote the manuscript. FJ conceived the project, led the design and participated in the study as acupuncturist, reviewed and integrated the manuscript. MC and PC participated in the study as acupuncturists. FM as an experienced teaching acupuncturist supervised the treatment method. CS took care of the appointment agenda with the patients. AS and PM made possible the realization of the project in oncology DH.

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- Acupuncture is spreading as an alternative treatment to drugs and is proving effective in reducing some of the side effects of cancer and the associated therapeutic burden
- The main objective of the study was to evaluate the effectiveness and safety of acupuncture to treat sleep difficulties in breast cancer women in hormonal replacement therapy, either exclusively or in

association with other anticancer therapies, in order to obtain an improvement in the quality and quantity of sleep.

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Tables

Tables 2 to 6 are available in the Supplementary Files section

Supplementary Files

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