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ARTIGO ORIGINAL

High versus low frequency transcutaneous acupoint electrical stimulation as an adjunct therapy to prevent nausea and vomiting in the first 24 hours after infusion of high-grade emetic chemotherapy: a randomized controlled trial

Estimulação elétrica transcutânea de alta versus baixa frequência como terapia adjuvante para prevenir náuseas e vômitos nas primeiras 24 horas após a infusão de quimioterapia emética de alto grau: um estudo controlado randomizado

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Abstract

Background: Transcutaneous acupoint electrical stimulation (TAES) has been tested as antiemetic therapy. *Objective*: Evaluation of the effectiveness of two different frequencies of the electrical current as adjunctive therapy in the prevention of nausea and vomiting. *Methods*: This placebo-controlled clinical trial compared the incidence of nausea and vomiting (within the first 24 hours after high-grade emetic chemotherapy infusion) of 61 women (54 ± 11 years) with breast cancer undergoing three modes of TAES: high frequency (HF:150 Hz), low frequency (LF:10 Hz), and placebo (P). Electrodes were fixed at the acupuncture point PC6 and a symmetric bipolar current (pulse width 200 µs) was applied in a single 30-minute session prior to the start of chemotherapy infusion. All patients receive fixed antiemetic treatment infusions (ondansetron 8 mg) and rescue

medication instructions, if necessary, according to the routine for infusions of cyclophosphamide associated with anthracycline. *Results*: The incidence of nausea was 47% in P, 45% in HF and 26% in LF. Although not significant, the intervention with LF-TAES at PC6 acupoint reached relevant values in reducing the relative risk of developing nausea (RR = 0.51; CI 95% = 0.18 to 1.44; p = 0.18) and a trend toward improved reported well-being (p = 0.06) and a lower Edmonton Symptom Rating Scale score (p = 0.08). The incidence of vomiting and the consumption of rescue antiemetic doses were very similar between the groups. *Conclusion*: New studies with LF and HF of TAES as adjuvant therapy for the prevention of nausea and vomiting should be carried out to confirm this hypothesis.

Keywords: Antineoplastic combined chemotherapy protocols; antiemetic agents; electrical stimulation therapy; acupuncture.

Resumo

Introdução: A estimulação elétrica transcutânea em pontos de acupuntura (TAES) foi testada como terapia antiemética. *Objetivo*: Avaliar a eficácia de duas frequências diferentes de corrente elétrica como terapia adjuvante para a prevenção de náusea e vômito. *Métodos*: Este ensaio clínico controlado por placebo comparou a incidência de náusea e vômito (nas primeiras 24 horas após a infusão de quimioterapia emética de alto grau) em 61 mulheres (54 ± 11 anos) com câncer de mama em três modos de TAES: alta frequência (HF:150 Hz), baixa frequência (LF:10 Hz) e placebo (P). Os eletrodos foram fixados no ponto de acupuntura PC6 e uma corrente bipolar simétrica (largura de pulso 200 µs) foi aplicada em uma única sessão de 30 minutos antes do início da infusão de quimioterapia. Todos os pacientes recebem infusões fixas de tratamento antiemético (ondansetrona – 8 mg) e orientação de uso de medicação de resgate, se necessário, conforme rotina para infusões de ciclofosfamida associada à antraciclina. *Resultados*: A incidência de náusea foi de 47% no P, 45% na HF e 26% na LF. Embora não significativa, a intervenção com LF-TAES no ponto de acupuntura PC6, alcançou valores relevantes na redução do risco relativo de desenvolver náuseas (RR = 0,51; IC 95% = 0,18 a 1,44; p = 0,18) e tendência de melhora na sensação de bem estar (p = 0,06) e pontuação mais baixa na Edmonton Symptom Rating Scale (p = 0,08). A incidência de vômitos e o consumo de doses antieméticas de resgate foram muito semelhantes entre os grupos. *Conclusão*: Novos estudos com LF e HF de TAES como terapia adjuvante na prevenção de náuseas e vômitos devem ser realizados para confirmar essa hipótese.

Palavras-chave: protocolos combinados de quimioterapia antineoplásica; agentes antieméticos; terapia de estimulação elétrica; acupuntura

Introduction

The Multinational Association of Supportive Care in Cancer (MASCC) cites that nausea and vomiting incidence in antineoplastic protocols that combine anthracycline with cyclophosphamide can reach 90% [1], but antiemetic drugs can reduce this incidence to values close to 50% [2]. Nevertheless, non-pharmacological techniques such as transcutaneous electric nerve stimulation (TENS) were proposed as complementary therapies to support in the control of nausea and vomiting in these patients [3,4] as well during postoperative period [5-7].

The last meta-analysis that evaluated the effect of electric stimulating a specific acupuncture point (PC6) associated with antiemetic drugs showed that the association of these interventions is more effective in preventing postoperative vomiting when compared to the exclusive use of drugs (RR = 0,56, CI 95% = 0,35 to 0,91; 9 trials, 687 participants). This therapy combination was not effective for the prophylaxis of nausea (RR = 0,79, CI 95% = 0,55 to 1,13; 8 trials, 642 participants), but there was a reduction in the necessity for antiemetic drugs in the postoperative period (RR = 0,61, CI 95% = 0,44 to 0,86; 5 trials, 419 participants) [7].

The mechanisms of action were studied in an animal model [8] and some clinical trials, conducted in cancer patients, have measured the effect of electrical stimulation under different isolated or associated acupuncture points that are traditionally used in the treatment of nausea and vomiting [3,4,8-11]. In an overview, there are many discrepancies between these studies, but the PC6 was the most frequently acupuncture point mentioned. The clinical characteristics of the patients allocated were quite variable. The interventions also expose a quite different between treatment time, weekly frequency and duration of the session. The parameters used in electrical stimulation showed important differences, such as the frequency of the electrical pulse, which in some studies was applied high frequency others low frequency. Another aspect observed in these studies is a tendency to applied electroacupuncture by transcutaneous acupoint electrical stimulation (TAES) to avoid the risk of infection, inherent to the invasive procedures. The results showed a favorable effect of TAES for the management of nausea and vomiting, but there are many variations in these responses and important discrepancies between the protocols.

The frequency of the electric pulse is one of the main variables that make up the electric current, but there is no consensus on whether high or low frequency is more effective. On the other hand, the rate of incidence for nausea and vomiting is treatment-depended. Some anticancer protocols are classified as high-grade emetic chemotherapy (HEC). One of the most used HEC protocols combines anthracycline with

cyclophosphamide. This combination can induce nausea and vomiting up to 90% in the first 24 hours after the infusion [12] and this specific characteristic induced by the pharmacological association of the antineoplastic protocol frequently used in the treatment of breast cancer, may be appropriate as a clinical trial model to study antiemetic agents. Therefore, this study aims to evaluate the acute effect of two frequencies of TAES on the incidence of nausea and vomiting in volunteers undergoing a fixed regimen of HEC associated with antiemetics usually prescribed in the care service.

Methods

This randomized, placebo-controlled clinical study was conducted at the chemotherapy outpatient clinic after approval by the local ethics committee (CAAE: 07489019.8.0000.5335) and registered on the clinicaltrials.gov platform (NCT03145727). The study was carried out in accordance with the ethical standards elaborated in the Declaration of Helsinki 1964 and later amendments. Informed consent was obtained from all individual participants included in the study (Form number: 3.265.023).

Sixty-one women (54 ± 11 years) with breast cancer assigned to the HEC constituted by anthracycline combined with cyclophosphamide were included. A fixed 8 mg ondansetron infusion (5-HT3 receptor antagonist) was administered prior to the chemotherapy session and rescue doses of ondansetron and/or antihistamines and/or antidopaminergics were instructed to use at home as needed. Only women with good functional capacity (Karnofsky score ≥ 70 points) and without previous (72 hours) nausea/vomiting symptoms were included. Patients with cognitive limitations, undergoing concomitant radiotherapy, gastrointestinal and/or brain metastases, cardiac pacemaker, or skin changes that did not allow electrical stimulation to be performed were excluded.

Clinical evaluation

All participants received guidance and training to record nausea and vomiting in the first 24h post-infusion of HEC. The intensity/severity of nausea (visual analog scale 0-10) and vomiting were recorded as recommended by the European Society of Medical Oncology (ESMO) and the MASCC [12]. Home use of antiemetic drugs has been strictly controlled. Telephone contact was maintained to answer questions and request form

(photographic) submission. The Edmonton Symptom Rating Scale (ESRS) was incorporated into the form to control adverse symptoms [13].

Treatments

Eligible patients were randomized into three groups: placebo (P); high frequency (HF) and low frequency (LF) of the TEAS. An independent researcher used a random sequence generated at randomizer.org to make opaque envelopes that were sealed and kept completely confidential until the volunteers were assigned to one of the three interventions. Neurodyn® III electro stimulator (Ibramed, Brazil) was applied 30-90 minutes before chemotherapy. Reusable adhesive electrodes were positioned at the acupuncture point PC6 on the contralateral infusion arm. One electrode was attached to two "tsuns" proximal to the flexion groove of the wrist in the middle of the anterior surface of the forearm between the tendons of the palmar muscles and radial flexors of the carpus, and the second electrode was placed 5 cm above the CP6 towards the elbow (figure 1). For group P, the electric current was adjusted with 75 Hz/200μs and intensity at the lower limit of sensitivity. After 10 s, the intensity was reduced to zero, but the electrodes were kept fixed for 30 minutes. In the LF and HF groups, the currents were adjusted at the frequencies of 10 Hz and 150 Hz (respectively) and both at the 200 μs pulse width. The stimulation time was 30 minutes and the intensity was constantly increased to keep the electric current at the upper tolerance limit.

Statistical analysis

An independent researcher used Shapiro-Wilk, Fisher's exact, G (Williams), chi-square, relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) to test the acute effect of TEAS on the incidence of nausea and vomiting. Mann-Whitney was conducted to analyze the intensity of nausea and vomiting as well the systemic symptoms (ESRS) between interventions and placebo.

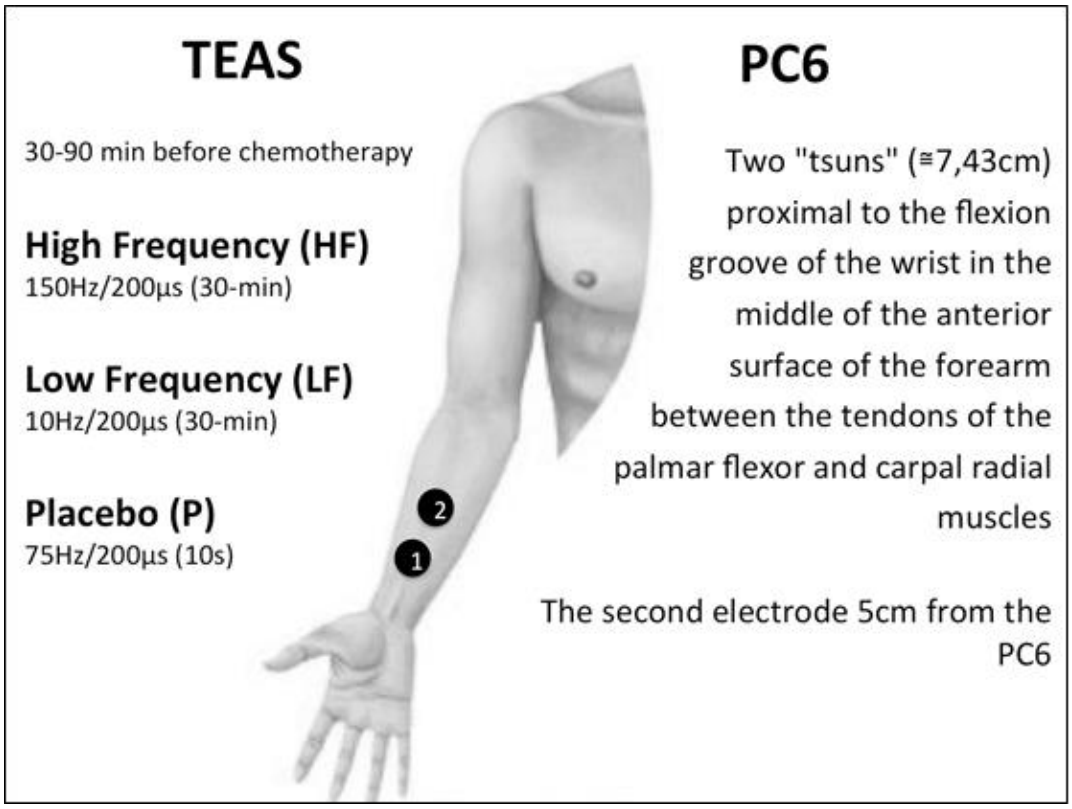


Fig. 1 - *The PC6 acupuncture point is represented by the anatomical location demarcated by the first black circle (1). The second black circle (2) indicates the position where the second electrode was connected to complete the electrical circuit. The intervention by transcutaneous electrical stimulation (TEAS) was performed in the arm opposite to the chemotherapy infusion*

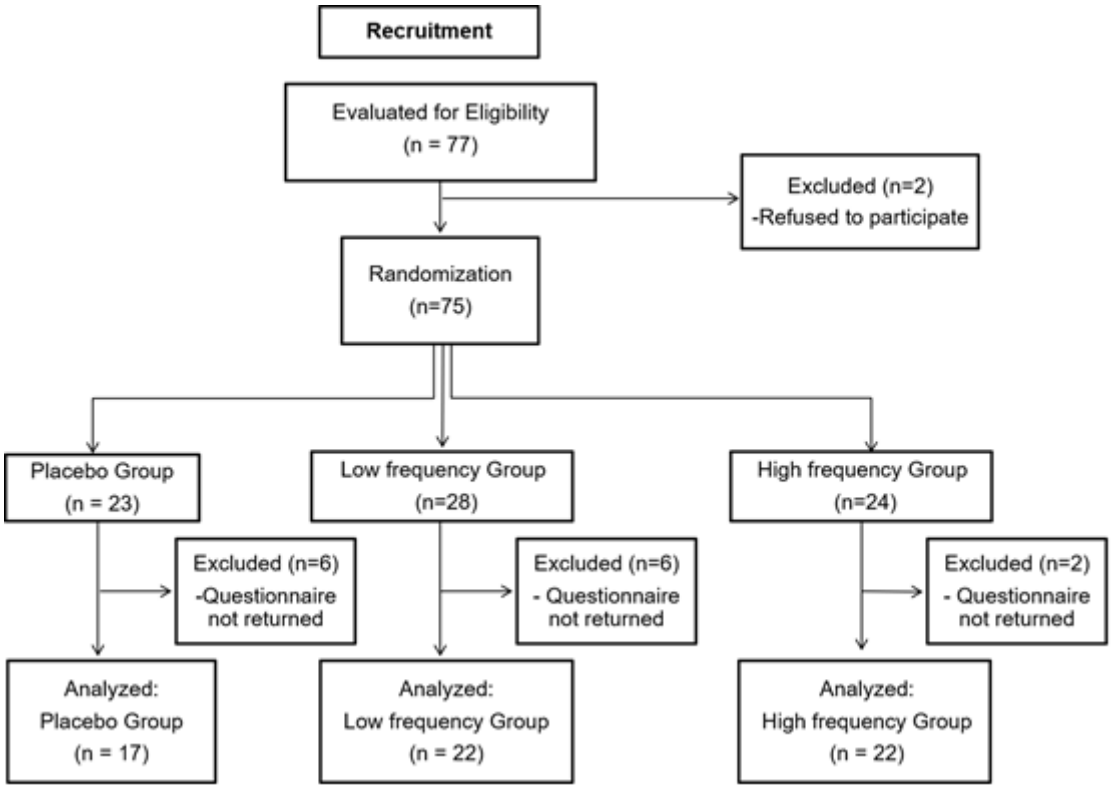


Fig. 2 - *Study procedures flowchart (CONSORT -2010)*

Results

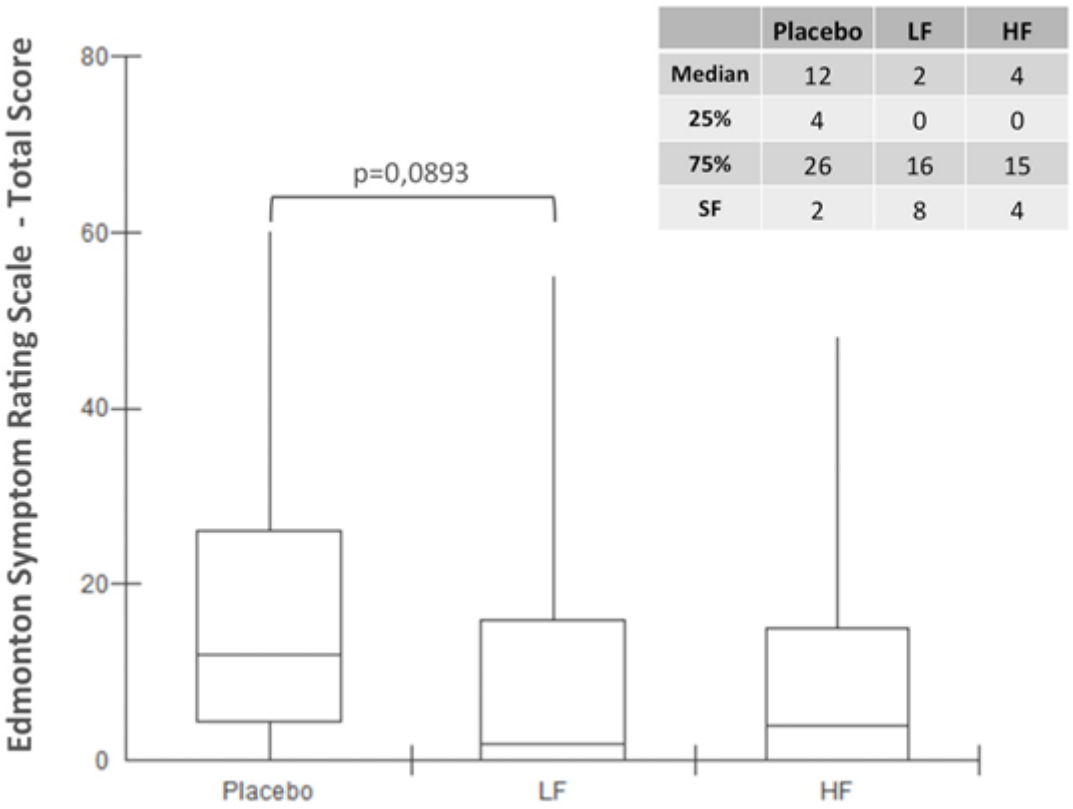
At baseline, 77 volunteers met the eligibility criteria, but 75 patients agreed to participate in the study and were randomized. However, only 61 completed and returned the nausea and vomiting registering form (Figure 2). The total loss rate of the study sample was 18%. There was homogeneity between the groups for age, type and phase of chemotherapy cycles (Table I).

Table I - *Clinical characteristics and nausea symptoms and vomiting episodes in the first 24 hours after infusion of high-grade emetic chemotherapy*

	P (n=17)	LF (n=22)	HF (n=22)	p
Age (years)	55.14±11.14	56.84±11.22	50.45±11.32	0.153
Adjuvant chemotherapy	9 (53%)	10 (45%)	14 (64%)	0.477
Neoadjuvant chemotherapy	8 (47%)	12 (55%)	8 (36%)	
Treatment Phase				
1º cycle of chemotherapy	9 (53%)	12 (55%)	13 (59%)	0.935
2º cycle of chemotherapy	2 (12%)	2 (9%)	3 (14%)	
3º cycle of chemotherapy	4 (23%)	4 (18%)	2 (9%)	
4º cycle of chemotherapy	2 (12%)	4 (18%)	4 (18%)	
Nausea (in the first 24h)				
Incidence	8 (47%)	6 (27%)	10 (45%)	0.473
Number of the episodes	4.0±4.9	3.0±2.2	5.1±5.2	0.431
Intensity of the symptoms	4.1±2.9	5.1±2.1	3.3±2.1	0.453
Vomiting (in the first 24h)				
Incidence	1 (6%)	3 (14%)	3 (14%)	0.712
Number of the episodes	1.0±0.0	2.0±1.0	2.0±0.6	0.709
Antiemetic at home				
Need for pharmacological rescue	5 (29%)	6 (27%)	5 (23%)	0.893
Number of doses administered	4.8±2.7	3.6±1.6	2.8±1.7	0.721

The results were summarized using values expressed in absolute terms and percentages, as well as mean and standard deviation. The comparison between independent samples was performed using Shapiro-Wilk, Chi-Square, G-test (Willians) and Fisher's exact tests

The incidence rate of nausea and vomiting was statistically similar between groups. The total notifications of nausea and vomiting were also similar between interventions. The same results were found between interventions regarding the intensity of nausea symptoms. Controlling the use of antiemetics in the domestic environment demonstrates that the need for additional pharmacological management was very balanced between interventions. The number of rescue doses of antiemetics was similar between interventions, although the mean number of doses consumed in the LF and HF groups represented 75% and 58%, respectively, of the mean number of doses ingested in the placebo group.



	Placebo	LF	HF
Median	12	2	4
25%	4	0	0
75%	26	16	15
SF	2	8	4

Fig. 3 - *Edmonton Symptom Rating Scale (ESRS) total score for placebo and low-frequency (LF) and high-frequency (HF) TAES interventions. The box plot presents data through the median and maximum and minimum values and interquartile range (25%-75%). The effect of LF and HF was compared individually to placebo using the Mann-Whitney test. SF = symptom free is the number of volunteers who remained asymptomatic during the first 24 hours after infusion of high-grade emetic chemotherapy*

The relative risk of nausea was very close between HF-TAES and placebo (RR = 0.97; p = 0.41; CI 95% = 0.49 to 1.91; RRR = 3%; ARR = 1.6%; NNT = 63), but when comparing LF-TAES with placebo, the relative risk reduction was much more expressive. There is a high probability of error in this estimation, but the magnitude of the relative risk was substantially high (RR = 0.58; p = 0.17; CI 95% = 0.25 to 1.35; RRR = 42%; ARR = 18%; NNT = 6).

The occurrence of symptoms assessed by the ESRS was evenly distributed among the interventions (data not shown). Symptom intensity was also equivalent between groups for pain, tiredness, drowsiness, nausea, appetite, shortness of breath, depression and anxiety. However, when compared to the placebo the LF-TAES showing a trend towards improvement in the perception of well-being (p = 0.06) and in the total ESRS score (p = 0.09) (Fig. 3). The number of volunteers who remain asymptomatic in the first 24 hours after HEC infusion also tends to be smaller in the LF group compared to placebo (RR = 0.72; p = 0.08; IC 95% = 0.50 to 1.03; RRR = 28%; ARR = 24%; NNT = 5).

Discussion

TEAS applied to a unilateral PC6 acupuncture point, as proposed in this protocol, showed an uncertainly effect in preventing nausea and vomiting in the first 24 hours after HEC infusion. The incidence of nausea in placebo and HF-TAES interventions was proportionally equivalent to the rates described by Roiola *et al.* [12], but with a LF-TAES, there was almost half and, additionally, there was a strong tendency to less intense manifestations. However, even with this reduction in the proportion of the incidence of nausea, we cannot consider it appropriate to attribute to LF-TEAS the effect of reducing the incidence of nausea in the first 24 hours due to the high level of type I error observed. The variability of the distribution reinforced the statistical requirement of expanding the sample size. However, omitting this information would be an even bigger mistake.

Nausea and vomiting can be controlled by serotonin receptor inhibitors, antihistamines and antidopaminergics [1,2] however, after cisplatin infusion, electroacupuncture (applied to the acupuncture point VC12) showed lower plasma serotonin concentration in animal [8]. This finding links the action of acupuncture's antiemetic mechanism to state-of-the-art pharmacological therapies that involve the serotonin-signaling pathway [14,15]. This connection between acupuncture and pharmacological therapies became more unequivocal after the latest review published by Lee *et al.* [7], PC6 acupoint stimulation was compared with six different types of antiemetic drugs (metoclopramide, cyclizine, prochlorperazine, droperidol, ondansetron and dexamethasone), and no difference was found in the incidence of nausea (RR 0.91, 95% CI 0.75 to 1.10; 14 trials, 1.332 participants), vomiting (RR 0.93, 95% CI 0.74 to 1.17; 19 trials, 1.708 participants), or the need for rescue antiemetic drugs (RR 0.87, 95% CI 0.65 to 1.16; 9 trials, 895 participants). The review included clinical trials that tested the effect of various types of PC6 acupuncture point stimulation (acupuncture, electro-acupuncture, transcutaneous electrical acupoint stimulation, transcutaneous nerve stimulation, laser stimulation, capsicum plaster, acu-stimulation device, and acupressure) as a way to prevent postoperative nausea and vomiting [5-7].

Another interesting result appeared when Lee *et al.* [7] analyzed clinical trials that compared the effect of PC6 stimulation combined with antiemetic drug and antiemetic drug alone. This assessment showed that stimulation of acupuncture points as an adjunctive therapy reduces the incidence of vomiting (RR 0.56, 95% CI 0.35 to 0.91; 9 trials, 687 participants) and the necessity for rescue antiemetic drugs (RR 0.61, 95% CI 0.44 to 0.86; 5 trials, 419 participants) but not nausea (RR 0.79, 95% CI 0.55 to 1.13; 8 trials, 642 participants). Our findings have progressed in a slightly different direction. The

incidence of vomiting and the consumption of rescue antiemetic doses were very similar between the groups, but the few occurrences of vomiting made the analysis unfeasible.

Postoperative nausea and vomiting are clinically distinct from chemotherapy-induced nausea and vomiting, particularly when HEC is infused, but there is some evidences that acupoint therapy could be useful to prevent nausea and vomiting induced by chemotherapy [16,17]. In patients under chemotherapy for lung cancer, the acupoint stimulation drastically decreased the nausea and vomiting at Grade II-IV when compared to the control group (RR, 0.46; 95% CI, 0.37-0.51; P = 1E-5, 8 studies, 501 patients). In addition, increases in hemoglobin, platelets and immunomodulatory response markers were also observed (increase of IL-2, CD3+ and CD4+ T cells and NK cells) [18]. Some studies showed an advantage in the improvement of performance status and quality of life (EORCT-QLQ-C30) [19].

The overall score of the main symptoms evaluated in our study showed a strong favorable trend for LF-TEAS. The benefits of LF-TAES on cancer-related symptoms open an opportunity for clinical studies on the effect of electro stimulation on the quality of life of patients undergoing anticancer treatment. The feeling of well-being was the best scored aspect by patients undergoing LF-TAES. In this sense, another important finding was the substantial number of volunteers who remained asymptomatic after the intervention with LF-TAES.

Nonetheless, our results indicate the possibility that the frequency used in the TAES may have a relevant role in the effects size of the intervention. This hypothesis was described before, but Xie *et al.* [9] found no statistical significant differences between placebo and low frequency (4Hz) applied under multiple acupuncture points simultaneously stimulated (PC6, E36 and LI4; with electrode patch placed on the skin surface, and intensity between 7-15 mA; twice a day, for 30 min to 60 min by six consecutive days) combined with a fixed dose of an antagonist of serotonin (palonosotron, 0.25 mg). The patients (active acupuncture, n = 72 or placebo acupuncture, n = 70) were followed for 5 days after cisplatin infusion (60 mg) and no significant differences were found.

Interpersonal variations play an important role in the development of anticancer chemotherapy-induced nausea/vomiting. As described by McKeon *et al.* [10], chemotherapy side effects worsen after the first infusion cycle. In this regard, it is worth noting that 56% of the volunteers who participated in our study had completed the first cycle of chemotherapy treatment. For prophylaxis purposes, evaluating the effect of antiemetic strategies in volunteers free of cumulative effects is the best scenario, but the interpersonal variations described in the literature bring with them the need for studies with large samples, especially when the incidence rate of symptoms is low, as observed

in our study in relation to episodes of vomiting. An interesting alternative would be to evaluate the adjuvant effect of TAES in the management of nausea and vomiting in patients who suffer recurrently from these disorders. Including only patients with nausea and vomiting refractory to antiemetic therapies could be useful to increase the accuracy of detection of the antiemetic effect of TAES. With more occurrences of symptoms, the consistency of the adjuvant effects of TAES could be explored in future clinical trials. In addition, the hypothesis of the existence of other antiemetic action pathways of acupuncture could be tested.

On the other hand, we must consider that the antiemetic mechanism of TAES is the same as that of some antiemetic. Duplicating or intensifying the same antiemetic pathway may be ineffective in preventing symptoms of nausea and vomiting, as this could be achieved simply by increasing drug doses. Therefore, it is possible that TAES involves other signaling pathways, but this hypothesis still needs to be confirmed. Our results may be contributing to this possibility, whether the recommended dose in routine cancer care is in fact the best dose established by the evidence described in the literature.

Even though our results were inconclusive due to intergroup variations and small sample size, this clinical trial supports the possibility of using TEAS as an adjuvant therapy for the management of undesirable effects of antineoplastic treatment and brings additional information that reinforces the role of stimulation frequency in the action pathway.

Conclusion

The results were inconclusive and reinforce the need to increase the sample size. However, there is no evidence to exclude the possibility of an antiemetic benefit from the use of TEAS as adjunctive antiemetic therapy. Keeping the proportion of reduction in the incidence of nausea observed in the intervention with LF-TEAS, it is perfectly expected that in studies with larger sample sizes, this finding will indeed be confirmed. The relevance of further studies is centered on the high number of patients undergoing anticancer therapies who may benefit from this therapeutic modality.

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Conflict of interest
The authors have no conflict of interest.

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Authors' contributions
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