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SHORT COMMUNICATION

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Acupuncture and acupressure for the prevention of chemotherapy-induced nausea—a randomised cross-over pilot study

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Abstract *Objective:* To investigate whether a combination of acupuncture and acupressure is effective for reducing chemotherapy-induced nausea and vomiting. *Patients and methods:* In a randomised cross-over trial, 28 patients receiving moderately or highly emetogenic chemotherapy and conventional standard antiemesis were treated for one chemotherapy cycle with a combination of acupuncture and acupressure at point P6 and for one cycle at a close sham point. The main outcome measure was a nausea score derived from daily intensity rating. *Results:* There was no difference between combined acupuncture and acupressure treatment at P6 and at the sham point for the nausea score, but the level of nausea was very low in both phases. The mean nausea score was 6.2 (standard deviation 9.0) for treatment at P6 and 6.3 (9.1) for treatment at the sham point (mean difference −0.1, 95% confidence interval −3.9 to 3.7; p=0.96). Seventeen of 21 participants completing the study would desire acupuncture and acupressure for future chemotherapy cycles, but there was no clear preference for either point. *Conclusion:* In this small pilot study a significant difference between treatment at P6 and a close sham point could not be detected. However, it cannot be ruled out that an existing difference was missed due to the small sample size.

Keywords Nausea · Emesis · Acupuncture · Chemotherapy · Randomised controlled trial

Introduction

Even in the era of 5-HT_3 antagonists, around 35% of patients undergoing moderately to highly emetogenic chemotherapy continue to suffer from vomiting or retching, and less than 60% achieve full protection from nausea by standard antiemetic prophylaxis [11]. Stimulation of the acupuncture point P6 (located on the anterior surface of the forearm, about 3 to 4 cm proximal of the wrist crease between the tendons of musculi. palmaris longus and flexor carpi radialis) by needles or pressure has been shown to be effective for post-operative nausea and vomiting [5]. Positive effects have also been shown for chemotherapy-induced nausea [10]. However, most studies have been performed before 5-HT_3 antagonists were available. We investigated whether a combination of acupuncture and acupressure at P6 is more effective than acupuncture and acupressure at a sham point in patients receiving moderately or highly emetogenic chemotherapy and modern standard antiemetic treatment.

Patients and methods

The study was a randomised cross-over study with patients, oncologists and nursing staff blinded to treatment. Randomisation (sequence generation with the computer program Random, idv, Gauting, Germany) was stratified for emetogenicity of the chemotherapy; block size was 4. Randomisation was concealed with sequentially numbered sealed opaque envelopes. The envelopes were stored centrally by the secretary of the unit. An envelope was accessed and opened only after inclusion and registration of the patient in the study. The study protocol was approved by the local ethics board. All patients gave written informed consent.

Patients were eligible if they fulfilled the following inclusion criteria: scheduled for moderately or highly emetogenic chemotherapy (grades III to V, according to Hesketh et al. [3]); standard antiemesis and additional medication for demand predefined for two chemotherapy cycles; ages between 18 and 75; Karnofsky index >50. Exclusion criteria were: anticipatory nausea or vomiting; chemotherapy within the last 3 months; cerebral metastases; chronic ileus or subileus; lymphedema of arms; knowledge of acupuncture points. Patients were recruited from the departments of hematology and gastroenterology of a large university hospital in Munich, Germany. Originally, a second hospital had planned to participate; however, it had to cancel all study activities due to organisational restructure.

All study participants received standard antiemesis according to the guidelines of the participating departments' specifications (see Table 1), which basically transcribed the recommendations set out in the ASCO guidelines effective during the recruitment period [2]. The same antiemesis was used before and after cross-over; only the rescue medication could vary. In addition, according to random allocation patients received acupuncture at P6 or at a close non-acupuncture point (about 3 to 4 cm proximal to the wrist crease; insertion of the needle under the radius) once before chemotherapy for 20 min. At P6, sterile single-use needles (0.25×25 or 40 mm, Wujang Acupuncture Needle Factory, Jiangsu, China) were inserted vertically to a depth of 0.5 to 1 cm and manipulated until an irradiating sensation, considered relevant for effective acupuncture (de qi), was achieved. In the sham group, needles were inserted to a depth of 0.5 cm without manipulation. Patients were instructed to wear acupressure bands (elastic bands with a plastic button) permanently for 72 h at the same points (at both arms if possible) and for additional 4 days if needed. The combination of acupuncture and acupressure was chosen as a previous study had suggested that acupressure prolongs the effect of acupuncture [1]. For the second chemotherapy cycle, patients who had been treated at P6 were treated at the sham point and vice versa. Both treatments were done by one of two physicians (one Chinese, one German) trained and experienced in acupuncture. To ensure blinding of the oncological staff, the acupuncture band was covered with a mull bandage. Patients had been informed that in the study the effectiveness of treatment at two different points was investigated.

In both study phases, patients were asked to fill in a diary for 7 days (with two ratings on day 1) to document intensity (rating scale 0 to 6), frequency and duration of nausea and vomiting, as well as the use of additional antiemetic medication. On day 7, patients were asked to rate effectiveness and side effects, or impairment by acupuncture/acupressure. In addition, patients were asked to fill in a shortened version of the MANE (Morrow Assessment of Nausea and Vomiting [6]). The oncological staff checked whether the diary was filled in adequately, whether standard antiemesis was performed as planned, and whether adverse events occurred, which were possibly related to acupuncture.

The predefined main outcome measure was the intraindividual difference of the nausea score (sum of intensity ratings for nausea in the diary with a possible range of 0 to 48) between the acupuncture and the sham phase. At the start of the study, it was unclear whether phase or carry-over effects might invalidate a cross-over analysis, and there was insufficient information about the size of group differences to expect. Therefore, the trial was planned as a pilot study and it was initially aimed to recruit 50 patients which would have been sufficient to detect an effect size of 0.5 standard deviation with a power of 80% (alpha=5%, two-sided test).

The study was stopped early due to recruitment problems and the observation that the nausea level was

Table 1 Patient characteristics and interventions (for the 27 patients completing the first study phase)

Female/male	9/18
Age in years (median; minimum–maximum)	57 (17–72)
Cancer	
Stomach	5
Testicles	4
Esophagus	4
Lung	4
Other (max. two patients per cancer type)	10
Previous chemotherapy (with nausea)	5 (3)
Risk factors for emesis[a] none/one/two/three	5/10/9/3
Curative/palliative treatment	5/22
Inpatients/daycare patients	22/5
Emetogenicity according to Hesketh III/IV/V	2/9/16
Antiemesis	
5-HT_3 antagonist	27
Glucocorticoid	26
Prescription of additional medication for demand	26
Other	7

[a]Female, age under 50 years, rarely or no alcohol, previous chemotherapy with nausea

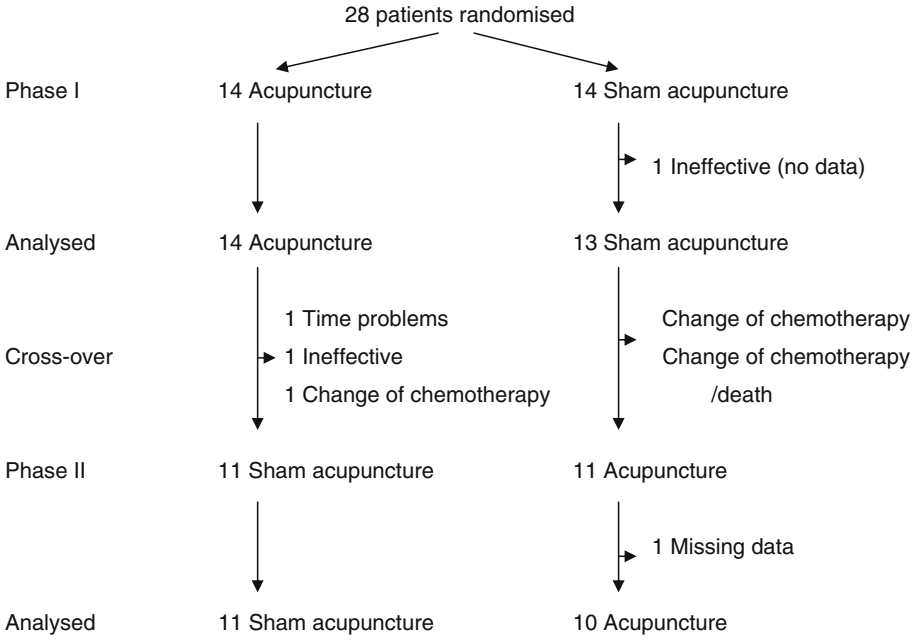

Fig. 1 Trial flow chart

very low in most patients regardless of treatment phase. The poor accrual was mainly due to the fact that most patients on the wards were treated within trials investigating the safety or benefit of experimental antineoplastic drugs, and the pertinent protocols stipulated that patients were not to be included into any other trial that studied specific treatment interventions. After checking for phase or carry-over effects (no significant interaction term between group factor and within-subjects factor) the *t* test for paired samples was used to investigate whether there were significant differences for the predefined main outcome measure. For further exploratory testing (calculating relative risks or mean differences with their respective 95% confidence intervals), data for both phases were pooled.

Results

Between June 2000 and January 2002, a total of 28 patients were randomised (14 to both groups; see Fig. 1). Patient characteristics and information on the treatment are summarised in Table 1 for the 27 patients who completed phase I. Patients suffered from a variety of cancers. Nine patients received chemotherapy with an emetogenicity level IV according to Hesketh et al. [3], 16 with the highest level, level V (mainly used drug cisplatin 50 to 100 mg/m^2). Standard antiemetic treatment consisted of 5-HT$_3$ antagonists, a glucocorticoid and prescription of additional demand medication.

Nausea scores were slightly higher in phase II compared to phase I, regardless of the treatment received. There was

Table 2 Secondary outcome measures (exploratory analysis; all available data for both phases pooled)

	Acupuncture *n*=24	Sham acupuncture *n*=24	Relative risk or mean difference (95% CIs)
No nausea at all	14	12	1.17 (0.69; 1.97)
No vomiting	17	18	0.94 (0.67; 1.33)
Complete control[a]	15	15	1.00 (0.65; 1.55)
Hours with nausea	13.8 (34.7)	9.8 (19.2)	4.0 (−11.1; 19.0)
Number of vomiting episodes	3.3 (8.7)	2.3 (5.8)	1.0 (−2.4; 4.4)
Use of rescue medication	12	12	1.00 (0.65; 1.55)
Acupuncture/acupressure helped a lot	9	5	1.80 (0.71; 4.59)
Preference	5	3	Not applicable

Values for the acupuncture and sham acupuncture group are absolute numbers or means (standard deviations)
[a]No vomiting and a nausea score <9

no difference between combined acupuncture and acupressure treatment at P6 and at the sham point for the nausea score, but the level of nausea was very low in both phases. The mean nausea score was 6.2 (standard deviation 9.0) for treatment at P6 and 6.3 (9.1) for treatment at the sham point (mean difference −0.1, 95% confidence interval −3.9 to 3.7; p=0.96), the median values and ranges were 1 (0 to 37) and 1.5 (0 to 29), respectively. Results for secondary outcome measures are given in Table 2. Seventeen patients did not vomit at all under treatment at P6, compared to 18 patients under sham treatment. With both treatments, half of the patients used additional antiemetics once or more often. Seventeen of 21 participants completing the study would desire acupuncture and acupressure for future chemotherapy cycles, but there was no clear preference for treatment at one of the alternative points.

Adverse effects of the treatment were reported in five cases. One patient suffered a hematoma when wearing the acupressure band at P6. In the sham group, one hematoma was reported after acupuncture, and three adverse effects from the acupressure band (one hematoma, one skin eczema, one skin irritation).

Discussion

In this small pilot cross-over study, patients receiving combined acupuncture and acupressure as antiemetic prophylaxis for moderately or highly emetogenic chemotherapy suffered only moderate breakthrough nausea and vomiting, but it did not matter whether the treatment was performed at the correct acupuncture point (P6) or at a close non-acupuncture point. Our results have to be interpreted with great caution as the small sample size and the low incidence of nausea and vomiting in the sham group might have obscured an existing point-specific effect.

Compared to most other studies of acupuncture and acupressure [8–10], standard antiemesis including 5-HT_3 receptor antagonists with or without dexamethasone used in this study was more intense. Therefore, with the availability and reliable utilisation of vigorous pharmacological antiemetic prophylaxis, our results suggest that the combination of acupuncture and acupressure as used by us provides little or no additional benefit in this situation.

Our study was performed to meet the needs of clinical observations, reporting that a relevant proportion of patients does suffer from significant, especially delayed nausea when receiving highly emetogenic chemotherapy in spite of standard antiemesis. If the current acupuncture protocol contributed to emesis control at all, it might be possible that treatment at the sham point induced a relevant point-unspecific effect, particularly as—following a request of the ethical review board to ensure blinding—patients were not informed of the use of a "sham" point but of a comparison of two "different" points. Another possibility is that we chose our sham point too close to the correct point and that needling at this point was too deep. However, close sham points have been used in positive trials, too [10]. Although the so-called de qi sensation (an irradiating feeling considered by many acupuncturists to indicate effective needling) was not sought for when employing the sham treatment, this was reported by more than half of the patients.

As our study did not include a no-acupuncture control group, we cannot directly assess whether both the sham and the true interventions provided an additional benefit over standard antiemetic prophylaxis. However, we compared our results with those from a cohort study partly performed in the same departments within a similar time period, which measured the incidence of nausea and vomiting under routine conditions [4]. The primary objective of this study had been the assessment of health care resource utilization in patients undergoing highly emetogenic chemotherapy. Incidence of nausea and vomiting were similar in the two studies. This suggests that both the true and the sham intervention in our trial did not significantly improve emesis control at the time points selected in our study. Obviously, such a non-randomised comparison of studies using also slightly different measurement methods is methodically flawed and, therefore, must be interpreted with great caution.

As we completed our protocol, three larger studies were published on acupuncture for chemotherapy-induced nausea and vomiting. Shen et al. [8] reported significantly less vomiting in women receiving myeloablative chemotherapy treated with electro-acupuncture (needle insertion with electrostimulation) at P6 than in women treated at a remote sham point or receiving no acupuncture. Antiemesis in this trial, however, consisted of prochlorperzine, lorazepam and diphenhydramine hydrochloride. Streitberger et al. [9] did not find a difference between needling P6 and a so-called placebo needle (a telescope needle with a blunted tip not penetrating the skin, and fixed by a ring and a plaster) at the same site in patients with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. By far the largest study has been performed by Roscoe et al. [7]. Seven hundred thirty-nine patients about to begin chemotherapy with a regimen containing cisplatin or doxorubicin were randomised to acupressure at P6, transcutaneous electrical nerve stimulation (TENS) at P6 or no treatment at P6. All patients received a 5-HT_3 antiemetic; corticosteriods were allowed. Nausea on the day of treatment was significantly lower in the two treatment groups, but delayed nausea and vomiting did not differ significantly.

In summary, the available evidence on the effectiveness of the stimulation of P6 by needling or pressure for chemotherapy-induced nausea and vomiting is inconclusive. As there is good evidence for effectiveness in postoperative nausea [5, 10], and as at least some of the available studies also show benefits in chemotherapy-induced nausea, further

research is clearly justified. Future studies should include both a sham acupuncture group and a group not receiving acupuncture to quantify potential unspecific effects. Acupressure bands can easily be used in busy oncological wards and might, therefore, be a priority intervention for further research. Experienced acupuncturists will rarely be available. However, any physician can easily learn to needle P6. The high costs of novel antiemetics should be a further motivation to further investigate whether acupuncture and acupressure are effective and efficient additional tools for the prevention and treatment of chemotherapy-induced nausea and vomiting.

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