Effect of Acupuncture Compared with Placebo-Acupuncture at P6 as Additional Antiemetic Prophylaxis in High-Dose Chemotherapy and Autologous Peripheral Blood Stem Cell Transplantation: A Randomized Controlled Single-Blind Trial

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ABSTRACT

Purpose: **The purpose is to investigate an additional antiemetic effect to ondansetron with needle acupuncture at P6 compared with nonskin-penetrating placebo acupuncture in patients undergoing high-dose chemotherapy and autologous peripheral blood stem cell transplantation.**

Experimental Design: **Eighty patients who were admitted to hospital for high-dose chemotherapy and autologous peripheral blood stem cell transplantation were included into a randomized placebo-controlled single-blind trial. The patients were randomized to receive acupuncture ($n = 41$) or noninvasive placebo acupuncture ($n = 39$) at the acupuncture point P6 30 min before first application of high-dose chemotherapy and the day after. All patients received 8 mg ondansetron/day i.v. as basic antiemetic prophylaxis. The main outcome measure was the rate of patients who either had at least one episode of vomiting or required any additional antiemetic drugs on the first 2 days of chemotherapy.**

Results: **The main outcome measure showed no significant difference ($P = 0.82$): 61% failure in the acupuncture group and 64% in the placebo acupuncture group (95% confidence interval of 3% difference: −18.1 and 24.3%). Comparing nausea, episodes of vomiting or retching and number of additionally required antiemetic drugs did not provide any discrepancy with the main result.**

Conclusions: **This study suggests that in combination with ondansetron i.v., invasive needle acupuncture at P6 compared with nonskin-penetrating placebo acupuncture has no additional effect for the prevention of acute nausea and vomiting in high-dose chemotherapy.**

INTRODUCTION

The NIH conference on acupuncture in 1997 came to the conclusion that promising results have emerged showing the efficacy of acupuncture in adult postoperative and chemotherapy-induced nausea and vomiting and in postoperative dental pain (1). The conclusion about nausea and vomiting was based on a review of 33 controlled trials of which 27 showed positive results in favor of acupuncture, electroacupuncture, transcutaneous electrical nerve stimulation or acupressure at the acupuncture point P6 (2).

The methodology, including number of patients, selection of control group, statistical analysis, and the mode of stimulation of the acupuncture point, was very heterogeneous in these studies. For example, sham control (acupuncture at nonacupuncture points) subjects were included in only 7 of 21 controlled trials of treatments for postoperative emesis, 2 of 5 trials of cancer chemotherapy-associated emesis, and 6 of 7 controlled trials of treatments for morning sickness. Most of the other studies had no intervention as control.

All 5 trials about prevention of chemotherapy-associated emesis showed a positive effect of P6 stimulation. Besides severe methodological shortcomings such as small numbers of patients, the use of historical controls, and multiple testing, these trials were mainly not on needle acupuncture. Only in one study, the intervention was needle acupuncture (3), the other studies investigated acupressure (4, 5), transcutaneous electrical nerve stimulation (6), or electroacupuncture (7).

On the basis of the encouraging results of these trials, we conducted a rigorously designed randomized, placebo-controlled, single-blind study with the question: Is there a beneficial effect of acupuncture compared with placebo acupuncture at P6 in addition to 8 mg of ondansetron i.v. to prevent acute emesis in the first 2 days of HDCT[2] before autologous PBSCT?

PATIENTS AND METHODS

Patients. This study was conducted at the Department of Hematology and Oncology, University of Heidelberg. The participants were patients assigned to treatment with HDCT and PBSCT between December 1999 and September 2001. They were informed about the study design, including the use of

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[2] The abbreviations used are: HDCT, high-dose chemotherapy; PBSCT, peripheral blood stem cell transplantation.

penetrating and nonpenetrating needles, and the possible risks of acupuncture treatment (hematoma, infection, and fainting). Patients were included in the study when they fulfilled the inclusion criteria, did not violate the exclusion criteria, and gave their informed consent (Table 1). The study protocol was approved by the Ethics Committee of the University of Heidelberg.

Interventions. According to the diagnosis, the patients were scheduled for different regimen of HDCT, mainly melphalan (Ref. 8; 200 mg/m^2, day 1), but also BEAM [Ref. 9; BCNO (300 mg/m^2), day 1; cytosine Arabinoside (200 mg/m^2) and etoposide (100 mg/m^2), day 2–5; melphalan (140 mg/m^2), day 6], VIC [Ref. 10; ifosphamide (4000 mg/m^2), etoposide (500 mg/m^2), and carboplatin (500 mg/m^2), day 1–3], and interleukin 1β converting enzyme [Ref. 11; ifosphamide (2400 mg/m^2), epirubicin (36 mg/m^2), carboplatin (180 mg/m^2), day 1–5]. None of the chemotherapy regimen included steroids. On the first and second day of HDCT, all patients received once the $5HT_3$ antagonist ondansetron (8 mg i.v.) as antiemetic prophylaxis followed by the randomized intervention, acupuncture or placebo acupuncture, respectively. If patients received Melphalan as single dose HDCT only at the first day, study intervention was performed at the second day without HDCT. From the third day antiemetic prophylaxis was continued with 8 mg of ondansetron three times daily until PBSCT. Any additional antiemetics were given only on request. The first application of ondansetron was given i.v. 1 h before HDCT. Thirty min before HDCT, patients of both groups were prepared for study treatment by marking the acupuncture point P6 (Neiguan) at both forearms with a plastic ring covered by a band aid. The acupuncture point P6 is located on the inside of the forearm, 2 cun (Chinese measure 1 cun ~ 1.5 cm) proximal the midpoint of the transverse crease of the wrist, between the tendon of musculus palmaris longus and musculus flexor carpi radialis.

According to randomization, the acupuncture group received acupuncture at P6 bilaterally through band aid and plastic ring with a 0.25 × 40-mm stainless steel needle (asia med, Munich, Germany) until a deqi sensation occurred. The control group received placebo acupuncture with a blunted, telescopic placebo needle designed by Streitberger (12) and manufactured by asia med. This placebo needle simulates an acupuncture procedure without penetrating the skin (Fig. 1). In both cases, the needle remained for 20 min without additional stimulation. Both interventions were performed by two trained acupuncturists (K. S., M. F-R.).

Chemotherapy, ondansetron, and additionally required antiemetics were given by an independent staff physician, blinded to the acupuncture treatment. Rescue antiemetics were administered subsequently as required, starting with additional ondansetron (8–16 mg), metoclopramide (10 mg), and triflupromazine (5 mg). If necessary also other drugs with antiemetic potency like steroids and benzodiazepines were allowed as indicated by the staff physician.

Objectives. The objective of this study was to compare the antiemetic effect of P6 acupuncture with P6-placebo-acupuncture. The null-hypothesis was: There is no beneficial effect of acupuncture compared with placebo acupuncture, at P6 in addition to 8 mg of ondansetron i.v., to prevent acute emesis in the first two days of HDCT before PBSCT.

Table 1 Inclusion and exclusion criteria

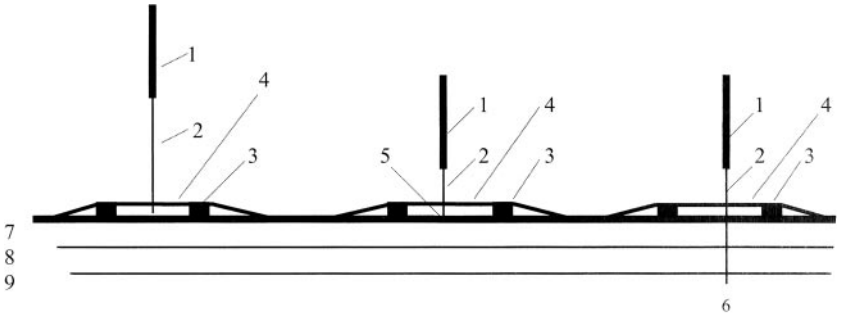
Inclusion criteria
Age ≥18 years.
Patients receiving HDCT and PBSCT.
No acupuncture treatment during the last 6 months.
Written informed consent.
Exclusion criteria
Patients suffering from nausea or vomiting during the past 24 h.
Patients receiving antiemetic drugs during 24 h before chemotherapy (*e.g.*, ondansetron, metoclopramide, dexamethason).
Patients treated with benzodiazepines with the exception for one application at night.
Patients who had already received an antiemetic therapy before the start of chemotherapy with exception of steroids, if these were part of the chemotherapy treatment or a physiological supplement therapy.
Eczematous skin changes at the location of the acupuncture point P6.
Allergy against plaster.
Patients receiving another acupuncture treatment during the same time period.
Start of a therapy with opioids.
Coagulopathy.

Outcome Measurement. Outcome measurement was evaluated by a patients diary on the evening of the first two days and completed by the staff physician, blinded to the acupuncture treatment.

Primary outcome measure was the number of patients who either had at least one episode of vomiting or required any rescue antiemetic drugs on the first day of HDCT and the day after.

Secondary outcome criteria were nausea on a 4-point scale (none = 0, mild = 1, moderate = 2, severe = 3), episodes of vomiting, episodes of retching, additionally required rescue antiemetic drugs, side effects because of acupuncture, subjective opinion whether treatment was helpful and questions concerning the credibility of the therapeutic setting.

Sample Size. Calculation of the sample size for the primary outcome variable was based on a pilot study with 15 patients with multiple myeloma receiving ondansetron and acupuncture before HDCT and PBSCT and on results of a previously published small study (6). On the basis of a failure rate (vomiting and/or additional treatment necessary) of 70% with an antiemetic treatment with ondansetron only a decrease of the failure rate to 50% was judged as clinically relevant. For the detection of this difference (70 *versus* 50%) with a power of 80% a necessary sample size of 100 patients/group was calculated (Fisher's exact test, $\alpha = 0.05$, two-sided). During the course of the study results emerged which resulted in the abolishment of HDCT and PBSCT for patients with breast cancer (13). Therefore, recruitment for our study decreased to an extend which made it unlikely that the calculated sample size could be reached in an acceptable period of time. It was decided to stop recruitment after 80 patients and to perform an interim analysis calculating the conditional power (*i.e.*, the probability of proving superiority of acupuncture after 200 patients given the results of the first 80 patients). In case of unpromising results, *i.e.*, a low conditional power, we decided to terminate



1 needle handle, 2 needle corpus, 3 plastic ring, 4 plaster, 5 blunt tip of the needle, 6 sharp tip of the needle, 7 cutis, 8 subcutis, 9 muscle

Fig. 1 Placebo-needle when touching the skin (*left*) and after retraction of the needle into the handle (*middle*), real acupuncture needle (*right*; Ref. 12).

the study. This decision was determined by an amendment to the study protocol before the number of 80 patients was reached.

Randomization and Blinding. Immediately before treatment the acupuncturist obtained randomization allocation by phone from a member of the Department of Medical Biometry, University of Heidelberg, who had no contact with study patients, thus an adequate concealment was assured. Randomization was stratified by type of chemotherapy (containing or not containing platin) to ensure balance between groups.

Only the acupuncturists knew the randomization profile. The patients and the staff physicians were not informed about the allocation. Blinding of the patients was ensured by using the placebo needle in the same therapeutic setting as acupuncture. The acupuncturists answered questions about acupuncture using an identical answer-catalogue. To assess blinding, questions about the credibility of the treatment according to Vincent (14) were posed to each patient after treatment.

Statistical Methods. Baseline data of the two groups were compared computing descriptive *P*s (*t* test for continuous variables, Fisher's exact test for categorical variables). The analysis of the primary outcome variable was carried out using Fisher's exact test ($\alpha = 0.05$, two sided). Secondary outcome variables were analyzed in the form of a descriptive comparison using adequate methods (Fisher's exact test for categorical variables).

According to the intention-to-treat-principle all patients were included in the analysis. Patients who discontinued the treatment were assessed too. If assessment was not possible the patient was to be counted as a therapeutic failure.

RESULTS

Baseline Characteristics and Participants. Of 220 patients receiving HDCT and PBSCT between December 1999 and September 2001, 50 were outpatients, 40 took part in other clinical trials and 50 either did not fulfil the inclusion criteria or did not consent to participation. Of the 80 randomized patients 41 patients were assigned to the acupuncture treatment group, 39 to the control group (Fig. 2). Baseline characteristics revealed no relevant differences between the two groups (Table 2). The study was strictly conducted according to the protocol. All patients received the treatment allocated at randomization.

Outcomes. No patient discontinued the study and outcome criteria were assessed in each patient. The primary outcome variable showed no significant difference between the two groups (Table 3). Failure rate (emetic episodes and/or additional antiemetic medication on days 1 and/or 2) was 61% (25 of 41 patients) in the acupuncture group and 64% (25 of 39 patients) in the control group ($P = 0.82$; Fisher's exact test) with a minimal difference of 3%; 95% CI, −18 and 24%.

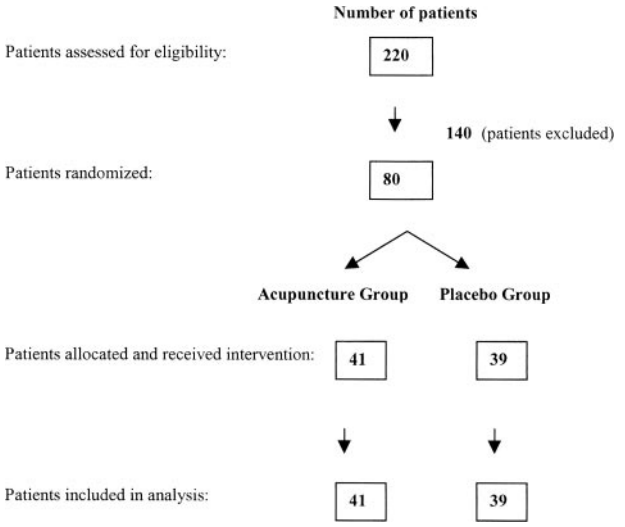


Fig. 2 Patient's flow chart.

Given the results of the first 80 patients, the conditional power under the optimistic assumptions of the alternative hypothesis was 40%. Therefore, it was not likely to see a change in the results if the study was continued to a total number of 200 patients. Analysis of secondary outcome measures confirmed these results (Table 4). Regarding the occurrence of nausea, the acupuncture group showed even a higher incidence (83%) compared with the placebo group (67%). The study was therefore stopped at a total number of 80 patients.

The credibility assessment of the therapeutic setting showed no significant differences between the two groups (Table 4). There was no difference in the subjective question whether acupuncture had helped. No acupuncture-specific adverse events or side effects occurred in either groups.

Table 2 Baseline demographic and clinical characteristics

Characteristics	Acupuncture group (n = 41)	Placebo group (n = 39)	P
Age in years	54,9 (SD 9,0; R[a], 29–69)	53,3 (SD 9,3; R, 20–67)	
Sex			0.66
Male	20 (49%)	21 (54%)	
Female	21 (51%)	18 (46%)	
Diagnose			0.39
Multiple myeloma	28 (68%)	25 (63%)	
Breast cancer	6 (15%)	5 (13%)	
Non-Hodgkin lymphoma	7 (17%)	5 (13%)	
Amyloidosis	0 (0%)	3 (8%)	
Hodgkin lymphoma	0 (0%)	1 (3%)	
Chemotherapy			0.85
Melphalan (200 mg/m^2)	28 (68%)	28 (71%)	
BEAM	7 (17%)	4 (10%)	
VIC	1 (3%)	2 (5%)	
Interleukin 1β converting enzyme	3 (7%)	2 (5%)	
Others	2 (5%)	3 (9%)	
Prior chemotherapy			
Conventional	40 (98%)	38 (97%)	1.0
Mobilization	41 (100%)	39 (100%)	
High dose	8 (20%)	7 (18%)	1.0
Nausea in prior chemotherapy			0.24
None	15 (37%)	10 (26%)	
Mild	11 (27%)	17 (43%)	
Moderate	10 (24%)	5 (13%)	
Severe	5 (12%)	7 (18%)	
Vomiting in prior chemotherapy	14 (34%)	18 (46%)	0.36
Other diseases			
None	21 (68%)	19 (49%)	
Gastrointestinal	3 (7%)	1 (3%)	
Central nervous system/Ear Nose Throat	2 (5%)	1 (3%)	
Tumor	0 (0%)	2 (5%)	
Metabolic	1 (2%)	1 (3%)	
Hypotension	4 (10%)	3 (8%)	
Migraine	2 (5%)	1 (3%)	
Others	13 (32%)	16 (41%)	
Medication			
None	20 (49%)	15 (39%)	
Blood pressure	9 (22%)	9 (23%)	
Pain	5 (12%)	5 (13%)	
Other	13 (32%)	18 (46%)	
Experience with acupuncture			0.13
None	27 (65%)	33 (85%)	
Yes, positive	6 (15%)	4 (10%)	
Yes, no effect	8 (20%)	2 (5%)	
Positive attitude toward acupuncture	35 (85%)	35 (90%)	0.74

[a] R, range; BEAM, BCNO (=Carmustin), Etoposide, cytosine Arabinoside (=cytarabin) and Melphalan; VIC, VP16 (=etoposide), Ifosphamide and Carboplatin.

Table 3 Primary outcome measures in absolute numbers (%)

Categories	Acupuncture group (n = 41)	Placebo group (n = 39)	Difference 95% CI
At least one episode of vomiting or additional antiemetic drugs required on days 1 and 2	25 (61%)	25 (64%)	3% (95% CI, 18%, 24%)

DISCUSSION

Previous studies of P6 stimulation in the prevention of nausea and vomiting because of chemotherapy (2, 15) showed significant results, but most of these studies had some methodological shortcomings. Our study is the first published randomized controlled study in this field with nonsignificant results leading to the conclusion that there is no beneficial effect of invasive acupuncture at P6 in addition to 8 mg of ondansetron for the prophylaxis of acute nausea and vomiting in HDCT and PBSCT.

Table 4 Secondary outcome measures (number of patients, Fisher's exact test)

	Day 1			Day 2			Day 1 and 2		
	Ac (n = 41)	PI (n = 39)	P	Ac (n = 41)	PI (n = 39)	P	Ac (n = 41)	PI (n = 39)	P
Nausea			0.19			0.54			0.12
None	23	26		8	13		7	13	
Mild	13	5		14	10				
Moderate	3	6		13	12				
Severe	2	2		6	4				
Vomiting			0.52			0.66			0.82
None	37	32		20	20		19	20	
Once	3	5		6	8				
More than once	1	2		15	11				
Retching			0.49			0.38			0.21
None	39	38		28	31		27	31	
Once	2	0		6	2				
More than once	0	1		7	6				
Additional antiemetics			0.85			0.75			1.0
None	32	31		21	20		21	20	
Once	3	4		5	7				
More than once	6	4		15	12				
Adverse effects	0	0		0	0		0	0	
Credibility assessment (12)									
Received intervention:									
Was helpful	21	18	0.66	18	18	1.0	18	16	0.82
Is further recommended	26	28	0.48	26	28	0.48	26	27	0.64
Seems to be logical	29	30	0.62	28	30	0.46	28	30	0.46
Effective in other diseases	30	29	1.0	30	28	1.0	30	28	1.0

[a] Ac, acupuncture; Pl, placebo.

This study concentrates on one specific question in acupuncture research: Is it necessary to penetrate the skin for effective stimulation of an acupuncture point? The answer to this question may be different at different acupuncture points and in different conditions. It is not known exactly which are the therapeutic effective elements of acupuncture therapy (*e.g.*, correct choice and exact location of the acupuncture point, mode of stimulation, and psychological influences). This leads to much confusion in the definition of acupuncture. We suggest a definition strictly according to the translation of the Latin term acupuncture, which means to penetrate (pungere) the skin with a needle (acus). All other stimulation techniques than pure needle stimulation should be termed differently like acupressure, electroacupuncture, transcutaneous nerve stimulation, and so forth.

To investigate the specific effects of acupuncture, we designed a nonskin-penetrating placebo needle, which simulates penetration of the skin (12). A previous study using the placebo needle showed the importance of the needling effect of acupuncture in shoulder pain (16), but in P6 stimulation for prevention of nausea and vomiting in chemotherapy it may be different. According to our definition of acupuncture, we decided to define skin penetrating acupuncture at P6 as verum acupuncture and the nonskin-penetrating procedure at P6 as placebo acupuncture.

Placing the placebo needle in the same manner and at the same location as the acupuncture needle, it was possible to ensure the blinding of the patients. The credibility assessment according to Vincent (14) did not reveal differences between the groups. Therefore, we concluded that blinding was successful. Blinding of the acupuncturists still is not possible using this placebo method (17). However, the negative result did not indicate preferential influence of the acupuncturist to the verum group.

The main reason to perform the interim analysis was decreasing patient recruitment because of abolishment of HDCT and PBSCT for patients with breast cancer. Additionally, ward nurses noticed that study patients seemed to complain more about nausea and vomiting than patients who did not participate in the study and received 8 mg of ondansetron three times daily without acupuncture. Therefore, it was necessary to investigate whether it was worth continuing the study. Performing an interim analysis after 80 patients reduced the overall power of our study from 80 to 75% under the original planning assumptions (200 patients, reduction from 70 to 50%). To reach the same power with this group sequential design as with our original design without an interim analysis, the total number of patients would have to be increased by ~10%. Calculating the conditional power for the increased sample size led to the same decisions as reported above. Even under optimistic assumptions about the future course of the study, it was unlikely to show superiority of acupuncture treatment. We are well aware that the reduced sample size of 80 patients results in a power of only 36% under our original assumptions of a clinically relevant reduction from 70 to 50%. Therefore, the main limitation for the interpretation of the results is the reduced sample size. However, the low probability to detect a clinically relevant difference in the main outcome criteria and the even higher rate of nausea in the acupuncture group (83%) compared with placebo (67%)

in the analysis of secondary outcome criteria did not justify to continue the study.

$5HT_3$ antagonists represent the most effective antiemetic drugs preventing nausea and vomiting in HDCT (18, 19). It is rather unlikely that acupuncture has the same antiemetic potential as $5HT_3$ antagonists. Because of the highly emetic potency of HDCT, it was considered unethical to withhold a $5HT_3$ antagonist such as ondansetron as an effective standard prophylaxis. Therefore, all patients received the recommended dose of 8 mg ondansetron/day (20) to investigate whether acupuncture had an additional effect. To avoid interference of acupuncture effects with steroids, those were not considered as part of the antiemetic therapy. It was considered that an antiemetic effect of acupuncture might be partly because of increased serum cortisone level (21, 22).

The only methodologically rigorous study of antiemetic acupuncture effects in chemotherapy compared electroacupuncture at P6 in combination with the acupuncture point ST36 with sham electroacupuncture and no needling (15). Because of different interventions, different basic pharmacological antiemetic regimen, and less rigorous outcome criteria, the positive result of this study is not comparable with the negative result of our study. Electroacupuncture may be effective in addition to weaker antiemetics than ondansetron. It might be worth to evaluate in future trials whether there is any additional effect of electroacupuncture in combination with $5HT_3$ antagonists. In our study, the stimulation of P6 might have been to weak to enhance the antiemetic effect of ondansetron. However, the question of the adequate form of stimulation is not clarified yet. Also, acupressure with sea bands might have an antiemetic effect in chemotherapy as shown in two small studies (4, 5). Large methodologically well-conducted trials are needed to prove these results. In our study, the minimal stimulation of the skin by the blunted tip of the placebo needle may have led to a small acupressure effect at P6. In this case there would be no additional effect of acupuncture compared with minimal acupressure. Stimulating P6 with minimal acupressure may be as effective as acupuncture. Applying the placebo needle at acupuncture points, only controls for the specific effect of needle insertion. An effect may be attributable to stimulation at the specific location regardless of the kind of stimulation. A new approach for future studies would be to avoid acupuncture point specific acupressure effects and apply the placebo needle at nonacupuncture points.

In conclusion, in combination with ondansetron acupuncture at P6 showed no beneficial effect compared with placebo acupuncture at the same location to prevent acute emesis in the first 2 days of HDCT before PBSCT. The interpretation of the results are limited because of the reduced sample size of the interim analysis of 80 patients. Feasibility reasons, low conditional power, and a high incidence of nausea did not justify to continue the study.

Even if there is an antiemetic effect of acupuncture in HDCT, it is probably much less than the proposed clinically relevant reduction of 20% in our main outcome criteria. Besides increasing sample size, future trials should also consider to enhance acupuncture effects by electrical stimulation or the combination of P6 with other acupuncture points. However, in the presence of $5HT_3$ antagonists, it will be a challenge to show an antiemetic effect of acupuncture which justifies to recommend it routinely as antiemetic prophylaxis in HDCT.

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