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Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology

Interim results of a multicenter crossover study

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Abstract *Goals:* In this multicenter crossover study, our aim was to evaluate the efficacy and acceptance of acupuncture as a supportive antiemetic approach during highly emetogenic chemotherapy in pediatric oncology. *Patients and methods:* Eleven children receiving several courses of highly emetogenic chemotherapy for treatment of solid tumors were included. Randomization allocated patients to start chemotherapy either with antiemetic medication plus acupuncture or antiemetic medication alone. During all study courses, patients continued to receive their programmed and additional antiemetic

medication as needed. Acupuncture was given at day 1 of chemotherapy and at subsequent days on patient's demand. The amount of baseline and additional antiemetic medication during chemotherapy was documented. Patients maintained a daily diary of vomiting episodes and completed an evaluated nausea score at the end of every course. Their body weight was taken before and after a chemotherapy course. *Main results:* Twenty-two courses with or without acupuncture were compared. The benefits of acupuncture in adolescents with respect to the reduction of additional antiemetic medication were observed. Acupuncture enabled patients to experience higher levels of alertness during chemotherapy and reduced nausea and vomiting. Except for needle pain, no side effects were noted. Patient's acceptance of acupuncture was high. *Conclusion:* Our data indicate that acupuncture might reduce antiemetic medication and episodes of vomiting in pediatric oncology.

Keywords Acupuncture · Pediatric oncology · Supportive care · Nausea and vomiting

Introduction

Nausea and vomiting, loss of appetite, and decreased intestinal motility are among the most prevalent chemotherapy-

induced side effects in pediatric oncology that significantly reduce the quality of life during cancer therapy. Modern concepts of antiemetic medication include serotonin (5-HT₃) antagonists, glucocorticosteroids, and phenothia-

zines. Combinations of these drugs show warranted effectiveness but cause considerable side effects such as drowsiness and mood disturbances. Furthermore, glucocorticosteroids may interfere with antitumoral effects of chemotherapeutic agents [6]. Acupuncture as part of traditional Chinese medicine (TCM) is used as a non-pharmacological supportive therapy element in adult and pediatric oncology [5]. Studies have shown that use of acupuncture in adult patients with cancer resulted in significant improvement in chemotherapy-induced nausea and vomiting. In a crossover study that included a large group of patients ($n=130$), Dundee et al. showed that acupuncture of the point Pericardium 6 (Neiguan) plus antiemetic medication produced superior effects than antiemetic medication plus sham acupuncture or antiemetic medication alone [4]. Later, Aglietti et al. confirmed these findings [1]. Shen et al. demonstrated that acupuncture with electrical stimulation of the applied needles plus antiemetic medication resulted in significantly fewer episodes of nausea than antiemetic medication alone [11]. However, in pediatric oncology no corresponding publications exist so far. Trials on acupuncture and acupressure in children for postoperative antiemesis after tonsillectomy and strabismus correction showed no significant improvement [7, 10, 12, 14, 15]. In the USA, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) strongly support further research on the use and effectiveness of acupuncture [8].

A pilot study on acupuncture during chemotherapy at the Pediatric Oncology Department of the Charité, Berlin, included seven patients (unpublished data). Median age was 14 years (range 2.0–17.5) and male to female ratio was 1:1.3. In this study, we observed that acupuncture was feasible and acceptable in children with cancer. Periods of vomiting were reduced and acupuncture had a comforting and relaxing effect as shown by induction of sleep and heartbeat normalization. Thus, we conducted a multicenter crossover study to evaluate the effects of acupuncture in combination with antiemetic medication during chemotherapy compared with antiemetic medication alone. In this study, we tested whether acupuncture reduces the need for baseline and additional antiemetic medication and periods of vomiting. Furthermore, we were interested in obtaining patients' personal acceptance of acupuncture using short essays in an unlimited open form.

Patients and methods

Study design and data collection

This was a randomized, multicenter, and prospective crossover trial approved by the ethics committees of all participating centers. According to power calculation, 35 patients were required for the study. After inclusion of 11 patients, an interim analysis was performed and results of

the data were presented, as the study had been going on for more than 2 years and yet we were not able to accrue a sufficient number of patients for testing the hypothesis with the required power. The data of the pilot study did not contribute to the results of the main study.

As the primary objective of the study, i.e., reduction of the need of antiemetic medication by use of acupuncture, documentation included daily amounts of antiemetic drugs and doses. These were the baseline antiemetic medications [serotonin (5-HT₃) antagonists] and additional antiemetic medications (dexamethasone, phenothiazines). Furthermore, daily episodes of vomiting, anticipatory vomiting, and weight loss during a chemotherapy course were documented. The acupuncture procedure was documented by the acupuncturist. In addition, patients were asked to report on an evaluated subjective nausea score concerning sensations of nausea, vomiting, and appetite [2]. At the end of the study, patients were asked to document their subjective experience of acupuncture.

Patients and eligibility

Patients aged between 6 and 18 years who received several courses of highly emetogenic chemotherapy as part of therapy protocols for Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma, including 5-HT₃ antagonists as basic antiemetic medication, were eligible to participate in this study. Patients were recruited in four German pediatric oncology centers. Written informed consent was obtained from the patients and their parents.

Antiemetic therapy

On days of chemotherapy, standard antiemetic therapy consisted of daily doses of 5-HT₃ antagonists as recommended in the respective chemotherapy protocols. Antiemetic prophylaxis contained either i.v. ondansetron (5 mg/m² twice a day) or i.v. tropisetron (0.2 mg/kg once a day). Additional antiemetic medication consisted of i.v. dexamethasone and/or i.v. phenothiazines.

Acupuncture

Simple centrally performed randomization allocated patients to start chemotherapy either with antiemetic medication plus acupuncture or antiemetic medication alone. Randomization decision was given by phone. Experienced acupuncturists offered needle acupuncture and, alternatively, laser acupuncture for the few patients who felt pain from needling. Acupuncture was applied on day 1, preferably before starting systemic chemotherapy, and was offered at consecutive days of the chemotherapy course. Needles were placed uni- or bilaterally for about 20 min

Table 1 Baseline data of patients participating in the study

Patient no.	Sex	Age (years)	Study center ^a	Tumor entity	Therapy protocol ^b	Length of a course (days) ^c	Acupuncture	5-HT ₃ antagonist (mg/day)	Dexamethasone (mg/day)	Phenothiazine (mg/day)	Phenothiazine (mg/day)	Vomiting (times/day)	Weight loss (kg/course)
1	F	10.0	4	ES	VIDE	5	0	4.0	0.0	20.4	0.49	1.00	1.3
2	F	11.5	4	ES	VIDE	5	1	4.0	0.0	0.0	0.00	0.60	2.2
3	F	12.0	1	RMS	I2VA	4	1	5.0	0.0	24.8	0.71	0.20	0.8
4	F	14.9	1	OS	IP	5	0	10.0	4.0	10.0	0.23	1.50	0.4
5	F	15.0	1	RMS	I2VA	4	1	22.4	17.6	12.4	0.24	2.80	2.0
6	M	15.2	3	ES	VIDE	5	0	4.0	2.0	31.0	0.42	0.75	0.5
7	M	15.3	3	US	I2VAd	4	0	12.0	6.0	28.0	0.37	1.25	2.0
8	F	15.7	3	ES	VIDE	5	0	14.4	4.0	0.0	0.00	0.60	2.4
9	M	16.3	1	RMS	I2VA	4	1	19.2	4.0	24.8	0.38	0.60	0.8
10	F	16.8	3	ES	VIDE	5	0	40.0	3.0	31.0	0.59	1.50	3.0
11	M	16.8	2	SS	I2VA	4	1	14.0	0.0	15.5	0.32	1.25	1.1
							0	20.8	4.0	43.4	0.80	2.00	1.3
							1	14.4	4.0	0.0	0.00	0.80	0.8
							0	16.0	8.0	31.0	0.49	0.00	1.8
							1	13.0	2.0	31.0	0.48	1.75	1.3
							0	19.2	4.0	72.4	1.30	2.00	1.2
							1	20.8	4.0	37.2	0.66	1.80	1.1
							0	14.0	0.0	15.0	0.22	1.25	0.0
							1	10.0	0.0	0.0	0.00	1.25	0.9

ES Ewing's sarcoma, RMS rhabdomyosarcoma, OS osteosarcoma, US undifferentiated sarcoma, SS synovial sarcoma

^aStudy centers: Berlin (1), Bonn (2), Erlangen (3), Hannover (4)

^bCumulative doses of chemotherapy: VIDE: vincristine 1.5 mg/m², ifosfamide 9,000 mg/m², doxorubicin 60 mg/m², etoposide 450 mg/m², I2VA: vincristine 1.5 mg/m², ifosfamide 6,000 mg/m², actinomycin D 1.5 mg/m², I2VAd: vincristine 1.5 mg/m², ifosfamide 6,000 mg/m², adriamycin 80 mg/m², IP: ifosfamide 6,000 mg/m², cisplatin 120 mg/m²

^cThe length of a study course includes days of i.v. fluid therapy post chemotherapy

including needle stimulation. Acupuncture was then given on a course-alternating base for the first two study courses and additionally in the third course (not evaluated). After three courses, patients could decide whether to continue acupuncture. The needle type and a catalog of TCM reflex body points were given. Point combinations depended on the acupuncturist's decision. Auxiliary points were documented. In concordance with all acupuncturists, we did not use sham acupuncture. TCM diagnosis preceding acupuncture was desirable but not necessary.

Statistical analysis

The average amount of 5-HT₃ antagonists per day, the average amount of dexamethasone and phenothiazines given as additional antiemetic medication per day, the average number of episodes of vomiting per day, and the single items of the nausea score were compared. For statistical evaluation, the Wilcoxon test was used with $p < 0.05$ indicating significant differences.

Results

Between September 2001 and August 2003, 47 patients fulfilled the eligibility criteria. Of the 47 patients, 22 were primarily not willing to participate and read patient's information on the protocol. In 11 patients, we were not able to provide acupuncture at the suitable moment. Of the remaining 14 patients who were interested in participation, 11 definitely agreed to participate. Median age was 15.2 years (range 10.0–16.8). Of the 11 patients, 2 discontinued due to death from progressive disease after two study courses (patient 4) or cessation of chemotherapy after three study courses (patient 7), and 1 was lost to follow-up after two study courses (patient 2). In 3 other patients, reasons for discontinuation were pain from needling in 1 patient (patient 9) and rejection of additional procedures during chemotherapy in 2 patients (patients 3 and 11). Five patients (patients 1, 5, 6, 8, and 10) proceeded with acupuncture after three study courses; 4 of them, aged between 15 and 16.8 years, decided to add acupuncture to every further course of chemotherapy. In their short essays, personal reasons for continuation were reduced chemotherapy-related side effects (nausea, vomiting, peripheral paraesthesia, shivering) and higher levels of mental alertness when treated with acupuncture. Demographic and clinical baseline data of patients as well as length and contents of chemotherapy courses are summarized in Table 1.

Whereas the amount of baseline antiemetic medication was statistically not significantly different ($p = 0.074$) between a patient's first course with and his first course without acupuncture, additional antiemetic medication was reduced in courses with acupuncture ($p = 0.024$). Episodes

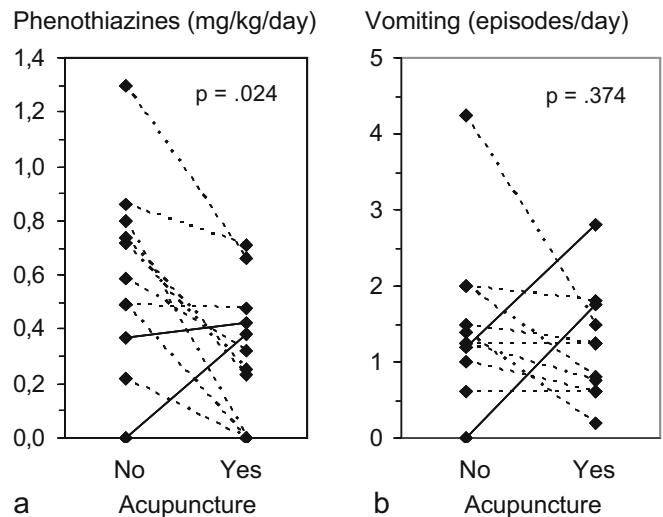


Fig. 1 Comparison between a patient's first course with and without acupuncture with respect to the use of phenothiazines (a) and the average number of episodes of vomiting per day (b). *Solid lines* indicate increase, *dashed lines* decrease or equality

of vomiting were not significantly different ($p = 0.374$) with and without acupuncture (Fig. 1).

Side effects of acupuncture were noted in only one patient who felt pain from needling. Weight loss during chemotherapy was comparable in courses with and without acupuncture. Nausea scores of patients were not significantly different between courses ($p > 0.10$, each item).

Most commonly used points were Pericardium 6 (Pc 6 or Neiguan; located 2 cun, twice the width of an individual's thumb, proximal to the distal wrist crease, between the tendons of the M. palmaris longus and M. flexor carpi radialis), Stomach 36 (ST 36 or Zusanli; located 3 cun below the inferior border of the patella, one finger breadth lateral to the anterior crest of the tibia), Conception Vessel 12 (CV 12 or Zhongwan; located on the midline, 4 cun superior to the umbilicus), and Large Intestines 4 (LI 4 or Hegu; located on the dorsum of the hand, approximately at the midpoint of the second metacarpal bone, in the belly of the first interosseus dorsalis muscle).

Discussion

First results of our small study sample demonstrate that acupuncture is principally feasible in pediatric oncology patients. It seems to be especially applicable in adolescents. Although we were not able to demonstrate the potency of acupuncture to significantly reduce the amount of baseline antiemetic medication, our results indicate that the amount of additional antiemetic medication (phenothiazines) to prevent episodes of cancer chemotherapy-induced vomiting may be reduced by the use of acupuncture. Since baseline medication is given in a standardized manner in all centers, differences in the need for these medicaments in

courses with and without acupuncture were not detectable. Furthermore, in case of persisting nausea and vomiting despite antiemetic prophylaxis, additional antiemetic medication is used rather than increasing the dose of 5-HT₃ antagonists. Interestingly, patients reported no significant differences in the subjective nausea scores despite reduced amounts of daily additional antiemetic medication in courses with acupuncture. The lower average amount of phenothiazines used may in part have contributed to patients' sensation of higher mental alertness when treated with acupuncture. Consequently, nausea and loss of appetite may have been more consciously perceived. Due to our small sample size, the study could not prove a significant, acupuncture-triggered reduction of chemotherapy-induced nausea and vomiting. In contrast to some studies in adults, we did not use sham acupuncture. Whether sham acupuncture is an "inactive control" in clinical trials remains controversial in literature. Some publications point to the possibility of blinding of patients by sham acupuncture, whereas others argue that placebo control cannot exist in needle acupuncture because of its ubiquitous effects upon the circulation of internal energy Qi independently of a specific point [9, 13]. In accordance with the practicing acupuncturists of our study and due to the impracticability of sham procedures in pediatric oncology, we decided not to use sham acupuncture.

In studies on adults, the most effective point was Pericardium 6 (Neiguan). Interestingly, only few studies evaluated other points, e.g., Stomach 36 (Zusanli) [3]. Our study allowed the TCM physicians to tailor the acupuncture to the current, individual need and may therefore be close to the original TCM approach. Thereby, we did not examine

acupuncture of defined points but the procedure as such. Nevertheless, the reduction of episodes of vomiting and consumption of antiemetic medication (phenothiazines) was not as strong as observed in the studies using acupuncture in adult oncology patients. This may be attributable to the shorter duration of chemotherapy in adults. Another cause may be that the very potent 5-HT₃ antagonists were not used in the adult studies, allowing an overt difference between patients receiving acupuncture or not.

With regard to our small sample size despite a multicenter setting, we learned that the psychologically complex situation after diagnosis of a malignant disease in children may lead to rejection of additional, non-pharmacological procedures like acupuncture. Furthermore, we experienced the difficulties of how to put into service a new therapeutic approach within an established medical system. Although there was an interest in the procedure from patients and their parents, acupuncture was logistically not always available. As a consequence, eligible patients were not able to participate in the study. With regard to further studies, we therefore emphasize the necessity of established conditions of acupuncture in participating clinics.

To conclude, we consider that our results are encouraging. Further studies with higher numbers of patients need to corroborate these findings and will prove which patients profit the most.

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