

Original Article

Manual Acupuncture Reduces Hyperemesis Gravidarum: A Placebo-Controlled, Randomized, Single-Blind, Crossover Study

Christer P.O. Carlsson, MD, Pia Axemo, MD, PhD, Anita Bodin, RN, Hanne Carstensen, MD, Birgitta Ehrenroth, RN, Ingalill Madegård-Lind, RN, and Christina Navander, RN

Physical Medicine Unit (C.P.O.C.), Department of Rehabilitation, University Hospital, Lund; and Department of Women's and Children's Health (P.A., A.B., H.C., B.E., I.M.-L., C.N.), Section for Obstetrics and Gynaecology, University Hospital, Uppsala, Sweden

Abstract

Hyperemesis gravidarum, severe vomiting, develops in about 1–2% of all pregnancies. Acupuncture on the point PC6 above the wrist on the palmar side has been found to prevent some types of nausea and vomiting. The purpose of the present study was to see if acupuncture, in addition to standard treatment, could hasten the improvement of hyperemesis gravidarum. Thirty-three women with hyperemesis were evaluated in a randomized, single-blind, crossover comparison of two methods of acupuncture, active (deep) PC6 acupuncture or placebo (superficial) acupuncture. The women estimated their degree of nausea on a visual analogue scale (VAS). The daily number of emesis episodes were documented. Crossover analyses showed that there was a significantly faster reduction of nausea VAS and more women who stopped vomiting after active acupuncture than after placebo acupuncture. This study suggests that active PC6 acupuncture, in combination with standard treatment, could make women with hyperemesis gravidarum better faster than placebo acupuncture. J Pain Symptom Manage 2000;20:273–279. © U.S. Cancer Pain Relief Committee, 2000.

Key Words

Acupuncture, hyperemesis gravidarum, nausea, vomiting, placebo-controlled randomized study

Introduction

Nausea and vomiting are experienced by 50–80% of all women in early pregnancy.^{1,2} Of these 1–2% develop hyperemesis gravidarum with severe vomiting. The result can be weight loss, de-

hydration, and ketonemia. This can lead to hospitalization and the need for nutritional support.³ The pathogenesis of hyperemesis is not fully understood. Some claim that hormonal factors are responsible^{1,4} whereas others emphasize altered gastrointestinal function or psychosomatic factors.^{5,6} Methods used to control hyperemesis gravidarum include drugs (such as antihistamines), parenteral nutrition,⁷ multivitamin supplements,⁸ corticosteroids,⁹ or psychotherapy in combination with medical treatment.

Address reprint requests to: Christer Carlsson, MD, Physical Medicine Unit, Department of Rehabilitation, University Hospital, S-221 85 Lund, Sweden.

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As originally suggested in traditional Chinese medicine, acupuncture and topical mechanical stimulation (acupressure) at a specific acupuncture point (PC6), approximately 5 cm proximal to the wrist crease on the volar aspect of the forearm, have been found to reduce postoperative nausea provoked by opioids.^{10,11} The same stimulation has been claimed to prevent cisplatin-associated vomiting^{12,13} and to reduce morning sickness.¹⁴⁻¹⁶ As pregnancy sometimes is regarded as a relative contraindication to acupuncture (because of old Chinese proposals of an increased frequency of abortion), its use under such circumstances has been limited in western countries.¹⁷ Thus, only acupressure has been used for morning sickness. However, in a report of 242 pregnant women treated with acupuncture for different conditions during pregnancy, there was no report of major side effects.¹⁸ As acupuncture seems to be more effective than acupressure,¹⁹ we decided to perform a randomized, single-blind, placebo-controlled, crossover study to see if manual acupuncture on PC6 could facilitate the improvement of hospitalized women with hyperemesis gravidarum.

Methods

Patients

The study was performed at the University Hospital, Department of Obstetrics and Gynaecology in Uppsala, Sweden. This clinic admits approximately 50 women due to hyperemesis gravidarum yearly. The standard therapy is parenteral nutrition (glucose 5%), antiemetics, and bedrest for a couple of days. Consecutively

admitted women suffering from hyperemesis gravidarum and not responding to conventional outpatient treatment were offered participation in the study. The inclusion criteria were that they were otherwise healthy and mastered the Swedish language. No medication was allowed during the study period. The study period was from September 1995 to August 1997.

Randomization

Fifty papers with "A" or "B", 25 of each, were put in envelopes. The envelopes were sealed and randomly numbered from 1 to 50. When a new patient was accepted for the study the midwife in charge took the envelope with the smallest number in order, opened it, and on the basis of the code "A" or "B," decided to what group the woman was allocated. Thus, there was no way the midwife could possibly influence the randomization.

Study Design

The study was undertaken during 8 consecutive days for each patient. During day 0 (at admission), only baseline registrations were made. On days 1 and 2, as well as days 5 and 6, the acupuncture treatments were given. No acupuncture was performed on days 3 and 4, regarded as a "wash-out-period." On day 7 (at discharge), the evaluations were terminated. Group A first received the active acupuncture, whereas Group B started with the placebo acupuncture (see below). After the "wash-out" period the treatments for the groups were switched (Figure 1). During the study, the women received parenteral nutrition with 5% glucose.

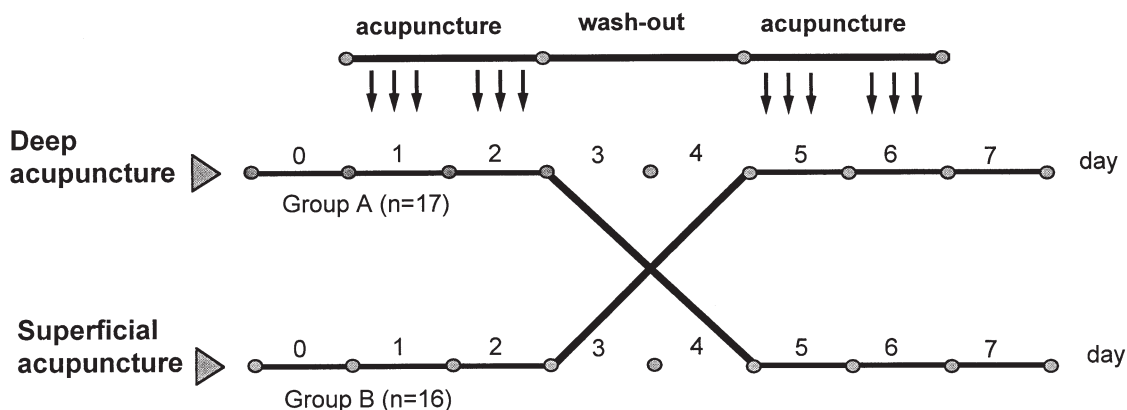


Fig. 1. Flow chart of study design.

Outcome Measurements

Every study day, the women estimated their degree of nausea on a visual analogue scale (VAS), on which 0 meant “no nausea at all” and 10 “worst possible nausea.” They did this by themselves 1 hour after the last acupuncture treatment of the day, or at the same time on the days that acupuncture was not performed, without any midwife present. However, on day 7 the scoring was done with a doctor present, before the woman left the hospital. This doctor did not know to what group the woman belonged. Instances of vomiting and intake of meals were documented by the patient. The ward staff documented the amount of intravenous fluid every day.

Acupuncture

The acupuncture treatments were given three times daily on treatment days. Each treatment lasted for 30 minutes. Specially trained midwives who did not interact with the patients concerning the type of acupuncture method used performed the treatments. These midwives did not belong to the ward staff. Two methods of acupuncture were used: (1) active, deep (“de-qi”) acupuncture, in which a needle was inserted approximately 5 cm above the wrist crease on both forearms. The traditional acupuncture point PC6 is located between the tendons of the palmaris longus and flexor carpi radialis muscles at a depth just above the median nerve. A tingling sensation (“deqi”) radiating to the hand and/or fingers was searched for when inserting the needles and again each 10 minutes of treatment; and (2) placebo (superficial) acupuncture, in which a needle was inserted 10 cm from the wrist on the thumb side of both forearms. The needle was just inserted 1–2 mm in the skin, intracutaneously or superficially subcutaneously. No “de-qi” sensation was searched but the needles were twisted a little every 10 minutes of treatment.

Ethics

The Ethical Committee at the University of Uppsala approved the study. Written consent was obtained from all participants. Information was given that some studies of acupuncture concerning vomiting had been undertaken, but not on hyperemesis. Therefore, we did not know if acupuncture could reduce

their discomfort or what form of acupuncture was most effective. In order to find out we wanted to compare two methods of acupuncture of unknown efficacy.

Statistical Analysis

The data from the study was stored in a SPSS database from which all the statistical analyses were performed. Nonparametric tests (Mann-Whitney, Wilcoxon signed ranks test, χ^2 -test, and McNemars test) and the Student *t*-test were used. For the crossover analyses, we used the method described by Armitage and Berry.²⁰ We used nonparametric statistics for analyses of VAS changes because it is not possible to regard the VAS for nausea as a ratio scale. For sensitivity analysis, we used the results from the crossover study¹² of cisplatin-induced sickness as a basis, where it was shown that 9/10 patients receiving real de-qi acupuncture at PC6 as compared with 1/10 receiving acupuncture at a “dummy” point were improved. In a larger study, it was shown that 63% of the patients responded very well to real acupuncture.¹³ For a two group parallel study we would need 17 patients in each group if real acupuncture was positive in 60% and superficial in 10%. This number is calculated with $\alpha = 0.05$ and power = 80%. As this study was of crossover design, we estimated that a little more than 30 patients completing the study would be enough. For VAS-values there are no figures in the literature for calculations of sample size.

Results

Study Population

During the study period, 72 women were admitted to the hospital with a diagnosis of hyperemesis gravidarum. Thirty-two were not randomized for the following reasons: 7 women asked for legal abortion; 6 women refused acupuncture; 11 did not speak Swedish; and 8 suffered from other diseases (Figure 2). Thus, 40 women underwent randomization. Seven (17.5%) of the 40 women did not complete the study. Two belonged to Group A (and thus started with deep acupuncture) and five belonged to Group B. Six of the seven dropouts tried the first form of treatment in their group before leaving the study.

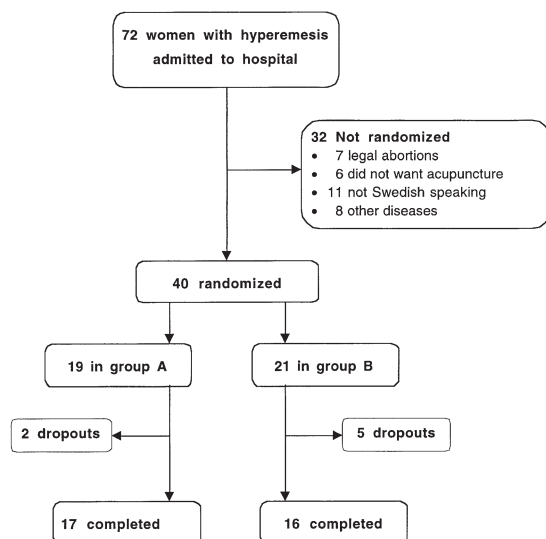


Fig. 2. Trial profile.

In Group A, one woman was afraid of the needles and stopped after just two treatments. Another was so much improved that she went home on day 5. In Group B, two women decided to undergo legal abortion, another was afraid of needles, and one was so much improved on day 4 that she left the hospital. One became worse on day 4 and did not want to continue. These seven women are not included in the statistical analyses below. In summary, there were 17 women in Group A and 16 in Group B.

Background Data

The mean age for the 33 women who completed the study was 28.4 years (range 23–37). There was no significant difference between the groups concerning age, number of previous pregnancies and deliveries, gestation week at admittance, or use of antihistamines (Student *t*-test). Seven participants in Group A and nine in Group B had experienced hyperemesis in earlier pregnancies. The women were admitted to hospital at mean gestation week 9.9, with a range from 6 to 16. They had been sick for mean of 4 weeks before admission to hospital. Twenty-five women had tried antihistamines.

Nausea

The VAS estimates for nausea experienced on day 0 was different between Groups A and B, ($P = 0.009$, Mann-Whitney). Due to this finding, it was not possible to directly compare

the VAS values between the groups. Instead, we have analyzed the speed of VAS-reductions in our crossover analyses (Figure 3). The VAS-reductions were calculated as the difference between the VAS estimates the day before acupuncture and those the day following the two acupuncture days for each patient. This intergroup crossover analysis showed a significantly faster reduction of nausea when giving the patients active acupuncture than when giving them placebo acupuncture ($P = 0.032$, Mann-Whitney). There was no period effect ($P = 0.138$).

It was also found that the VAS-reductions between day 0 and day 1 and between day 4 and day 5 were significantly faster when the patients received the active treatments ($P = 0.009$, Mann-Whitney). This, too, was not a period effect, ($P = 0.828$). Intragroup analyses showed that the changes in absolute VAS-values from day 0 to day 1 and day 4 to day 5 were significant only in the active acupuncture group ($P = 0.007$ and 0.019 , Wilcoxon) and not in the placebo acupuncture group ($P = 0.475$ and 0.570).

Vomiting

All women were vomiting on day 0. The number of women vomiting on the third day (the day following the two acupuncture days) was reduced to 7/17 in Group A (active treatment) and 12/16 in Group B (placebo treat-

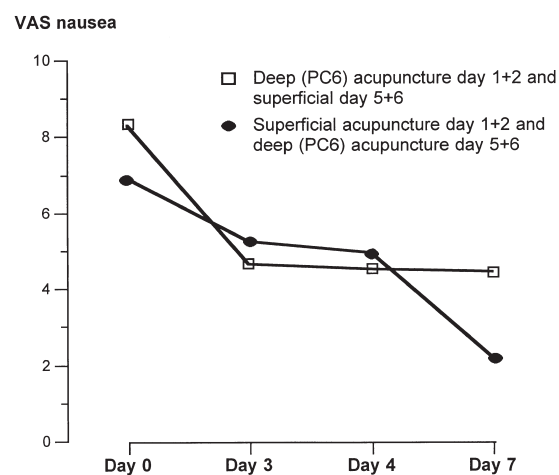


Fig. 3. Changes in VAS estimates (nausea) in the two groups from the day before acupuncture was given (day 0 and 4) to the day after the two treatment days (day 3 and 7).

ment). This difference is significant between the two groups ($P = 0.049$, χ^2 -test). After day 4 a further significant decrease in the number of women vomiting was observed in Group B, which included patients who received active treatments day 5 and day 6 ($P = 0.031$, McNemars test).

Food Intake

The increase in food intake from day 0 to day 2 was significant in Group A ($P = 0.030$) but not in Group B ($P = 0.564$, McNemars test). No significant difference was seen between the groups.

Intravenous Fluids

The amount of intravenous fluid fell in both groups very fast from admission to discharge. There were significant reductions in both groups from day 0 to all other days, but no overall group difference could be seen.

Side Effects

No side effect of any kind was seen during or after the study.

Discussion

In this first crossover, placebo-controlled study of manual acupuncture for hyperemesis gravidarum, the addition of active acupuncture to intravenous fluid therapy improved outcomes faster than placebo acupuncture and intravenous fluids. Both the reduction of nausea (VAS estimates) and the number of women who stopped vomiting were higher when active acupuncture was performed. This was seen irrespective of whether the active treatments were given at the beginning or at the end of the hospitalized week. This study confirms the results from other studies on the effectiveness of manual acupuncture, acupressure, electroacupuncture, and transcutaneous electrical nerve stimulation in the acupuncture point PC6 against different types of nausea/vomiting. In a review article, 27 of 29 controlled studies with acupuncture performed on nonanesthetized patients were in favor of real PC6 acupuncture.²¹

As placebo treatment in our study, we used superficial acupuncture on an area away from a "real" acupuncture point. The needles were

inserted only 1–2 mm in the skin. This kind of stimulation minimizes the specific effects of acupuncture. It may not be an entirely inert placebo, as some sensory stimulation does occur. It has in fact been called minimal acupuncture and could be regarded as a "near placebo" stimulation.²²

The midwives performing the acupuncture treatments were not blinded regarding what kind of acupuncture they performed, as this is impossible. However, the patients performed all the scorings on their own (except concerning the amount of intravenous fluids), with no midwife present. The midwives also did not discuss anything with the patients about the techniques of stimulation and they did not belong to the usual ward staff but were only present to perform the treatments.

This study only investigated the immediate effects after 2 days of acupuncture. This was because no other study exists and we therefore wanted to detect whether effects occur at all, and also determine that side effects did not present a problem.

We gave acupuncture treatments three times daily because an 8-hour effect had been shown in other studies.^{12,13} In forthcoming studies, it should be enough with twice a day, as we saw effects of more than 8 hours after just a few treatments.

Possible Mechanisms of Action for Acupuncture Against Vomiting

The mechanisms of action for acupuncture have been studied extensively, especially when trying to explain the pain relieving effects.²³ Acupuncture works within the gate-control mechanism and inhibits nociceptive transmission, as well as autonomic reflexes. Acupuncture also seems to work through the endogenous descending pain relieving system from peri-aqueductal grey, which partially works through endorphinergic mechanisms.^{24,25}

The pathogenesis of hyperemesis gravidarum is not fully understood but it is known that pregnancy is associated with a decreased gastric peristalsis and a delayed gastric emptying. This is believed to be an effect of the increased level of progesterone, which is known to relax smooth muscles and thereby to reduce the gastric emptying speed early in pregnancy.^{6,26,27} These factors are not believed to

be the only ones causing the hyperemesis, but they may exacerbate the symptoms of nausea and vomiting to the severe degree that is found in the fully developed cases of hyperemesis.

From experimental studies, acupuncture seems to influence the gastrointestinal system. In one study, it was shown that electrical stimulation of the sciatic nerve (in order to mimic electroacupuncture) decreased the rate of fluid secretion in the small bowel. The effects were not seen when the autonomic nerves to the intestines were interrupted.²⁸ This is one example of a somatovisceral reflex, of which there seems to be many. These reflexes occur in different systems and have been reviewed in detail by Sato et al.²⁹ An interesting possibility to explain the acupuncture effects on nausea/vomiting is that gastric emptying may be influenced by acupuncture by means of such somatovisceral reflexes. Sato et al.'s research group has shown that noxious and acupuncture-like stimulation can induce both inhibitory and facilitating responses on the motility in the stomach and small intestine of anesthetized rats.³⁰ When stimulation was performed to the abdominal skin, an inhibitory effect was found. When stimulation was done on the lower or upper limbs (in the area approximately at PC6), an immediate motility facilitating effect, transmitted by vagal efferents, was found. These effects were not influenced by naloxone, and are thus probably not mediated through the endorphin system.

In our study, we observed that the effect of acupuncture on vomiting was very fast, often within minutes of stimulation, indicating a neural substrate. The somatovisceral reflexes might give us an understanding of the acupuncture effects on different kinds of nausea and vomiting, as their effect duration is consistent with what we clinically observe.

In conclusion, the present study, however limited, strongly indicates that acupuncture has a clinically useful effect in hyperemesis gravidarum. The clinical impact of the technique, however, has to be evaluated in further studies.

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