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Acupressure for the in-patient treatment of nausea and vomiting in early pregnancy: A randomized control trial

Alexander Heazell, MBChB(Hons),[a,*] Joy Thorneycroft, MBChB,[b] Victoria Walton, MBChB,[c] Ian Etherington, MD[d]

Maternal and Fetal Health Research Centre, St. Mary's Hospital, Manchester, UK[a]; The Hawthorns Surgery, West Midlands, UK[b]; Springfield Medical Practice, Springfield, Birmingham, UK[c]; Rockhampton Hospital, University of Queensland, Rockhampton, Australia[d]

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KEY WORDS
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Objective: The purpose of this study was to evaluate the efficacy of acupressure at the P6 point for the in-patient treatment of severe nausea and vomiting in early pregnancy.
Study design: This was a prospective single-blind randomized control trial that involved 80 patients with nausea and vomiting plus ketonuria before 14 weeks of gestation.
Results: There was no difference between length of stay, amount of medication, or fluid required between the acupressure and placebo groups, although acupressure reduced the number of patients who stayed $\geq$4 nights in the hospital. Acupressure was well tolerated and not associated with an increase in perinatal morbidity or death.
Conclusion: The use of acupressure at the P6 point does not reduce the amount of antiemetic medication that is required, the requirement for intravenous fluid, and median duration of in-patient stay more than the use of placebo. A small reduction was seen in the number of women who required $\geq$4 days in the hospital.

Nausea and vomiting associated with pregnancy (NVAP) are common, with a reported incidence of 50% to 90%.[1,2] Vomiting may be associated with dehydration, weight loss, electrolyte disturbance, or ketosis; if symptoms are severe, patients may require admission to a hospital for intravenous fluid therapy and antiemetic medication. It is estimated that 0.6% to 2% of pregnant women have severe NVAP.[3-5] In addition, to its physical effects, NVAP may have important psychosocial effects, interfering with normal work and family relationships and potentially leading to psychologic morbidity.[6,7]

Acupressure at the P6 Neiguan point is associated with a reduction in emesis that is associated with cesarean delivery,[8] laparoscopy,[9] chemotherapy,[10] and motion sickness.[11] A review of studies with acupuncture or acupressure for the control of nausea found a wide range of reported differences between treatment and placebo groups; the greatest magnitude of effect is in the control of postoperative nausea and vomiting.[12] Many

* Reprint requests: Alexander Heazell, MBChB(Hons), Department of Obstetrics and Gynaecology, Maternal and Fetal Health Research Centre, St. Mary's Hospital, Whitworth Park, Manchester M13 0JH, UK.
E-mail: alex_heazell@talk21.com

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Figure 1 Placement of acupressure wristband at the treatment (P6) point. Image reproduced by kind permission of Seaband UK Ltd.

studies of acupressure use either crossover studies or placebo-controlled randomized methods, with small numbers of participants, often fewer than 100 patients.[12]

The evidence for acupressure in the treatment of NVAP is equivocal. A systematic review of all treatments for NVAP concluded that there was no evidence of benefit from acupressure in the treatment of severe NVAP.[13] A randomized controlled trial of acupressure at the P6 point in patients with mild NVAP found no subjective improvement in NVAP over and above that experienced by the placebo group.[14] However, a study with a longer term follow-up of 14 days showed a significant reduction in symptoms as assessed by a visual analogue scale with acupressure compared with placebo, both in immediate and long-term assessments.[15] In many cases, studies were complicated by selection bias and subjective reporting of symptoms. Crossover studies of P6 acupressure in NVAP have described a reduction in symptoms when P6 acupressure is compared with placebo.[16] However, crossover studies are complicated by the fact that NVAP resolves as pregnancy progresses, particularly beyond 12 weeks of gestation. To date, there have been no randomized studies that have addressed whether acupressure at the P6 point can reduce symptoms in patients with severe NVAP who require hospital admission.

Method

We studied the efficacy of acupressure on inpatients with nausea and vomiting of pregnancy, hypothesizing that the length of inpatient stay and inpatient parenteral drug and fluid use would be decreased by the use of acupressure bands.

Participants and setting

This study was granted ethical approval by the West Birmingham Local Research Ethics Committee. The trial was carried out in a single secondary care center that serves a diverse inner-city population that includes a high proportion of recent immigrants.

We recruited women with NVAP on their first inpatient admission between 5 and 14 weeks of gestation. To require inpatient admission, patients had at least 2+ of ketonuria on urinalysis, an inability to tolerate oral fluids, and a requirement for antiemetic medication. Patients were excluded if they had prior knowledge of or use of acupressure because they could not remain blind to the treatment. Women were also excluded if there was evidence of urinary tract or gastroenterologic infection, because this may potentiate nausea and vomiting. Finally, women who were unable to communicate with the medical team were also excluded; patients would did not speak English as a first language were admitted to the study because the catchment area serves a diverse ethnic population with $>50\%$ of pregnant patients of Asian origin, and the medical team included staff members who were able to speak Asian languages.

Intervention and randomization

Patients were given written and verbal information before they gave written informed consent. After informed written consent, patients were randomly allocated to either the treatment or placebo group by an independent remote researcher with no prior knowledge of the patient. A ticket that indicated either placebo or treatment group was drawn from an opaque bag. During their stay in the hospital, the patients remained blind to the group to which they were assigned.

Acupressure bands (Seaband Ltd, Hinckley, UK) that consisted of a plastic bead contained within a woven elastic band were used to apply acupressure to both wrists. Patients who were assigned to the treatment group had the bead placed at the P6 meridian point (Figure 1), which is found on the anteromedial aspect of the forearm between the 2 flexor tendons, at a distance of 3 of the patients finger breadths from the distal palmar crease.[8,17,18] Those assigned to the placebo group had the beads placed at a site on the dorsal aspect of the forearm which is not thought to be effective, this method of placebo band placement has been used in other placebo controlled trials.[14,15] Patients wore the wristbands for 8 hours a day, from 9 AM to 5 PM.

Patients were treated according to a standard protocol: 3 L of intravenous fluid in 24 hours and parenteral antiemetic medication while the patient was unable to tolerate oral fluids and thiamine 100 mg that was taken orally once daily. When the patient could tolerate oral fluids, the antiemetic medication was administered orally. There was a defined antiemetic protocol that used cyclizine as a first-line agent, prochlorperazine as a second-line agent, and metoclopramide, ondansetron, or phenothiazine as a third-line agent. According to the protocol, patients were deemed fit for discharge when they were able to tolerate oral fluids and diet and no

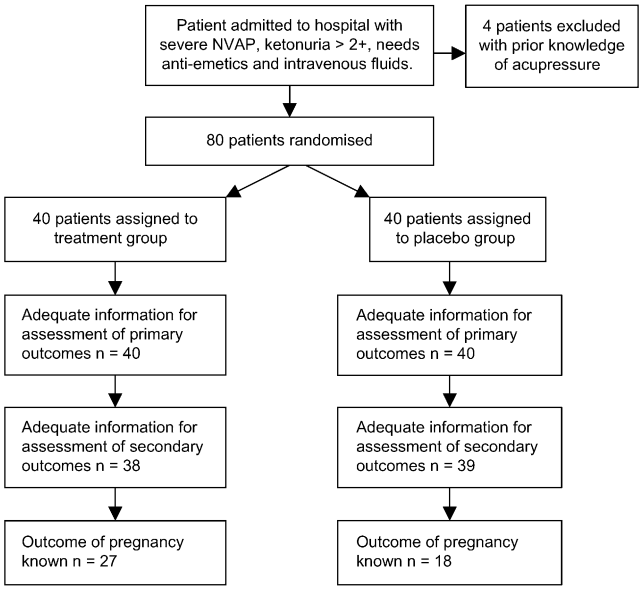

Figure 2 Profile of patient recruitment and follow-up following randomisation to either placebo or treatment groups.

Table I Baseline characteristics of participants randomised to treatment or placebo groups. Figures in brackets are standard error of the mean and range

Group	Treatment (n = 40)	Placebo (n = 40)
Mean age (years)	25.4 (0.95, 17-35)	27.7 (0.89, 17-40)
Mean gravidity	2.1 (0.18, 1-5)	2.3 (0.25, 1-7)
Mean parity	0.9 (0.18, 0-4)	0.9 (0.16, 0-4)
Mean gestation at presentation (weeks)	8.5 (0.32, 6-14)	9.0 (0.36, 5-14)

longer required parenteral antiemetic medications or intravenous fluid.

Outcome measures

Objective measures of outcome were chosen to assess the efficacy of the intervention because subjective measures may not accurately assess the severity of symptoms, because they are subject to responder bias, namely increased reporting of symptoms to justify hospital treatment and the occupancy of the sick role, which exempts the patient from tasks at home or work. In addition, patient questionnaires would be difficult to administer because English was not the first language of a large proportion of the women who were studied. The primary objective outcome measures that were chosen included the number of days of hospital stay and, more specifically, the number of patients who required ≥ 4 days in the hospital (4 days was chosen because this was greater than the mean of 3.4 days). Secondary measures of outcome included the number of antiemetic doses that were required, the amount of intravenous fluid that

Table II Outcome measures among women randomised to treatment with acupressure

Primary outcome measures	Treatment (n = 40)	Placebo (n = 40)
Median length of stay in days (IQR)	3 (2-4)	3 (2-5)
Number of women staying >4 days	11*	18*
Secondary outcome measures	**Treatment (n = 38)**	**Placebo (n = 39)**
Median total number of anti-emetic doses (IQR)	7.1 (3-10)	7.5 (4-9.8)
Median number of anti-emetic doses per day (IQR)	2.5 (1.4-3)	2.3 (1.5-2.8)
Median total amount of intravenous fluid (litres) (IQR)	4.0 (2-7)	5.0 (3-6)

IQR, Interquartile range.
* $P < 0.05$.

was required within a 24-hour period, and whether the patient required treatment with a second- or third-line antiemetic medication.

Patient details were kept to collect data regarding the safety of acupressure at the P6 point during pregnancy. Nine months after the recruitment of the last patient, the written and electronic clinical records of all patients who had been recruited were reviewed, and the outcome of the pregnancy was noted. If there was no written information regarding the outcome of pregnancy, a written questionnaire was sent to patients.

A pilot study that showed that the mean length of stay was 3.4 nights (range, 2-9 $\pm$ 1.5 [SD] nights) was undertaken with 35 patients at City Hospital. It was estimated that, to achieve 80% power to detect a difference ($\alpha = .05$) of 1 night of inpatient hospital stay, 36 patients would be required in each group. Assuming a noncompliance rate of 10%, we planned to recruit 40 patients to each group.

Statistical analysis

This was carried out with Minitab software (version 1.3; State College, PA). The data were analyzed on an intention-to-treat basis. Demographic data were assessed with the Student *t* test, because these data followed a parametric distribution. Differences between the groups were assessed with the Mann-Whitney *U* test and the chi-squared test. These tests were selected in anticipation that the data would be skewed, as was the case in the pilot study.

Results

Eighty patients were recruited to the study and were assigned randomly to groups between December 2002

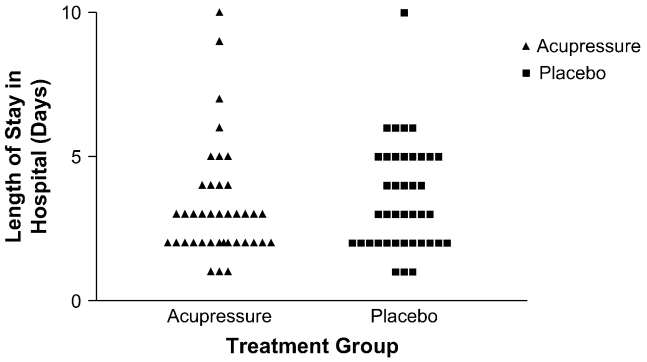

Figure 3 Dot-plot of the length of Inpatient Stay in Hospital.

and July 2004, which provided 40 patients each in the placebo and treatment groups. Four patients were not recruited to the study because of prior knowledge of or use of P6 acupressure (Figure 2). There was good adherence to the trial protocol, with no patients removing the wristbands because of discomfort or moving their bands from either the placebo or treatment position. Three sets of patient records contained insufficient information for data collection regarding secondary outcomes and therefore were excluded from the analysis. Data regarding the final outcome of pregnancy were available in 56% of cases (Figure 2). There were no statistically significant differences in the demographic characteristics of each group (Table I). There was no difference in severity of NVAP as assessed by ketonuria on admission.

Analysis of outcomes

Table II shows the length of stay, the total amount of antiemetic medications that were used, the total amount of intravenous fluids that were required, and the adjusted values for the amount of antiemetic medication and intravenous fluids per length of stay. There is no statistically significant difference between the treatment or placebo groups for any of these outcome measures. However, further analysis of the length of inpatient stay shows a significant reduction in the number of patients who stayed ≥ 4 nights in the treatment group from 18 to 11 women ($P < .05$; degrees of freedom, 1; Figure 3). The number of patients who were needed to treat to achieve a reduction in inpatient stay to 3 nights is 6.5 women. There was no statistically significant difference in the number of patients who required second- or third-line antiemetic medication ($P > .1$; degrees of freedom, 2; Figure 4).

Outcome of pregnancy

Table III shows data regarding the early and late outcomes of pregnancy, respectively. Data regarding early outcomes were available for 72% of women who were recruited into the study; data for late outcomes of pregnancy were available for 56% of patients who were

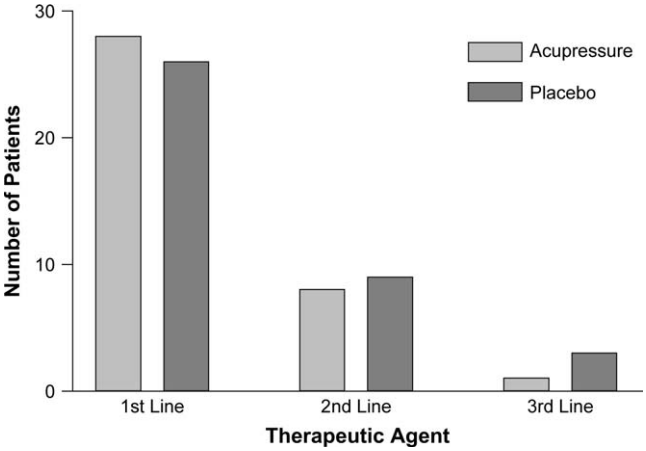

Figure 4 Number of patients requiring 2nd and 3rd line anti-emetic medication.

Table III Early outcomes of pregnancy in women recruited to randomised controlled trial of acupressure. Late outcomes of pregnancy in women recruited to randomised controlled trail of acupressure with pregnancies known to continue beyond first trimester (n = 70)

Early outcomes	Treatment (n = 29)	Placebo (n = 28)	Statistical significance
Normal anomaly scan	25	22	$P > 0.8$
Miscarriage before 20 weeks	1	2	$P > 0.8$
Termination of pregnancy	3	4	$P > 0.8$
Outcome of pregnancy	**Treatment (n = 23)**	**Placebo (n = 13)**	**Statistical significance**
Live delivery after 37 weeks	22	10	$P = 0.2$
Live delivery before 37 weeks	0	2	$P = 0.2$
Intra-uterine fetal death after 20 weeks	1	1	$P = 0.2$

Data were analyzed using Chi-squared test.

known to have a continuing pregnancy after the second trimester (n = 70). There were no statistically significant differences in birth weight, gestation time at delivery, or incidence of miscarriage between the 2 groups. There were 2 third-trimester intrauterine deaths in patients who were recruited to this study, 1 death in each group. In these cases, there was no evidence of fetal anomaly either on mid-trimester ultrasound scan or external post-mortem examination. The low percentage of patients with full follow-up for pregnancy outcome reflects the increased migration of the population within the catchment area of this secondary care service.

Comment

This randomized controlled trial is the first such study to assess the role of acupressure at the P6 point in the

inpatient treatment of severe NVAP. In addition, it is the first published trial to follow patients until the end of their pregnancy. Although there was no statistically significant difference in the length of stay, the amount of medication that was required, or the amount of intravenous fluid that was used, there was a small reduction in the number of patients who required hospital admission for ≥ 4 nights. Patients found the acupressure wristband easy to tolerate; no women ceased the trial because of discomfort. These data suggest that there may be a small beneficial effect of acupressure in the treatment of severe NVAP, particularly for women with the most severe symptoms.

The comparatively small effects of acupressure that were observed in this study may be a result of the combination of acupressure with pharmacologic agents that are known to reduce NVAP, such that one is comparing acupressure with pharmacologic therapy to placebo with pharmacologic therapy. It is possible that pharmacologic therapy provides a large reduction in symptoms of NVAP and that any additive effect of P6 acupressure is comparatively modest. The only means to test this hypothesis would be to try the use of P6 acupressure alone against placebo in severe NVAP. However, the organization and ethical approval of such a trial would be complicated by the omission of pharmacologic agents that are effective in the treatment of NVAP, potentially increasing maternal morbidity.

The smaller effect of P6 acupressure in NVAP when compared with studies in patients after laparoscopy, cesarean delivery, motion sickness, and cancer chemotherapy may be due to the mode of action of P6 acupressure. P6 acupressure has been shown to alter gastric myoelectric activity, in normal subjects, in subjects with systemic sclerosis, and in subjects who are exposed to extreme motion.[19-21] In patients who undergo laparoscopy and cesarean delivery, impaired gastric emptying may be cause symptoms of nausea and vomiting. However, in NVAP and cytotoxic chemotherapy, emesis is thought to result from the central stimulation of the chemoreceptor trigger zone in the brainstem. This underlying difference in pathophysiologic factor may explain the differential effects of P6 acupressure that have been reported in studies.

The smaller than expected effect of P6 acupressure may also result from the use of the objective measures of symptom control not being able to record improvements in patient well-being, the amount of food taken, and the subjective nausea, all of which may have responded to P6 acupressure. The use of objective measures, with treatment given according to a protocol, was designed to assess a change in the patient's clinical condition. This decision was made because of the difficulties of subjective assessment in our study population and the lack of evidence regarding cultural and ethnic differences in the perception of symptoms in NVAP. Although subjective assessments have been validated in the assessment of symptoms in NVAP, these have not been specifically assessed in patients of different ethnicities, whose first language may not be English.[22] This is important because some ethnic groups, especially those of Pakistani origin, have been reported to have an increased incidence of NVAP, which may reflect altered cultural perception of symptoms of nausea and vomiting.[23] The use of the duration of the hospital stay also enables comparisons with studies of other pharmacologic agents that have used similar objective outcome measures.[24,25]

It is important to acknowledge that the objectivity of this assessment is dependent on the clinical staff rigidly in adherence to the treatment protocol (ie, the administration of intravenous fluid, antiemetic medication, and most importantly for discharge) to minimize any resulting bias towards different treatment groups. Furthermore, it is dependent on the patient being concordant with medical advice and not taking their own discharge. In our study, there appeared to be good patient concordance, because no patients removed or moved the wristbands and no patients self-discharged. Finally, the goal of treatment in severe NVAP is not only the reestablishment of oral diet and fluids but also includes symptom control and a perception of wellness. These were not assessed by the objective measures that were used in this trial but, nevertheless, are important outcomes of treatment for NVAP. Further assessment of the impact of P6 acupressure on these outcomes is required.

The findings of this study do not provide a clear answer regarding the use of P6 acupressure in severe NVAP. Earlier randomized studies of acupuncture and acupressure in women with mild-to-moderate NVAP in primary care have found conflicting results, with an improvement noted in both placebo and treatment groups and a decrease in symptoms as treatment progressed.[14,16,26] This effect was also observed in our study, both groups within the trial had a reduced length of inpatient stay compared with that of the initial pilot study. In our study, there was a nonsignificant trend towards a reduction in the use of second- and third-line antiemetic medication. This study did not have sufficient power to determine the statistical significance of these secondary measures and may be subject to type 2 errors.

Although epidemiologic studies have failed to identify a link between NVAP and psychologic morbidity, several detailed questionnaire-based studies have described increased social dysfunction, anxiety, and depression in women with severe NVAP; and much has been written regarding a psychologic component of NVAP.[27,28] Rather than having a psychosocial cause, patients with severe NVAP acknowledged that pre-existing life stress exacerbated symptoms of NVAP, but most patients noted that the stress and anxiety resulted from the condition itself.[28] It is possible that improvements in the symptoms that were observed in both treatment and placebo

groups result from the perceived treatment of NVAP as a result of decreased anxiety, stress, or an increased sense of patient control and social support over symptoms, rather than by a biochemical effect alone.

There does not appear to be an increase in the incidence of miscarriage, intrauterine fetal death, poor pregnancy outcomes that are associated with the use of acupressure compared with placebo, or an increase compared with studies of patients who required the inpatient treatment of NVAP.[4,5] The women who experienced intrauterine fetal death in the study population had normal 20-week anomaly ultrasound scans, normal external postmortem examinations, and a long interval between acupressure treatment and the diagnosis of intrauterine fetal death (ie, 32 and 33 weeks, respectively). Overall, the use of acupressure at the P6 point is not associated with an increased risk to the fetus.

This study shows there may be a small beneficial effect of acupressure at the P6 point over placebo for women with severe NVAP who require inpatient admission. This intervention appears to be well tolerated and is not associated with an increase in adverse fetal outcome. Further, appropriately powered randomized studies are required, preferably studies that will encompass a cohort of patients in both primary and secondary care settings, to determine the benefit that is derived from acupressure in all cases of NVAP. Further clinical research also is required to assess the mode of action of acupressure in this multifactorial condition. In addition, we would recommend that any future studies of acupressure during pregnancy report the outcome of pregnancy to ensure the safety of this treatment modality.

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