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Research

A double-blind cross-over study to evaluate the effectiveness of acupressure at pericardium 6 (P6) in the treatment of early morning sickness (EMS)

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SUMMARY. **23 patients were entered into a double-blind cross-over study to evaluate the use of P6 acupressure versus sham acupressure in the treatment of early morning sickness (EMS). 16 completed the study. P6 acupressure was significantly more effective than the sham acupressure in the relief of nausea as measured by daily visual analogue scales (P = 0.019). Two thirds of the patients preferred acupressure on P6 as compared to the sham point. Sham acupressure was specifically evaluated and shown to be a credible placebo.**

INTRODUCTION

Early morning sickness (EMS) affects at least 75% of pregnant women. Typically it occurs 6 weeks after the first missed period and continues for 6–12 weeks.[1,2] Symptoms may be very mild causing little or no disruption to the woman's life or they may lead to hyperemesis gravidarum which requires immediate hospitalisation and intravenous feeding.[3–7] There are many pathological causes of vomiting in pregnancy, these include: pre-eclampsia, hydatidiform mole and hydraminos.[8] Often there is no obvious cause of EMS despite extensive research; the precise aetiology of EMS is still poorly understood. It is, however, accepted that vomiting is more common in first and twin pregnancies.

A variety of remedies have been sought. The preferred approach involves avoiding fatty foods, while consuming frequent, small quantities of carbohydrates.[9] Others include hibernotherapy, ginger, intravenous honey and infusion of the father's testosterone! There are no studies to support the value of these approaches. Numerous antiemetics have been used in the treatment of EMS. All drugs are known to have side-effects but initially effects on an unborn fetus were not considered[10–12] and drugs were not tested on pregnant women. Even now that we are aware of the possible teratogenic effects of drugs, specific effects are often difficult to prove.[13] The congenital limb defects caused by thalidomide in 1956[14] are well-documented and have made women, doctors and the drug companies very wary of the use of any drugs

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in early pregnancy. Therefore drugs are not normally prescribed for EMS unless the sickness is such that the woman's daily life is severely disrupted.

These problems, along with the current and increasing interest in complementary medicine, have led a number of researchers to consider investigating the use of acupressure, acupuncture and transcutaneous electrical nerve stimulation (TENS) as treatments for EMS.

Acupressure is side-effect free and a non-invasive form of acupuncture. The mechanism of action of acupressure as an antiemetic in pregnancy is unclear. *Sea-Bands* resemble sweat bands with an attached plastic button; the correct position is 2 cun (a cun is a Chinese measurement found using a person's own fingers) above the wrist crease, equivalent to the patient's index, middle and ring fingers. This is the sixth point of the pericardium, jueyin, channel (P6).[15] *Sea-Bands* were initially marketed to combat travel sickness, but that use has been expanded to include the treatment of nausea and vomiting associated with chemotherapy, minor operations and pregnancy.

In China, acupuncture has been used to treat morning sickenss for thousands of years. As with most traditional Chinese medicine, the precise treatment depends upon the individual problem. Morning sickness is divided into three broad categories: stomach deficiency, liver heat or stagnancy of phlegm. Different points are used in each condition, though the principal points are: P6 (*Neiguan*), Ren12 (*Zhongwan*), St36 (*Zusanli*) and Sp4 (*Gongsun*).[16] Chinese research suggests this approach is effective. In a study of 39 pregnant women Rongjun found acupuncture to be effective in 38 cases. There was no record of the duration of action, or how the effectiveness was measured. The acupuncture was administered twice daily for 30–40 minutes each time. There were no control groups, or any measure of nausea levels without acupuncture; similar results were reported by Changxin.[17,18]

TENS involves the use of transcutaneous electrical nerve stimulation. Its major use has been in the field of pain, although Dundee[19] reports its use in stimulating *Pericardium* 6, and its consequent benefit in the treatment of nausea.

Recent studies of the efficacy of acupressure in the treatment of morning sickness highlighted the need for further more exact information. A non-placebo controlled cross-over by Hyde suggested that acupressure reduced morning sickness in 12 of 16 women. The women received 5 days of acupressure at P6 and 5 days of no treatment in random order.[9]

Dundee's parallel group's study in 1989 involved three groups of women experiencing EMS. A control group with no acupressure, a group having acupressure at P6 and a group having placebo acupressure near the elbow. There were approximately 120 people in each group but many of those entered did not complete the study; only 50% for the treatment and placebo groups and 70% for the control group. The difference in drop-out rate between the treatment and control groups is of great concern. Symptoms were recorded over 4 days and nausea was reduced in both the acupuncture and placebo group when compared with the control group. True acupressure showed a greater effect than the placebo acupressure. Unfortunately, the group receiving P6 acupressure were all a week further in their pregnancy, when their EMS may have been decreasing naturally.[20]

The objective of our study was to conduct a randomised, controlled, double-blind, cross-over trial to see if acupressure at P6 is a better treatment for EMS, than acupressure at a placebo position. It was also intended to assess the credibility of the placebo, basing the method used by Borkovec and Nau.[21]

METHOD

Patients were recruited via their GPs who distributed introductory leaflets to eligible women. The leaflet explained that there was a project involving the use of *Sea-Bands* in the treatment of morning sickness. Women were recruited from five general practices in central Southampton. The number of women likely to present in the early stages of pregnancy over 3 months was monitored within these practices and 55 women were expected to present to their doctors during the study period. As time progressed and insufficient patients were recruited, six more local general practices agreed to help.

Those entering the study were aged between 18 and 35. This excluded young mothers who may have been unreliable and unwilling to make their pregnancy well-known, and older women who are more likely to experience complications of pregnancy. The women were to be in the first 16 weeks of pregnancy and experiencing EMS. EMS most commonly occurs in the first 18 weeks of pregnancy, recruiting women up to the 16th week of pregnancy allowed for the 2–week treatment period.

The women wore the *Sea-Bands* at P6, or a placebo position, continuously for 7 days followed by 2 days with no treatment (a washout period) before commencing the second arm of the trial (Fig. 1). A washout period of 2 days was considered adequate; acupressure must be administered continuously as the effects only last a few hours. A placebo position above the elbow position was chosen. After the first few patients were entered it became obvious that this position was uncomfortable, as even the extra large bands were too small for many of the women. A different placebo position, just below the elbow, was then selected.

Randomisation was dictated by a random computer program and effected by the use of sealed envelopes given to the patient. Group 1 was to receive acupressure at P6 first and then at the placebo position; Group 2 was to receive acupressure at the placebo first and then at the P6. Details of the randomisation and instructions of

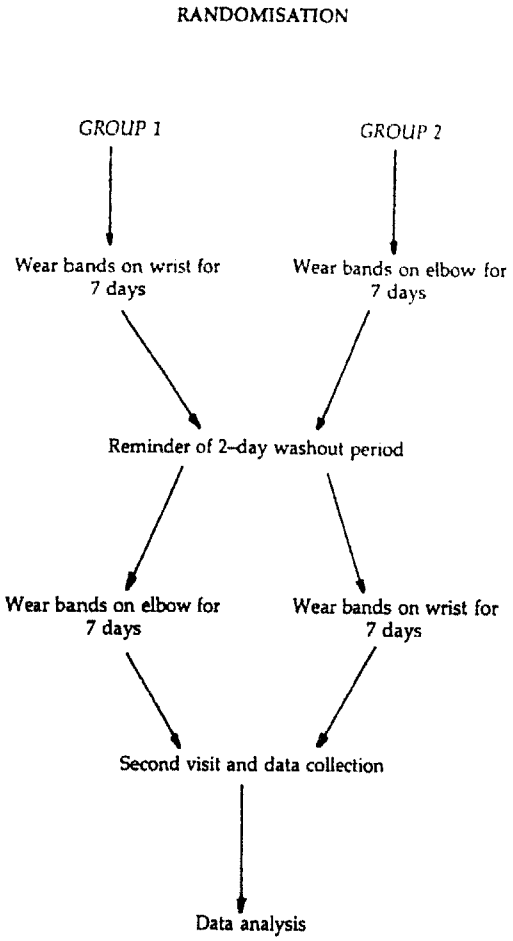

Fig. 1

how to position the bands in each position were placed in coded envelopes by an independent researcher; these were opened by the women when the investigator had left. Consequently, the investigator was completely blind to the nature and order of treatment.*

At the initial meeting the women were asked to sign a consent form before the questionnaire was administered. The women were asked questions regarding their age, marital status, parity, gestation and any previous knowledge of *Sea-Bands* and the interviewer then rated this on a scale of 1–3 (1 = no previous knowledge, 2 = heard of, 3 = previously used or insight into mechanism of action). The women were shown how to wear the *Sea-bands* in both positions, and provided with the randomisation envelope. It was explained that the study was to see which was the more effective of two acupressure points in treating the nausea and vomiting of early pregnancy. The women were told that acupressure had previously been used with safety and success for this condition.

The women were shown how to complete the visual analogue cards and the second questionnaire. They were given the opportunity to ask any questions and provided with a contact telephone number in case they thought of any questions, or had any problems.

The investigator recorded basic demographic information at the initial interview. The women were then asked to complete a daily visual analogue scale to assess their nausea. The lines were each of 10cm and the value for each day was measured by a blinded assessor, to the nearest millimetre.

They were also asked to state how many times they vomited each day. At the end of the trial they completed a second questionnaire in which they were asked whether they felt that the acupressure had improved their nausea at either position, and which position they had found most beneficial. At the beginning of the study the interviewer administered a previously validated questionnaire[21,22] in order to assess the credibility of the placebo (sham acupressure). The women were asked about the credibility and logic of each acupressure position. At the end of the study the women were again asked how confident they would be in recommending each position to a friend and how successful they felt each position would be in the treatment of other complaints.

After 7 days those entered were sent a postcard or telephoned to remind them to stop wearing the *Sea-Bands* for 2 days and then to start wearing them in the second position. The *Sea-Bands* and completed forms were collected at the end of the study. This provided a useful opportunity to check that the forms were completed correctly, and to discover any problems which the women may have had.

RESULTS

A total of 23 women entered the study but 8 were excluded from the main data analysis (4 women from group 1 and 4 women from group 2). The main data are therefore based on the 15 who completed the study, 7 in group 1 and 8 in group 2.

Two women had miscarriages. 4 other women failed to complete or return their forms, none of these 4 wore the bands for more than a week. 2 of these 4 claimed to have derived some benefit from the acupressure when telephoned by the investigator. 1 woman was excluded for

* The patient was never given any clue as to whether the correct position was P6 or the sham acupressure point indicated in the protocol. The study was therefore completely double-blind.

being a protocol violator because she was 36 weeks pregnant at entry, however she was still experiencing EMS and obtained benefit from treatment. As she completed the whole study, the data from this woman are quoted in brackets. Finally, 1 woman was excluded from analysis as she completed only 1 day of the diary prior to withdrawal because she found acupressure to be ineffective.

The two groups had a similar age distribution (mean age in group 1 was 25.6 years and in group 2 was 27.3 years) and an identical distribution in relation to marital status, both for people entering and completing the study. Other factors showed some greater differences. Women in group 1 were overall 1.5 weeks further on in their gestation and this may have meant that they were experiencing less nausea. However, group 1 also contained a greater percentage of primigravids who could be expected to experience more nausea (5 out of 7 in group 1, as opposed to 1 out of 8 primigravids in group 2).

Previous knowledge and experience of acupressure differed between the groups. Seven of the women who entered but failed to complete had no prior knowledge of acupressure. The one who did was 1 of the 2 who miscarried. Only 2 women had previously tried acupressure, both were in group 1. These minimal differences should have been adequately catered for by the use of our double-blind cross-over design.

Visual analogue diaries

Of the 15 women, only 11 vomited; 5 of these women vomited on average at least once a day. Vomiting was not significantly affected by the use of acupressure at P6. Nausea levels were averaged for each of the women and the mean levels of nausea for each group were calculated for both weeks, as were the mean levels of nausea with the bands worn at each position. Where two sets of results are quoted, the first results are based on 15 women and the results in brackets are based on 16 women including the woman at 36 weeks gestation (Table 1). The mean level of nausea was significantly lower at P6 (3.23 points on the VAS) compared with the placebo (4.92 points on the VAS) ($P = 0.019$). Table 2 shows a non-parametric analysis which also demonstrates significant results indicating that there is little 'carry over' effect between the two treatment groups.

Patient questionnaires

Where two sets of results are quoted, the main results are based on 15 women, and the results in brackets are based on 17 women including the woman at 36 weeks gestation and the woman who completed the final questionnaire, but only 1 day of the visual analogue cards.

Of the 15 women, 10 (66%) felt their nausea was reduced by acupressure at P6, whereas only 5 (33%) felt their nausea was reduced by acupressure at the placebo or sham point. These results are not statistically significant.

Table 1 Mean levels of nausea

Test	Mean (w - e)	Confidence interval	P - Value
Paired t-test of treatment at each position	1.69 (1.57)	0.32, 3.06 (2.87, 0.27)	0.019 (0.021)
Two sample t-tests of group difference for each week	1.67 (1.56)	0.24, 3.10 (0.23, 2.91)	0.025 (0.025)

Main results include 15 women, results in brackets include 16 women. Mean w - e indicates the treatment difference.

Table 2 Non-parametric analysis of mean nausea levels

Test	Mean (w - e)	Confidence interval	P - Value
Wilcoxon test of treatment at each position	1.65 (1.96)	0.14, 3.16 (0.032, 3.42)	0.037 (0.022)
Mean Whitney test of group difference for each week	1.61 (1.55)	-0.01, 3.17 (-0.04, 3.11)	0.049 (0.059)

Main results include 15 women, results in brackets include 16 women. Mean w - e indicates the treatment difference.

Of the 13 women who expressed a preference, 9 (69%) found P6 more beneficial and 4 (31%) found the placebo more beneficial. The remaining women had not found acupressure to be beneficial.

Was the placebo credible?

The credibility of the placebo position was assessed by asking the women two questions relating to both P6 and the placebo. These were:

- How confident are you that acupressure at the wrist/elbow will improve your nausea?
- How logical does this treatment seem?

The answers were rated on a scale of 0–6 and are shown in Table 3.

Table 3 shows that the women were equally confident that the acupressure would work at both positions and felt that the elbow was only a slightly less logical position to wear the *Sea-Bands*. At each level of the scale

numbers for the wrist and elbow were almost identical and no significant difference was detected.

At the end of the study the women were asked two further questions to see if their opinions of the treatments had changed. These questions were:

- How confident would you be in recommending acupressure at the wrist/elbow to your friends?
- How successful do you feel acupressure at the wrist/elbow would be in the treatment of other complaints?

Answers were rated on a scale of 0–6, the results are shown in Table 4.

The women were significantly more confident in recommending acupressure at P6 compared with acupressure at the placebo or sham point (P = 0.04). They also felt that P6 acupressure would be significantly better in the treatment of other complaints (P = 0.029).

DISCUSSION

The aim of this study was to demonstrate whether acupressure over P6 was able to reduce EMS. Our results based on the daily diaries demonstrate that there was a significant reduction in nausea in the group receiving real acupressure. 10 (66%) of the 15 women completing the study said their nausea was reduced by P6 acupressure and only 5 (33%) said their nausea was reduced by placebo or sham acupressure. Of the women who expressed a preference, 9 (69%) said they preferred P6 acupressure to the 4 (31%) who preferred the sham or placebo position.

Our results support those of previous studies in spite

Table 3 Number of women who rated their confidence in the two treatments before the study, at each level of the scale

Scale	Confidence in wrist	Confidence in elbow	Logic of wrist	Logic of elbow
0 None	0 (1)	0 (0)	0 (0)	0 (0)
1	1 (1)	1 (1)	0 (0)	0 (0)
2	1 (2)	1 (4)	1 (1)	1 (1)
3	7 (10)	7 (10)	3 (7)	5 (10)
4	3 (6)	3 (4)	3 (5)	3 (4)
5	3 (3)	3 (3)	5 (7)	3 (5)
6 Great	0 (0)	0 (0)	3 (3)	3 (3)

Main results include 15 women, results in brackets include all 23 women.

Table 4 How many women rated their confidence in the two treatments at the end of the study, at each level of the scale.

Scale	Recommend wrist	Recommend elbow	Success of wrist	Success of elbow
0	1	6	1 (2)	5 (6)
1	0	0 (1)	0	0 (1)
2	1 (2)	1 (2)	3	3
3	4	1	3	5
4	1 (2)	3	4 (5)	1
5	1	2	1	0
6	7	2	3	1

Main results include 15 women, results in brackets include 17 women.

of the fact that many of the previous reports demonstrated substantially flawed methodology. However, one study published after we began our investigation was of significantly better methodology and also demonstrated very similar results. Aloysio and Penachioni's study[23] involved 66 pregnant women who were between 7 and 12 weeks' gestation. They used *Sea-Bands* and placebo *Sea-Bands*; the placebo *Sea-Bands* involved the blunted buttons and both sets of treatment were carried out on P6. The study involved four treatments over 3 days; placebo on one wrist with true acupressure on the other. This procedure was then inverted so a placebo was used on the wrist which had previously had acupressure and the wrist which had previously had placebo had true acupressure. The other two groups involved patients having two placebo *Sea-Bands* or two active *Sea-Bands*. Symptoms were assessed at the end of each 3-day treatment. 60% of patients experienced an anti-emetic effect at P6, 30% an anti-emetic effect with placebo. It did not appear to matter whether the appropriate acupuncture point was stimulated unilaterally or bilaterally. Only 10% of patients did not complete the study, but unfortunately the study method is described only briefly and the magnitude of effect between the placebo and real *Sea-Bands* is not reported.

The overall impression gained from the studies involving acupressure at P6 as a treatment for EMS indicates a real treatment effect of approximately 60%, and a placebo effect of approximately 30% using a sham acupuncture point. This suggests that sham acupuncture, in the context of the treatment of nausea in EMS, has a true placebo effect. Previous studies on pain suggest that sham acupuncture has an effect greater than one would expect from a pure placebo[24] and may be seen to be ineffective acupuncture. Perhaps this difference may at least in part be explained by the different mechanisms involved in acupressure for nausea and acupuncture for pain. It is probable that acupuncture for pain is at least partially endorphin mediated. It is also probable that acupuncture or acupressure for nausea is largely autonomically mediated.

We have described this study as a double-blind controlled cross-over trial. At the outset, both the patients and the investigator were unaware as to whether they were receiving real or placebo treatment. A significant number of women felt confident in the effect of both acupressure points, and also felt that the selection of these points was logical and acceptable. Therefore, it could be argued that at the outset of the study, the expected outcome of both the real and placebo acupressure points were much the same. As each patient was handed an envelope describing the order of treatment, at randomisation, it was impossible for the investigator to be aware of which treatment the patient was receiving and it was also impossible for the investigator to influence outcome in any way. Patients used daily diaries throughout the study and therefore recorded treatment outcome blind to its real nature.

Treatments were crossed-over after 7 days and therefore each patient acted as her own control. The non-parametric analysis supports the argument that the 2-day wash-out period was effective, and that there was no obvious treatment benefit carried over from 1 week's treatment to the next. This study therefore represents quite a unique methodological approach. There are no other acupuncture or acupressure studies which have attempted to utilise the double-blind cross-over model, and furthermore have simultaneously attempted to assess the patient's views and beliefs in both real and placebo acupuncture, in order to further validate the placebo treatment.

The major problems associated with the study involve low numbers and a relatively high drop-out rate. Those not completing the study were largely single parents who were not in long-term stable relationships. For further studies it might be preferable to select those who are married or in long-term relationships. Numbers entered were far lower than estimated and this again provided some cause for concern. However, in spite of these problems and the relatively low power of the study, the results are quite consistent with other published studies attempting to evaluate the effects of acupressure in EMS. We believe that our study methodology has gone a long way to correct some of the previous mistakes perpetrated by methodologically inadequate studies. It is important to note that no negative studies have been published indicating that P6 has no effect on nausea. All the studies in the field of P6 in EMS indicate a 60–65% treatment effect and a 30% placebo effect. We believe our methodology represents a substantial advance on previous studies; however, it is quite clear that one or two much larger studies with better statistical power must be completed and published if the case for acupressure at P6, as a treatment for EMS, is to be completely proven.

References

1. Benson RC. Handbook of obstetrics and gynaecology. 4th ed. Edinburgh: Blackwell, 1971.
2. Pritchard JA, Macdonald P, Gant NF eds. Williams obstetrics. 17th ed. Norwalk: Appleton Century Crofts, 1985.
3. Jensen MD. Maternity care: the nurse and the family. St Louis: CV Mosby, 1977.
4. Jarnfelt-Samsioe A, Samsoie G, Velinder GM. Nausea and vomiting in pregnancy – a contribution to its epidemiology. Gynec Obst Invest 1983; 16(4): 221–229.
5. Midwinter A. Vomiting in pregnancy. Practit 1971; 206: 743–750.
6. Alley NM. Morning sickness: the client's perspective. JOGN Nurs 1984; 13(3): 1285–1289.
7. Vellacot ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. Int J Gynaec Obst 1988; 27(1): 57–62.
8. Symmonds M. Essentials of obstetrics and gynaecology. 2nd ed. Edinburgh: Churchill Livingstone, 1992.
9. Hyde E. Acupressure for morning sickness: a controlled clinical trial. J Nurs Midwif 1989; 34(4): 171–178.
10. Hays DP. Bendectin: a case of morning sickness. Drug Intel Clin Pharm 1983; 17(11): 826–827.

11 McCredie J, Kricker A, Elliott J et al. The innocent bystander. Doxylamine/dicyclomine/pyridoxine and congenital limb defects. Med J Aust 1984; 140(9): 525–527.
12 Elbourne D et al. Debonox revisited. Br J Obst Gynaec 1985; 92(8): 780–785.
13 Leatham AM. Safety and efficacy of antiemetics used to treat nausea and vomiting in pregnancy. Clin Pharm 1986; 5(8): 660–668.
14 Dilorio C. The management of nausea and vomiting in pregnancy. Nurs Pract 1988; 13(5): 23–28.
15 (Anon). Outline of Chinese acupuncture. Peking: Foreign Language Press, 1975.
16 Sea-Band leaflet. Sea-Band UK Ltd.
17 Chagxin Z. Acupuncture treatment of morning sickness. J Trad Chin Med 1988; 8(3): 228–229.
18 Rongjun Z. 39 cases of morning sickness treated with acupuncture. J Trad Chin Med 1987; 7(1): 25–26.
19 Dundee JW, Yan J, McMillan C. Non-invasive stimulation of the P6 (Neiguan) antiemetic acupuncture point in cancer chemotherapy. J Roy Soc Med 1991; 84: 210–212.
20 Dundee JW, Yan J, McMillan C. P6 acupressure reduces morning sickness. J Roy Soc Med 1988; 81: 456–457.
21 Borkovec TD, Nau SD. Credibility of analaogue therapy rationales. J Behav Therap Exp Psychiat 1972; 3: 257–260.
22 Vincent C. Credibility assessment in trials of acupuncture. Compl Med Res 1990; 4(1): 8–11.
23 Aloysia D, Penachioni P. Morning sickness control in early pregnancy by Neiguan point pressure. Obst Gynec 1992; 80: 892–894.
24 Lewith GT, Machin D. On the evaluation of the clinical effects of acupuncture. Pain 1983; 16: 111–127.

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