Study Protocol

Clinical efficacy and safety evaluation of thumbtack needle in nausea and vomiting in pregnancy: a randomized controlled clinical trial

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1. Study background

Nausea and vomiting in pregnancy (NVP) is symptoms of nausea and/or vomiting that occur during pregnancy before 16 weeks' gestation and exclude other causes of nausea and vomiting. NVP affects up to 90% of pregnant women, usually starting at the 4^{th} ~ 7^{th} week of pregnancy, peaking around the 9^{th} week, and the symptoms of 90% patients resolving naturally at the 20^{th} week. NVP has become the most common and intractable problem in the first trimester and is the second most common cause of presentation during pregnancy whereas threatened miscarriage is the first[1]. According to a large-scale survey in China [2], the incidence of NVP in the first trimester population (n=3337) was 62.51%, and 47.2% in the second trimester population (n=2915) still had NVP. Combined with the first and second trimesters, NVP occurred in 73% of pregnant women (2129 people, including those that occurred in the first or second trimester). Among the 2129 patients who developed NVP during pregnancy, 1832 (86.05%) had symptoms that began in the first trimester.

Symptoms and severity of NVP vary widely, ranging from simple nausea to the most severe form of hyperemesis gravidarum (HG). HG is the most severe stage of nausea and vomiting during pregnancy, accounting for 0.5~2% of all pregnant women[3]. Although NVP is very common during pregnancy, it is generally considered normal and self-limiting, and its adverse effects on pregnancy are largely underestimated. However, there is evidence that all types of NVP affect the quality of life of pregnant women, and that the magnitude of the impact increases with the frequency of symptoms[4]. In addition, NVP increases the risk of postpartum depression, and the risk increases with the severity of NVP[2]. Due to the lack of awareness of NVP and concerns about the teratogenicity of drugs to embryos, NVP treatment is always insufficient, and the choice of medication regimen is conservative, and symptomatic supportive therapy is generally used. The survey found that only 3.64% of patients in China were treated for NVP in the first trimester, which was much lower than the level of the United States (18%) and other countries[2]. Therefore, pregnant women in China have to endure more discomfort caused by NVP during pregnancy.

The treatment of NVP is generally focused on symptomatic supportive treatment, such as antinausea, rehydration, and correction of acid-base balance. Doxylamine-pyridoxine) (Xonvea®, the first-line drug recommended in the guidelines of the United States and the United Kingdom [5-6], considering that it may be related to birth defects, has not been approved for its use in pregnancy in many countries, including China. Due to its special taste, traditional Chinese medicine is difficult for pregnant women to swallow, thus limiting its application in NVP. Acupuncture has good efficacy in the treatment of NVP. In a recent large-sample, multicenter RCT study [7], 352 pregnant patients with moderate or severe NVP were recruited in 13 tertiary hospitals in China (the severity of NVP was determined by the pregnancy-unique quantification of emesis and nausea (PUQE) score, which ranged from 3~15, <6 is mild, 6~12 is moderate, and ≥13 is severe), and was treated with acupuncture combined with doxylamine-pyridoxine for 2 weeks. It was found that acupuncture or drugs (docemin-pyridoxine) alone were effective in both moderate and severe NVP, and that the effect of acupuncture was comparable to that of doxymine-pyridoxine, and that the combination of acupuncture and doxymine-pyridoxine may be more effective than their alone. The research results won the top ten academic advances in traditional Chinese medicine in 2023.

Although acupuncture using traditional millineedle has a good effect on NVP, it is inevitably painful when the millineedle is inserted, and the needle sensation of soreness, numbness, swelling and pain during acupuncture is sometimes so strong to cause fear and discomfort in pregnant women, which would produce an adverse effect on pregnancy. Moreover, acupuncture with millineedle needs to be conducted once a day, and pregnant women need to go to the hospital frequently every day, and pregnant women are already inconvenient, which increases the difficulty of pregnant women's medical treatment. Pregnant women, especially in the early stages of pregnancy, should not be stimulated, should recuperate, and maintain physical and mental peace. Therefore, although acupuncture with millineedle has a good effect on NVP, it is still difficult to promote its application in clinical practice.

As a kind of intradermal needle, thumbtack needle (TN) is a method of shallow

puncture and long-term needle. Although the amount of stimulation of TN is weaker than that of millineedle, it has a much longer effect and can produce continuous and stable stimulation, and therefore, the cumulative effect is often better than that of traditional millineedle acupuncture. Moreover, due to the small needle body of TN (the diameter of the needle body is only 0.15 ~ 0.25mm, and the length of the needle body is only 1.2 ~ 2.5mm), it will not hurt the subcutaneous nerves, blood vessels, viscera and other tissues, which is very comfortable and safe to treat, and overcomes the needle sting pain of traditional millineedles. Therefore, TN is especially suitable for some patients who are afraid of needles [8]. In addition, the TN can be retented for 3~5 days after one treatment, which greatly reduces the duration and frequency of patient's visits. In recent years, some small-sample, non-randomized controlled clinical studies have shown that TN is effective in the treatment of hyperemesis gravidarum [9-11].

For the treatment of VNP, acupoints such as Zhongwan (CV12), Neiguan (PC6), and Zusanli (ST36) are often used. CV12 is the recruitment point of the stomach, which has the effect of strengthening the spleen and stomach, promoting gastrointestinal peristalsis and emptying. PC6 is the key point for relieving vomiting, rationalizing qi and widening the chest, calming the heart and calming the nerves, and reducing stomach inversion and relieving nausea; Acupuncture ST36 can strengthen the spleen and stomach, nourish qi and nourish blood. Those with disharmony in the liver and stomach are added BL17 or BL18 to relieve the liver and regulate qi, and reconcile the liver and stomach. Those with obstruction of phlegm and dampness are added Fenglong (ST40) to dissolve phlegm and dampness, and those with spleen deficiency and dampness are added to Yinlingquan (SP9) to strengthen the spleen and dispel the dampness.

Since the effect of acupuncture is accumulated over time, the effect is no less than that of traditional milli-needle acupuncture, and the treatment is comfortable, safe and painless, and it can be treated once in 3~5 days, which is simple and easy. Although there are several small, non-randomized clinical trials that suggest that acupuncture has good clinical efficacy in the treatment of VNP, multi-center and large-sample

RCTs are still needed to provide high-quality evidence-based evidence. This project intends to use multi-center, large-sample, randomized, controlled, double-blind clinical trials to observe the effects of nausea and vomiting, quality of life, anxiety and depression, weight change, blood electrolyte levels, liver and kidney function, thyroid function, intravenous infusion therapy, use of additional drugs, hospitalization, pregnancy complications (gestational diabetes and hypertensive diseases), pregnancy outcomes and neonatal outcomes in women with VNP, and evaluate their safety, so as to provide high-quality evidence support for the clinical promotion and application of needles in the treatment of VNP.

2. Study objectives

A multicenter, large-sample, randomized, controlled, double-blind clinical trial was conducted to observe the effects of TN on nausea and vomiting, quality of life, anxiety and depression, weight change, blood electrolyte levels, liver and kidney function, thyroid function, intravenous fluid therapy, use of additional drugs, hospitalization, pregnancy complications, pregnancy outcomes, and neonatal outcomes in women with VNP, and to evaluate its safety.

3. Study content

3.1 The selection and exclusion of subjects

We will choose moderate or severe 320 VNP patients who take a visit during Oct. 2024 to Oct. 2028 to the departments mentioned below: Department of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; Fujian Provincial Maternal and Child Health Care Hospital; Jingzhou Traditional Chinese Medicine Hospital, Jingzhou, Hubei, China; Qianjiang Maternal and Child Health Care Hospital, Qianjiang, Hubei, China; Xiaogan Maternal and Child Health Care Hospital, Xiaogan, Hubei, China; Qianjiang Central Hospital, Qianjiang, Hubei, China; Shiyan People's Hospital, Shiyan, Hubei, China; Wuhan Jinxin Gynecology

and Obstetrics Hospital of Integrative Medicine, Wuhan, Hubei, China; Xiangyang Traditional Chinese Medicine Hospital, Xiangyang, Hubei, China; Suizhou Maternal and Child Health Care Hospital, Suizhou, Hubei, China; Nanzhang County Traditional Chinese Medicine Hospital, Nanzhang, Hubei, China; Dongchangfu District Maternal and Child Health Care Hospital of Liaocheng City, Liaocheng, Shandong, China; Xiangyang Central Hospital, Xiangyang, Hubei, China; Aksu Prefecture Maternal and Child Health Hospital, Aksu, Xinjiang, China.

The age of the patients is between 20 to 45 years. According to the Network version of the central randomization system, patients are allocated randomly as 1:1 to TN group, sham TN group and blank control group with 160 patients in each group. The network version of the central randomization system designs the random parameters. The clinical researchers log in the system and input the information of the subjects to be enrolled, after that they can obtain the random number and grouping information assigned by the system. The randomization protocol and the parameters set during the generation of the protocol are collectively called blind substrates, and are all kept by people who are not involved in the process of treatment, evaluation and statistical analysis.

3.1.1 Inclusion criteria

Pregnant women who meet the standers below will be included in this study.

3.1.1.1 The mother's age is 20 ~ 45 years old, the gestational age is 6 ~ 12 weeks, and the ultrasound confirms that it is an intrauterine single or multiple pregnancy, and the weight loss is less than 10% compared with before pregnancy.;

3.1.1.2 Women diagnosed with moderate to severe NVP in the first trimester: the severity of NVP was determined by the PUQE score (see Table 1), and the PUQE score ranged from 3 ~ 15, < 6 was mild NVP, 6 ~ 12 was moderate NVP, and ≥13 was severe NVP. PUQE score ≥ 6 may be included in this study;

3.1.1.3 Women voluntarily sign the informed consent form.

Table 1 Quantification of NVP in the US ACOG guidelines

1. In general, how often do you feel nauseous or nauseous each day?
Never (1) ≤1 h (2) 2～3 h (3) 4～6 h (4) ＞6 h (5)
2. In general, how many times a day do you vomit?
Never (1) 1～2 (2) 3～4 (3) 5～6 (4) ≥7 (5)
3. In general, how many times a day do you retch (no contents) ?
Never (1) 1～2 (2) 3～4 (3) 5～6 (4) ≥7 (5)

Total score (add all the points together): Mild NVP: < 6, moderate NVP: 6～12, severe NVP: ≥13

3.1.2 Exclusion criteria

Pregnant women who meet any of the following conditions will not be included.

3.1.2.1 Age < 20 years, or > 45 years.

3.1.2.2 Gestational age < 6 weeks, or > 12 weeks.

3.1.2.3 PUQE score < 6.

3.1.2.4 frequent nausea and vomiting, weight loss of >10% compared with before pregnancy; or symptoms such as listlessness, paleness, dry skin, sunken eye sockets, and a marked decrease in urine output (less than 400ml of urine in 24 hours or less than 5 times and a small amount of urine in 24 hours).

3.1.2.5 At rest, body temperature > 38 ℃, systolic blood pressure < 90 mmHg or > 140 mmHg, diastolic blood pressure < 60 mmHg or > 90 mmHg, heart rate ⩾ 100 beats per minute, or oxygen saturation < 95%.

3.1.2.6 Urinalysis: urine ketones: +++ and above; or (and) urine protein: ++ and above.

3.1.2.7 Blood biochemistry: serum potassium ⩽ 3.0mmol/L, serum sodium ⩽ 130mmol/L; or abnormal liver function: elevated liver enzymes ≥ 2 times the upper limit of normal; or renal dysfunction: elevated serum creatinine and urea nitrogen.

3.1.2.8 Other digestive diseases that cause nausea and vomiting, such as gastrointestinal infections (with diarrhea), gastric ulcers (with epigastric pain

or hematemesis), cholecystitis, biliary roundworms, pancreatitis (with abdominal pain, plasma amylase levels rise to 5 ~ 10 times normal), viral hepatitis (positive hepatitis virology, liver enzyme levels ≥ 1 000 U/L) or acute fatty liver during pregnancy, tumors of the digestive tract.

3.1.2.9 Suffering from immune diseases such as systemic lupus erythematosus, scleroderma, dermatomyositis, IgG4-related diseases, immune nephropathy, etc.

3.1.2.10 Have uncorrected diseases of the endocrine system, such as diabetes, Addison's disease, hyperthyroidism, hypothyroidism, thyroid tumors, adrenal tumors, etc.

3.1.2.11 Suffering from neurological diseases such as migraine, neuromyelitis optica, epilepsy, and neurologic tumors.

3.1.2.12 In the past 1 week, have taken antiemetic drugs such as ondansetron, metoclopramide (metoclopramide), promethazine, and anti-vomiting Chinese medicine.

3.1.2.13 Monoamine oxidase inhibitors are used.

3.1.2.14 Had TN treatment in recent 3 months.

3.1.2.15 Unwilling to sign the informed consent of this study.

3.2 The intervention program

According to the theory of traditional Chinese medicine, the treatment plan of TN is formulated, and the study protocol follows the CONSORT and STRICTA regulations, and details the number of TN used, the frequency of treatment and the duration of treatment. Both the TN group and the sham TN group were treated with a fixed treatment regimen, which was treated once every 3 days, for a total of 5 treatments for 15 days. During the same period, the blank control group was not given TN or sham TN treatment. All three groups of patients were given pregnancy care and dietary guidance.

3.2.1 Protocol for TN group

The main acupoints of treatment are Zhongwan (CV12), bilateral Neiguan (SP6), and

bilateral Zusanli (ST36), with a total of 5 acupoints. Patients with Qi stagnation should be given Danzhong (CV17) or the Ashi acupoint (Identify the most prominent tender point between the Danzhong (CV17) and Zhongwan (CV12). If such a tender point exists, apply a TN at the tender point, that is, the Ashi acupoint. If no tender point is found, apply the TN at the Danzhong acupoint. Just choose one of the two.), patients with liver and stomach disharmony should be given bilateral Geshu (BL17), patients with phlegm-dampness obstruction should be added bilateral Fenglong (ST40), and patients with weak spleen and stomach should be added bilateral Weishu (BL21). The above acupoints are treated with TN.

The doctor disinfects his hands, strictly disinfects the local skin of the acupoint, applies the disposable sterile TN to the sterilized acupoint, and after a slight pressure, removes the isolation paper (the function of the isolation paper is to avoid direct contact with the sterile glue surface when adhering it to the skin), and press again to ensure that the TN stick the surface of the acupoint firmly. The TN will be kept in the acupoints for 3 days. During the 3-day retention of TN, the patient presses the TN 3 times a day and half a minute per time per acupoint. After 3 days retention of TN, the patient will be instructed to go to the hospital, where the doctor will remove the TN, disinfect the local skin of acupoints and conduct the next treatment of TN. A total of 5 sessions treatment will be applied for a duration of 15 days.

3.2.2 Protocol for sham TN group

The sham TN will be used for the sham TN group. Even though the appearance and shape of sham TN are similar to the real TN, the sham TN has no needle body. Therefore, the sham TN does not produce a needle-like effect of TN

The acupoints of sham TN group are the same as those of TN group. The use of sham TN was the same as that of the TN group. After 3 days retention of sham TN, the patient was instructed to go to the hospital, where the doctor removed the sham TN, and conducted the next treatment after local skin disinfection. A total of 5 treatments were given for a duration of 15 days.

3.2.3 Record for the treatment

The treatment date, time and the name of the acupuncturist are recorded when the patient receives TN or sham TN treatment. No treatment is given to the blank control group, but the date and times of the inquiry of blank control group are also recorded. During the treatment, the local hematoma or turquoise, pain or skin allergies that may occur during the treatment, as well as other discomforts after the treatment (nausea, vomiting, palpitations, dizziness, headache, anorexia and insomnia), should be recorded in detail and disposed in time.

3.3 Outcome measures

3.3.1 Primary outcome measure

PUQE scores were evaluated before treatment and on days 3, 6, 9, 12, and 15 of treatment. The primary outcome measure was the change of PUQE score on day 15 at the end of the treatment when compared with the baseline.

3.3.2 secondary efficacy endpoints

3.3.2.1 Questionnaires

Evaluation is performed before and after treatment.

3.3.2.1.1 Quality of life survey: The NVP Quality of Life questionnaire (NVPQOL) is used to evaluate the quality of life of pregnant women.

3.3.2.1.2 Anxiety and depression status survey: Zung anxiety self-rating scale (Zung-SAS) and Zung depression self-rating scale (Zung-SDS) are used to evaluate the anxiety and depression status.

3.3.2.1.3 Sleep status survey: The Pittsburgh sleep quality index (PSQI) was used to survey the sleep status of patients.

3.3.2.2 changes in the patient's weight; changes in electrolytes (sodium, potassium, chloride, magnesium, calcium, iron, and zinc) in the blood; arterial blood gas analysis; changes in liver and kidney function; Changes in thyroid function.

3.3.2.3 Situation of intravenous fluid therapy, use of additional medications, hospitalization, and termination of pregnancy.

3.3.2.4 Pregnancy complications, including miscarriage (first and second trimester), hypertensive disorders during pregnancy, and gestational diabetes.

3.3.2.5 Pregnancy outcomes, including termination of pregnancy and delivery outcomes (including live birth, vaginal birth, caesarean section, gestational age, etc.)

3.3.2.6 Neonatal outcomes, including preterm birth, birth weight, and small for gestational age (SGA). "Small gestational age" refers to babies with birth weight below the 10th percentile according to the sex and gestational age of the Chinese population.

3.3.2.7 Patient's satisfaction with treatment.

3.3.2.8 Patient's adherence to treatment.

3.4 Follow-up

After 15 days of the treatment, participants will be followed up once a week for a total of 4 weeks, and then once a month until live birth.

3.5 Safety assessment

Adverse events will be classified, and the percentage of adverse events and severe adverse events occurred during treatment will be recorded in detail. Chi-square test is used to analyze the total proportion of adverse events in each treatment regimen and the differences between the classifications. Unless otherwise formally requested, each data safety oversight board report will report details and summaries of adverse events in a double-blind manner.

3.6 Statistics

3.6.1 Calculation of sample size

The calculation of the sample size is based on the measurement of the primary outcome. The primary outcome is the change of PUQE score on day 15 at the end of the treatment when compared with the baseline.

The change of PUQE score from baseline is used to compare the efficacies between the TN group and the sham TN group. Since there are no randomized controlled trials

of TN for the treatment of VNP, this project hypothesizes that TN can achieve the same efficacy as acupuncture, and the sample size is calculated according to the effect of acupuncture in the references [7], assuming that the PUQE score decreased by 4.9 points from baseline with a standard deviation of 2.4 after TN treatment, and the PUQE score also decreased by 4 points from baseline with a standard deviation of 2.7 after sham TN, the combined variance was 2.0, and the $\alpha = 0.05$ (bilateral), $\beta = 0.20$, and power = 0.80 were taken to allocate each group according to 1:1, and the statistical sample size was 128 cases in each group. Considering factors such as dropout/rejection, the number of enrolled cases was increased by 20%, and 160 subjects in each group were planned to be enrolled, with a total of 320 cases.

3.6.2 Statistical test

The method of intention analysis set is used to detect the difference of the change of PUQE scores among three groups. Persenka square test is used to compare the live yield of the main index. The secondary indicators are analyzed by the corresponding statistical methods (Chi-Square test is used for counting data, and t test is used for measuring data with equal variance). The primary outcome was analyzed according to the intention-to-treat (ITT) principle. Chained multiple imputation under the missing-at-random assumption was used to generate 20 imputed data sets for missing PUQE scores over the intervention period in participants who withdrew (MI procedure in SAS), and the estimates were combined using the Rubin rules (MIANALYZE procedure in SAS) across the imputed sets. The modified ITT population was defined as the participants who completed the primary outcome measurement. The per protocol set (PPS) referred to participants who adhered to the treatment protocol they were originally allocated to.

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