

Original Research

# A Clinical Trial of Wrist-Ankle Acupuncture for Abirritation during High-Intensity Focused Ultrasound Treatment of Adenomyosis

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## Abstract

**Background:** Wrist-ankle acupuncture (WAA) has promising analgesic effect during high-intensity focused ultrasound (HIFU), but evidence-based clinical test is scarce. The purpose of this research is to assess the efficacy of WAA for relieving pain during HIFU treatment of adenomyosis. **Methods:** Fifty-eight patients with adenomyosis treated with HIFU were enrolled in this study. Among them, 30 patients chose the WAA group, and the others selected the pethidine injection. The visual analog scale (VAS) pain score was recorded to assess the pain during HIFU before and after analgesic therapy. The VAS at 10 min, 30 min and 1 h after analgesic therapy, and the adverse effects, were noted and calculated to compare these two approaches. **Results:** The median pain score in the WWA group at 10 minutes was 6 [6, 7], which was higher than that in the control group it was 5 [4, 6] ( $p < 0.001$ ). At 30 min and 60 min, the pain scores were 5 [4, 6] in the WAA group and in the control group. The statistically significant differences were not found in pain relief scores at 30 or 60 min ( $p > 0.05$ ). No side effects were observed in the WAA group. **Conclusions:** WAA is a safe and easily available technique to reduce the pain during HIFU treatment, with no severe effects. Thus, it can be widely used and promoted in clinical practice.

**Keywords:** high-intensity focused ultrasound; pain; wrist-ankle acupuncture; clinical trial

## 1. Introduction

Adenomyosis is a benign and common uterine disease. The prevalence varies widely due to differences in the diagnostic criteria and variations between and within pathologists [1]. The formation of this disease is through the invasion of the endometrium into the myometrium, then a diffusely enlarged uterus is produced. Microscopically, the hypertrophic myometrium is surrounded by ectopic endometrial glands and stroma with non-neoplastic [2]. The main clinical manifestations are various among the women with adenomyosis, such as menorrhagia, menostaxis, progressive dysmenorrhea, as well as infertility, which can severely affect their life quality [3]. To date, the only definite way to cure adenomyosis is hysterectomy [4]. However, women are mostly reluctant to accept it as a treatment; furthermore, it is unsuitable for patients who wish to preserve their fertility.

High-intensity focused ultrasound (HIFU) is a relatively new technique for the treatment of adenomyosis [5]. Many studies [6–10] have proved that HIFU is a safe and effective method to treat adenomyosis. Nevertheless, the

pain caused by HIFU treatment is hard to bear, which disturbs the patients [11]. Pethidine is generally used for pain relief. However, it has proven side effects including sedation, nausea, and numbness in clinical practice [12].

Acupuncture is a part of Chinese culture and has an important role in traditional Chinese medicine. By acting on the body's meridian system, it can help relieve pain. Wrist-ankle acupuncture (WAA) is a simple, safe, painless, and reliable acupuncture method developed by Professor Zhang Xinshu [13], an expert in the Department of Neuropsychiatry, Changhai Hospital of the Second Military Medical University. Several studies have shown that WAA is a eutherapeutic treatment for alleviating pain [14,15], including pain after laparoscopic surgery for eccyosis [16] and primary dysmenorrhea [17–22]. WWA does not have any serious side effects when compared with other analgesics, which may cause sensory disturbance, nausea, or vomiting [13]. Several animal studies [23,24] have shown that WWA alleviates spinal pain by suppressing or increasing the expression of some neurotransmitters such as 5-HT or endomorphin-1 in the spinal cord pathway of the pain-modulating system. However, there have been no studies



on the effect of WWA in relieving the pain caused by HIFU treatment for adenomyosis. Therefore, we designed the first clinical trial to investigate the analgesic effects of WWA compared to the pethidine injection in adenomyosis patients treated with HIFU.

## 2. Materials and Methods

This study was conducted from January to December in 2021 in Dongguan Maternal and Child Health Care Hospital. The inclusion criteria were as follows: (1) women of childbearing age, (2) patients who met the diagnostic criterion for adenomyosis and received HIFU treatment, (3) visual analogue scales (VAS) during HIFU treatment of  $\geq 6$ , and (4) no previous history of needle sickness or allergy to pethidine. Exclusion criteria were as follows: (1) use of other treatments to relieve the pain caused by HIFU treatment on adenomyosis, (2) intake of analgesics during the 24 hours prior to treatment, (3) having complications as a result of severe disease (e.g., cardio-cerebral vascular disease, liver and kidney diseases, or hematopoietic system diseases) or mental defects, (4) lack of compliance, and (5) incomplete clinical data. After filtering in accordance with the inclusion and exclusion criteria, 58 patients with adenomyosis treated with HIFU were enrolled in the study. Among them, 30 patients chose the WAA group, and the others selected the pethidine injection group according to their wishes.

Patients with VAS  $\geq 6$  during HIFU treatment was selected for analgesic therapy. WAA was used in the WAA group, and intramuscular injection of pethidine was used in the pethidine group. WAA was located at point 1 (3 inches over the bulge of medial malleolus) in both ankles (Fig. 1). A Huatuo brand stainless steel filiform needle (0.30 mm in diameter and 25 mm in length, Suzhou Medical Supplies Factory, Jiangsu Province, China) was used in this trial. The selected acupoint was disinfected with iodophors. Then the Chinese medicine acupuncturist use his thumb, index finger, and middle finger of the right hand to hold the needles. Pressing the skin around the acupoint gently until it slightly taut. The needle was then swiftly put into the acupoint along the skin until the body of needle inserted into the skin entirely. During the whole process, patients cannot feel stabbing pain brought by acupuncture. At last, adhesive tape was used to fix the handle to the skin. The needles were retained inside the subcutaneous tissue for 30 min. In order to prevent bleed of insertion points, dry sterilized cotton balls were firmly put on the acupoint. Pethidine was administered at a dose of 50 mg through intramuscular injection into the gluteus maximus muscle.

The VAS was recorded to assess the pain during HIFU before and after analgesic therapy. The VAS at 10 min, 30 min and 1 h after analgesic therapy would be recorded. During this process, the patients were shown a line marked from 0 to 10. They were then asked, "What is the pain intensity you feel now"? The patients pointed out the pain score on



Fig. 1. Wrist-ankle acupuncture inserted into point 1.

the line (0 = no pain to 100 = worst pain imaginable). The researchers also observed and inquired about any discomfort that the patients might be feeling. The VAS score and the adverse effects were recorded and analyzed.

Descriptive analysis was used to display the baseline and demographic features of the study participants by randomization group. Statistical analyses were conducted using SPSS 24.0 (IBM Corp., Armonk, NY, USA). For quantitative data, we would verify the distribution pattern and homogeneity of variance. For statistical description in a symmetric distribution, the mean (M)  $\pm$  standard deviation (SD) was applied, while skewed distributions were expressed as the median (25%, 75%). The quantitative indices of normal distribution before and after treatment were determined and compared the effect of acupuncture by paired samples *t*-test in one group and independent *t*-test between the two groups. The skew distribution data were compared by Mann Whitney U test. The entire statistical test used bilateral examinations, and the significance line was set at  $p < 0.05$ .

## 3. Results

### 3.1 Patients Characteristics

Patient demographics and clinical features at baseline are shown in Tables 1,2. There were no statistically significant differences in age, course of disease, lesion volume, CA125, CA19-9 levels, and dysmenorrhea score (VAS) before treatment ( $p > 0.05$ ).

Table 1. Clinical profile of the patients with adenomyosis.

Variables	WWA group	Pethidine group	<i>T</i>	<i>p</i>
Age (y)	41.67 $\pm$ 4.54	41.78 $\pm$ 4.89	0.086	0.931

### 3.2 Comparison of Pain Score between the 2 Groups

In Table 3, we could see that there were no statistically significant differences in the pain scores before the intervention ( $p > 0.05$ ). The median pain score in the WWA group at 10 min was 6 [6, 7], which was higher than that in the Pethidine group it was 5 [4, 6] ( $p < 0.001$ ). At 30 min and 60 min, the pain scores were 5 [4, 6] in the WWA group and in the Pethidine group. The differences in pain relief scores at 30 or 60 min were relatively meaningless ( $p > 0.05$ ).

**Table 2. Clinical profile of the patients with adenomyosis.**

Variables	WAA group	Pethidine group	Z	p
Course of disease (y)	5 [ 2, 10 ]	6 [3, 14]	-1.227	0.220
Lesion volume (mm <sup>3</sup> )	125102.93 [93566.24, 162220.85]	98938.70 [81281.64, 129463.81]	-1.341	0.180
CA125 (kU/L)	89.50 [39.43, 143]	74.30 [35.68, 142.63]	-0.025	0.980
CA19-9 (kU/L)	26.20 [12.94, 45.13]	33.71 [20.66, 46.79]	-0.622	0.534
Dysmenorrhoea score	8 [6, 8]	8 [6, 8]	0.453	0.651

**Table 3. Comparison of analgesia effects between the 2 groups.**

	WAA group	Pethidine group	Z	p
<b>Pain score**</b>				
Before intervention	8 [7, 8]	8 [7, 8.5]		
10 min	6 [6, 7]	5.41 ± 1.31		
30 min	5 [4, 6]	5.00 ± 1.00		
60 min	5 [4, 6]	5.04 ± 0.85		
<b>Pain relief***</b>				
10 min	1 [1, 1]	2 [2, 3]	-5.65	0.000
30 min	2 [2, 3]	3 [2, 3]	-1.382	0.167
60 min	2.5 [2, 3]	3 [2, 3]	-1.067	0.286
<b>Adverse effects (n)</b>				
Vomiting	0	18		
Dizziness	0	9		
Hidorrhea	0	5		
Skin burn	0	2		
Hematuria	0	0		

Pain score\*\* was estimated by Visual Analogue Scale (VAS).

Pain relief\*\*\* referred to the difference between the pain score before and after abirritation therapy.

### 3.3 Adverse Effects

No adverse effects were observed in the WAA group (Table 3). However, in the control group, 9 patients reported vomiting, 7 patients complained of dizziness, and 4 patients suffered from hidorrhea after the pethidine injection. 1 case developed HIFU treatment-induced skin scald, characterized by small skin blisters and skin redness. All these adverse reactions improved within 1 day. No fever, hematuria, or other severe complications occurred in either group.

## 4. Discussion

In this study, pethidine injection relieved the pain during HIFU treatment for adenomyosis more quickly when compared to the WAA, but eventually, the patients in the two groups had similar analgesic effects. No adverse reactions were observed in the treatment group, but adverse events were associated with 11 patients (55%) in the pethidine group, including skin burn, vomiting, dizziness, and hidorrhea. Therefore, WAA had similar analgesic effects during HIFU treatment with almost no adverse effect, which deserves our attention.

HIFU, which is a noninvasive therapeutic technique, has been applied to the treatment of adenomyosis in recent years. The therapeutic mechanism of HIFU treatment is using the ultrasound beams to penetrate the abdominal wall and focus on the target tissues, which can lead the heat over 65 °C, without damaging the surrounding structures [25]. The aim of this treatment is to reduce the area of the adenomyotic lesion, so as to relieving symptoms caused by adenomyosis. Nevertheless, the side effects of HIFU should not be overlooked. It was claimed that the main adverse effects during and after the therapy were lower limb movement disorder, urinary retention, bowel perforation, abdominal pain, and skin burns. Among these, abdominal pain is the most common and unbearable adverse event during HIFU treatment, which needs pain relief treatment.

Pethidine injection causes the body to feel less pain through the activation of central opioid receptors, therefore, it is widely used in various surgeries [26]. Pethidine is a synthetic opioid that exerts its analgesic effects by acting as an agonist at  $\mu$ -receptors [27]. Due to this mechanism of action, the sensory nerves of other areas of the body become insensitive. Therefore, the doctor cannot get immediate feedback such as the feeling of skin burning sensation caused by HIFU treatment from the patients. It may cause skin scald and the lesion being over treated [28].

Acupuncture has been used to relieve pain for a long time. Dawn *et al.* [29] reported that acupuncture was associated with statistically significant reductions in aromatase inhibitor-related joint pain at 6 weeks. Katherine *et al.* [30] demonstrated that acupuncture improved aromatase inhibitor-associated joint pain in women with early-stage breast cancer. WAA is a form of acupuncture, this therapy is based on the meridian and collateral theory, which has a regulatory action on the neuroendocrine system. It has been used as an efficient treatment for relieving pain in common gynecological disease, such as primary dysmenorrhea [17,19,31] and pain after gynecological surgery [21]. Nevertheless, it does not emphasize the sensation of obtaining qi, which is manifested as the sense of sourness, distention with a little pain. According to Chen [31], WAA is a more controlled method than traditional acupuncture because it has no uncomfortable sensation. In our trial, the pain score of the pethidine group in the first 10 min was lower than that in the WAA group, which shows that it may require more time for WAA to be effective. However, WAA is still an effective way to reduce pain, with a lower rate of adverse effects. This is the first time to investigate the

analgesic effect of WAA during HIFU treatment, and it is a convenient and safe method for clinical use. What's more, WAA relieves pain without affecting the sensory nerves of other parts of the body, so the patient can give feedback to the doctor in time during HIFU treatment, preventing the lesion over treated and other adverse effects.

Our study has several strengths and limitations. Firstly, our study was the first to combine traditional culture with modern technology, and it proved that acupuncture was efficient, without any severe adverse effects. Secondly, we chose different time points to evaluate the VAS of patients, which reflected the changes in the analgesic effect. The limitations of this study are as follows: First, VAS pain scores were seldom given to women who had never been evaluated, so the VAS might be subjective, which may cause bias. Second, this single-center study may not be generalizable. Multicenter and large sample data are needed in further studies.

## 5. Conclusions

WAA is a safe and easily available technique to reduce the pain during HIFU treatment, with no severe effects. Thus, it can be widely used and promoted in clinical practice.

## Author Contributions

HJY and HTL designed the research study. CNL, XYL performed the research and wrote the manuscript. YQW, XJZ, and YHL collected the data. MDZ and QXS analyzed the data. LT was responsible for quality control. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

All patients were counseled about the adverse reactions of the two treatments, and they signed the consent form for the therapeutic content and investigation protocol. The study was approved by Institutional Review Board of Dongguan Maternal and Child Health Care Hospital (approval number: 202007).

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## Conflict of Interest

The authors declare no conflict of interest. XJZ who comes from Shenzhen PRO HIFU Medical Co. Ltd only participated in the work of data collection. There is no conflict of interest with any company or group.

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