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Uterine Fibroids & Adenomyosis

Gonadotrophin-releasing hormone agonist combined with high-intensity focused ultrasound ablation for adenomyosis: a clinical study

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Objectives This study was to investigate the clinical efficacy of a gonadotrophin-releasing hormone agonist (GnRH-a) combined with high-intensity focused ultrasound (HIFU) ablation treatment for adenomyosis.

Design A non-randomized prospective study.

Setting Gynaecological Minimally Invasive Centre in a single hospital.

Population Patients with adenomyosis.

Methods Seventy-nine patients with adenomyosis were enrolled, including 55 patients in the control group treated with only HIFU and 24 patients in the study group treated with GnRH-a combined with HIFU. All the patients follow up 6 months after the HIFU procedure. The related parameters in the two groups were assessed before and 3 months as well as 6 months after treatment including serum levels of tumor marker and cytokine, volumes of uterine, adenomyotic lesion, and menstrual blood, as well as dysmenorrheal scores.

Main outcome measures Differences between the group treated with HIFU alone and the group treated with GnRH-a combined with HIFU.

Results Before HIFU treatment, no significant difference was observed in serum levels of CA125, CA19-9, and interleukin-6 (IL-6), the volumes of uterine, adenomyotic lesion, and menstrual blood, as well as dysmenorrhea scores between the two groups. ($P > 0.05$). The serum CA125 levels significantly decreased in both groups after HIFU, but the serum CA125 levels in the study group were still significantly lower than those in the control group ($P < 0.05$). The volume of uterine and adenomyotic lesion significantly decreased in both groups after HIFU procedure, and decreased even more in the study group 3 and 6 months after treatment ($P < 0.05$). Dysmenorrhea scores and menstruation volumes significantly decreased in both groups after HIFU treatment. Moreover in the study group were significantly lower than those in the control group after 3 and 6 months ($P < 0.05$). No significant difference was observed in the rate of adverse effects between the two groups.

Conclusions The short-term follow-up results indicate that the combination of GnRH-a and HIFU treatment significantly decreased serum CA125 levels, volumes of uterine, adenomyotic lesion and menstrual blood, as well as dysmenorrhea scores, and improved the clinical outcomes compared with the HIFU ablation alone in patients with adenomyosis. However, the further follow-up is needed to explore the long-term effects.

Keywords Adenomyosis, gonadotrophin-releasing hormone agonist, high-intensity focused ultrasound.

Tweetable abstract A combination of GnRH-a with HIFU in the treatment of adenomyosis significantly decreased serum CA125 levels, uterine and adenomyotic lesion volumes, dysmenorrhea scores, and menstrual blood volumes.

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Introduction

Adenomyosis is a common benign uterine disease in child-bearing age women. It is characterised by invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium.[1–3] Women with adenomyosis exhibit a variety of clinical manifestations such as menorrhagia, progressive dysmenorrhea and infertility, which seriously affect their quality of life.[2–4] So far, hysterectomy is the only definite treatment.

However, hysterectomy is not suitable for young women who wish to remain fertile. Gonadotropin-releasing hormone agonist (GnRH-a) therapy is a conservative treatment for women with adenomyosis, but the patients are susceptible to a recurrence of symptoms after cessation of therapy.[5,6] In recent years, several studies have investigated the role of high intensity focused ultrasound (HIFU) in the treatment of adenomyosis; the results showed that HIFU is safe and effective in the treatment of adenomyosis.[7–12] However, the follow-up results also found that a small number of patients treated with HIFU still had unsatisfactory symptom relief. Therefore, this study aimed to investigate the clinical efficacy of GnRH-a combined with HIFU ablation in symptom relief of women with adenomyosis.

Materials and methods

The prospective study was approved by the ethics committee at our institution and every patient signed informed consent form before the procedure was undertaken.

Patients

From June 2014 to June 2016, 79 ptients with adenomyosis were enrolled in this study. 24 patients were assigned to the study group, who were pretreated with three courses of GnRH-a. Patients underwent HIFU ablation on day 28 after the third injection of GnRH-a. 55 patients were assigned to the control group. These patients only received HIFU ablation. The average age of the patients in the study group was 41.00 ± 4.74 years (range: 31–3). Among them, 19 had childbearing histories. The average age of patients in the control group was 39.6 ± 5.3 years (range: 30–42). Among the 55 patients, 51 had childbearing histories. There was no significant difference between the two groups as regards baseline data ($P > 0.05$).

Inclusion criteria were as follows: (1) women were older than 18 years and had not yet undergone menopause; (2) the diagnosis of adenomyosis was made using magnetic resonance imaging (MRI); (3) women had either menorrhagia or dysmenorrhea, and the scores were greater than or equal to four; (4) a single layer of the junction zone of the uterus was thicker than 3 cm; (5) patients were unwilling to have hysterectomy or adenomyectomy; (6) patients had not received any treatment for adenomyosis within the past year. Exclusion criteria include: (1) women undergoing menstruation, pregnancy or lactation; (2) patients with suspected or confirmed endometriosis; (3) patients with pelvic adhesions; (4) patients with suspected or confirmed uterine malignancy.

Preparation before HIFU treatment

The protocol of preparation before HIFU treatment has been described in previous studies.[11,12] Briefly, following the approved protocol, specific routine bowel preparation was performed 3 days before HIFU treatment. The patients were required to ingest liquid food, no milk or other gas-producing food, and to fast for 12 hours before treatment. The morning of the treatment day, the skin from the level of the umbilicus to the upper margin of the pubic symphysis had to be carefully shaved, degreased and degassed before treatment. A urinary catheter was inserted to control the bladder volume by filling it with saline.

HIFU treatment

HIFU treatment was performed using an ultrasound-guided HIFU system (JC200; Haifu® Medical Technology Co. Ltd, Chongqing, China). The protocol has also been described in previous studies.[7–12] Briefly, the patient was positioned prone on the HIFU treatment table. A degassed water balloon was placed between the transducer and the anterior abdominal wall to compress or push away the bowel, and the abdominal wall was in contact with degassed water. The treatment was performed under sedation and analgesia with fentanyl and midazolam. The treatment started from the centre of the lesion as point sonication. The sonication power used was from 350 to 400 W. During the procedure, the treatment area and sonication intensity were adjusted based on changes in grey scale on ultrasound and tolerance of the patient.

Blood test and MRI evaluation

The blood samples were obtained from patients before and 3- and 6-month after HIFU. Serum tumour markers and cytokine levels were determined by drawing a venous blood sample of 5 ml from patients after overnight fasting. Serum levels of CA125, CA19-9 and interleukin (IL)-6 were measured in all patients.

All patients underwent MRI before and 6 months after HIFU. Uterine and lesion volumes were calculated according to T2 weighted image (T2WI) of MRI, using the formula: V = 0.5233 × long diameter × transverse diameter × anteroposterior diameter.[6]

Follow up

Patients in the two groups were clinically followed up 1, 3 and 6 months after HIFU ablation. The visual analogue scale (VAS) was used for subjective assessment of the degree of dysmenorrhea before and after HIFU. Menstruation volume was measured according to PBAC methods.[13]

Statistical analysis

Data were presented as mean ± standard deviation. SPSS 19.0 software was used for data analysis. The *t*-test was used to compare data between the two groups. A *P*-value <0.05 was considered to indicate a significant difference.

Results

Comparison of serum markers and cytokine levels

Before HIFU treatment, no significant difference in serum CA125, CA19-9 or IL-6 levels was observed between the study and the control groups ($P > 0.05$). CA19-9 and IL-6 levels in the two groups did not show any significant difference 6 months after treatment compared with pretreatment values ($P > 0.05$). Serum CA125 levels significantly decreased in both groups after HIFU, but the levels in the study group were significantly lower than those in the control group ($P < 0.05$) (Table 1).

Uterine and adenomyotic lesional volumes

Table 2 shows that uterine and lesional volumes did not show any significant differences between the two groups before HIFU treatment ($P > 0.05$). The uterine and lesional volume significantly decreased in both groups after HIFU compared with pretreatment levels (Figure 1). The decrease in the study group was significantly lower than that in the control group ($P < 0.05$).

Dysmenorrhea score and menstrual blood volume

Before HIFU treatment, there was no significant difference in dysmenorrhea score and menstrual blood volume between the two groups ($P > 0.05$). The dysmenorrhea score and menstrual blood volume significantly decreased in both groups after HIFU, but the decrease in the study group was significantly greater than in the control group, 3 and 6 months after HIFU ($P < 0.05$), as shown in Table 3.

Complications and adverse events

26 (32.9%) of the 79 patients reported a minor vaginal blood discharge. Thrombocytopenia was observed in two cases (2.5%) 48 hours after HIFU, after which the blood platelet counts returned to normal levels. One patient (1.3%) complained of acute pelvic inflammatory disease 1 month after HIFU; she was successfully treated with anti-inflammatory medications. No severe complications were observed in any patient. No significant difference in the rate of complications or adverse effects was observed between the two groups.

Table 1. Comparison of serum tumour markers and cytokine levels

No. of patients	Study group 24	Control group 55	*t*-value	*P*-value
CA125 (kU/l)				
Before HIFU	108.15 ± 77.28	110.37 ± 75.41	1.816	0.072
After HIFU	80.50 ± 56.67	92.87 ± 59.63	2.059	0.043
CA19-9 (kU/l)				
Before HIFU	26.50 ± 26.54	27.46 ± 23.17	1.915	0.067
After HIFU	31.31 ± 13.44	30.44 ± 14.21	1.949	0.055
IL-6 (g/l)				
Before HIFU	12.42 ± 5.28	13.14 ± 5.65	1.679	0.091
After HIFU	11.17 ± 3.63	11.35 ± 3.75	1.727	0.084

Discussion

Adenomyosis is a common gynaecological disease with an increasing prevalence in recent years, characterised by the invasion of endometrial glands and infiltration of the endometrial stroma. The pathological examination presented smooth muscle hyperplasia and hypertrophy of the surrounding myometrium. As the hypertrophic uterine smooth muscle tissue in the adenomyotic lesion is sensitive to HIFU, HIFU is an ideal way to treat adenomyosis. The mechanism of HIFU treatment includes thermal, mechanical and cavitational effects. These effects result in coagulative necrosis of the lesion and also lead to the occlusion of small vessels. Thus, the size of adenomyotic lesions decreased, resulting in the alleviation of clinical symptoms.[10,11]

GnRH-a is a synthetic derivative of gonadotropin releasing hormone, with a function similar to that of GnRH *in vivo*. It increases the release of pituitary LH and FSH effectively. However, the binding of GnRH-a to pituitary GnRH receptors is strong, and the sensitivity of pituitary GnRH receptors for enzymatic degradation is reduced. Therefore, the activity of GnRH-a is several-fold higher than that of natural GnRH. Application of GnRH-a will deplete pituitary GnRH receptors, leading to a relative decrease in gonadotropin levels secreted by the pituitary, which induces a decrease in ovarian hormones in the following 3–6 weeks and transient amenorrhoea.[14] GnRH-a treatment induces a state of amenorrhoea, which may alleviate dysmenorrhea and reduce menstrual blood volume appropriately. However, GnRH-a only alleviates short-term clinical symptoms, and the symptoms will recur after cessation of this treatment.[6] In recent years, GnRH-a has been used as a pretreatment before the conservative surgery for the treatment of adenomyosis. Neo-adjuvant GnRH-a therapy for three to six cycles may correct anaemia, reduce adenomyotic lesion size, shorten surgical time, reduce haemorrhages during operations, and improve the therapeutic outcome.[15] In this study, patients in the study group received HIFU treatment after three cycles of GnRH-a pretreatment, and the patients in the control group only received HIFU ablation. In the control group, the uteri and the lesions were significantly reduced after HIFU. Six months after HIFU, the average uterine volume was reduced by 21% and the adenomyotic lesion volume by 35%. We also found that the serum CA125 level decreased and symptoms of dysmenorrhea and menorrhagia were

Table 2. Comparison of the uterine volumes and adenomyotic lesion volumes

Grouping No. of patients	Study group 24	Control group 55	*t*-value	*P*-value
Uterine volume (cm^3)				
Before HIFU	218.41 ± 128.36	209.27 ± 75.89	1.917	0.066
3 months after treatment	164.38 ± 76.35	161.25.43 ± 81.36	2.495	0.023
6 months after treatment	136.66 ± 108.36	157.43 ± 103.28	2.489	0.025
Reduction rate(%)	30 ± 2.09	21 ± 1.07	2.292	0.036
Lesion volume (cm^3)				
Before HIFU	83.68 ± 79.12	81.36 ± 76.35	1.931	0.061
3 months after treatment	45.37 ± 49.27	51.26 ± 29.37	2.396	0.031
6 months after treatment	34.76 ± 44.12	52.48 ± 31.27	2.396	0.031
Reduction rate, %	58.54 ± 12.49	35.49 ± 11.31	1.996	0.047

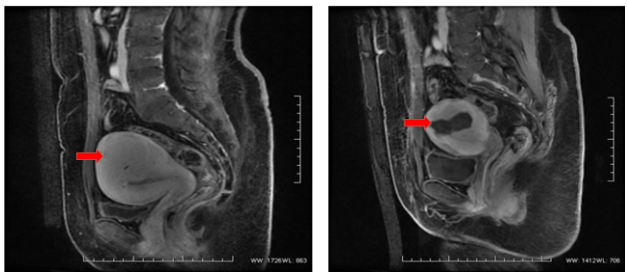

Figure 1. Sagittal view of the contrast enhanced magnetic resonance imaging (MRI) from a patient with adenomyosis. (A) The adenomyotic lesion located on the posterior wall of the uterus and enhancement of the lesion was observed before HIFU (arrow). (B) Contrast enhanced MRI obtained 6 months after HIFU showed the nonperfused area in the adenomyotic lesion (arrow).

relieved after HIFU treatment. Our results are consistent with previous studies.[10,11] We further compared the results from the two groups and found that the serum CA125 levels in both the control and the study group dropped after HIFU, althoughthe serum CA125 level of patients in the study group was lower than that in the control group. We calculated the uterine volume and the lesional volume in the two groups and found that both the uterine volume and the lesional volume significantly decreased in both groups after HIFU. In comparison with the control group, the uterine volume and the lesional volume of patients 3 and 6 months after HIFU in the study group were significantly smaller than those in the control group and the reduction rate was significantly larger. In addition, dysmenorrhea scores and menstrual blood volumes decreased significantly in both groups after HIFU, although they were significantly lower in the study group than in the control group. Therefore, a combination therapy of GnRH-a and HIFU not only prevented recurrence after drug withdrawal, but also improved the short-term clinical efficacy of HIFU ablation. Our results also demonstrated that either HIFU treatment alone or HIFU combined with GnRH-a is safe; no severe complications or adverse effects were observed in this study.

This study is limited because of the small number of subjects, and the inclusion of non-randomised enrolled patients may have caused result bias. The fact that the

Table 3. Comparison of dysmenorrhea scores and menstrual blood volumes

Groups No. of patients	Study group 24	Control group 55	*t*-value	*P*-value
Dysmenorrhea score (point)				
Before HIFU	8.00 ± 1.62	7.95 ± 1.65	1.813	0.077
3 months after treatment	4.73 ± 1.32	5.14 ± 1.27	2.559	0.014
6 months after treatment	2.21 ± 1.07	4.58 ± 0.95	2.495	0.023
Menstrual blood volume (ml)				
Before HIFU	54.59 ± 14.39	52.46 ± 15.12	1.657	0.097
3 months after treatment	41.62 ± 12.24	49.83 ± 13.47	2.549	0.016
6 months after treatment	32.85 ± 10.06	43.90 ± 12.56	2.573	0.011

patients were followed up after a short time is another limitation. Therefore, a multi-centre prospective study with randomised enrollment of a large number of patients is needed. A long-term follow up is also required.

Conclusions

In contrast to HIFU treatment alone, the combination of GnRH-a ablation and HIFU significantly decreased serum CA125 levels, uterine volumes, adenomyotic lesional volumes, dysmenorrhea scores, and menstrual volumes in patients with adenomyosis and improved the short-term clinical efficacy of HIFU. However, the long-term effects and recurrence rate still need to be investigated further.

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Disclosure of interests

There is no conflict of interest to declare.

Contribution to authorship

Yinshu Guo: data acquisition; analysis and interpretation; drafting the article and final approval of the version to be published. Jiumei Cheng: data acquisition; analysis and interpretation; final approval of the version to be published. Ying Zhang: assessed repeatability series; performed statistical analysis and interpretation of data. Hua Duan: responsible for the initial concept, study design and final review of the manuscript.

Details of ethics approval

The protocol of this study was approved by the ethic committee at the Obstetrics and Gynaecology Hospital of Capital Medical University of Beijing, China.

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