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ORIGINAL ARTICLE

The clinical study of ultrasound-guided intra-hysteromyoma injection of ethyl alcohol absolute combined with HIFU in the treatment of uterine fibroids

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Abstract

Objective The aim of this study was to investigate the energy deposition in the target area of high intensity focused ultrasound (HIFU) with ultrasound-guided intra-hysteromyoma injection of ethyl alcohol absolute

Methods Eighty patients with hysteromyomas were randomly divided into two groups: group HIFU (group H) and group HIFU combined with ultrasound-guided intra-hysteromyoma injectionn of ethyl alcohol absolute (group E + H). Patients in group E + H received an ultrasound-guided injection of absolute ethyl alcohol 1 h before HIFU treatment. The irradiation time, irradiation dose, energy efficiency factor (radiation energy required for ablation of a myoma per unit of volume), grey variation, pain score, and adverse reactions were compared between the two groups. An independent sample t-test was used with a two-tailed P-value of < 0.05.

Results The irradiation time, irradiation dose, and energy efficiency factor were significantly lower in group E + H than those in group H ($P < 0.05$). The hysteromyomas of patients in group E+H appeared as dominantly hyperechoic masses, and those of patients in group H appeared as hyperechoic tissue (non-mass). The incidence of adverse reactions and pain score were higher in group H than those in group E + H ($P < 0.05$).

Conclusion Ultrasound-guided intra-hysteromyoma injection of ethyl alcohol absolute can enhance the energy deposition of HIFU in the uterine fibroids, improve the treatment efficiency, shorten the treatment time, reduce the treatment dose, and reduce the pain and complications for the patients.

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Key words: high-intensity focused ultrasonography (HIFU); absolute ethyl alcohol; hysteromyomas; uterine fibroids; energy efficiency factor

High-intensity focused ultrasonography (HIFU) is widely used in the clinical treatment of uterine fibroids [1]. Because of its longer radiation time and lower efficiency, especially in obese patients or those with a large volume of uterine fibroids with rich blood flow located close to the pelvic wall, the risk and complications of HIFU treatment are increased, and patients and therapists' compliance decrease accordingly. In order to improve the efficiency of HIFU and shorten the treatment time, we herein investigated energy deposition in the target area of HIFU with ultrasound-guided intratumoral injection of absolute ethyl alcohol in the treatment of hysteromyomas.

Materials and methods

Subjects

The inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) women with a clinical and imaging diagnosis of a hysteromyoma; (2) premenopausal women or women after childbearing age who were in a nonmenstrual period; (3) women who refused to undergo surgical treatment and had a

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strong desire to retain their uterus; (4) women with a hysteromyoma that could be clearly observed and treated safely by ultrasonography; (5) women with an intramuralmyoma, subserosal myoma, or submucosal myoma (classified as II or III according to the International Federation of Gynecology and Obstetrics classification [2]); (6) women with a single myoma or fewer than three myomas; and (7) women without an allergy to alcohol. The exclusion criteria were as follows: (1) pregnant and lactating women; (2) women who also had other gynecological diseases (vaginitis, pelvic inflammation, cervical cancer, and so on); (3) women receiving large doses of abdominal radiotherapy; (4) women with cerebral infarction and cerebral hemorrhage within half a year earlier; and (5) women who also had serious systemic diseases, including heart, brain, lung, and kidney diseases.

Eighty patients who presented with hysteromyomas (92 uterine fibroids) from January 2012 to December 2014 were selected in our study. All patients with hysteromyoma were randomly divided into group HIFU (group H) and group HIFU combined with ultrasound-guided intra-hysteromyoma injectionn of ethyl alcohol absolute (group E + H) with 40 patients in each group. Patients in group E + H received an ultrasound-guided injection of absolute ethyl alcohol 1 h before HIFU. Informed written consent was obtained from all patients before HIFU treatment and myoma puncture.

Reagent

The main reagent was absolute ethyl alcohol (Tianjin Kemiou Chemical Reagent Co., Ltd., China), which had an ethanol content more than 99.7%.

Instruments

The Siemens S2000 color Doppler ultrasonic apparatus was connected to a convex array probe with a frequency of 3.5 MHz, and it was equipped with a puncture guide frame, puncture needle from (21 gauge × 200 mm, Japanese BaGuang Corporation), and percutaneous alcohol injection therapy needle with three holes. The JC HIFU tumor therapy system (Chongqing Haifu Technology Co., Ltd., China) consists of a treatment system, water management system, monitoring ultrasound system, and power source. The diameter of the head of the system was 200 mm with a working frequency of 0.8 MHz and focal length of 170 mm. A high-energy ultrasonic wave was used as the medium of degassing water *in vitro*; it was focused on the tumor through the skin, and it produced an instant high temperature (60–100°C) to achieve its therapeutic purposes due to tissue coagulation and necrosis [3].

Methods

Preoperative regimen

Two groups of patients were completed with related examination two days before HIFU treatment with dregs diet, at 3 p.m one day before treatment with oral catharsis, cleansing enema on the treatment day, with retention catheterization and intravenous catheter. Skin preparation, degreasing and degassing were prepared for the lower abdomen.Informed written consent was obtained from all patients before HIFU treatment and myoma puncture

Ultrasound-guided intratumoral injection of absolute ethyl alcohol

The patients in group E + H were lied supine, ultrasound-guidedly injected with ethyl alcohol absolute 1 h before HIFU treatment, routinely sterilized, with 2% lidocaine as local anaesthesia in the lower abdomen. They were ultrasound-guidedly penetrated into the deep part of the myoma through the abdominal wall, avoiding intestinal tube and bladder with 21G alcohol injection puncture needle, about 1 to 1.5 cm near deep capsule, and ethyl alcohol absolute was injected slowly. The hyperechoic reflex was seen immediately, and the needle body was rotated to make sure ethyl alcohol absolute diffuse evenly. According to the size of the fibroids, the injection volume ranged from 3 to 5 mL, less than 10 mL. Patients were observed to make sure if there was any adverse reaction during the injection.

Outcomes

Both groups of patients were treated with fentanyl and midazolam for analgesia and sedation, respectively. The pain score (Ramsay classification [4]) was less than 4 points. Lying prone on the treatment bed, combining with the preoperative imaging results to set the treatment plan, with the point scanning, the interlayer spacing of 5 mm, the power of 400 W, the treatment mode of 1S /2S, the patients of group E+H can be seen as hyperechoic reflex in the ultrasound after ultrasound-guided injection of ethyl alcohol absolute, helping to locate the site where began treatment from deep to shallow. According to the standard, effective treatment was evaluated in real time by gray variation in the treatment area or the increase of the overall gray level [5], and the curative effect was evaluated by contrast-enhanced ultrasound. Two groups of patients were confirmed as satisfactory therapeutic effect by pelvic enhanced MRI after HIFU treatment, and the difference was not statistically significant.

Data collection and analysis

The following observational indices of the two patient groups were assessed: the irradiation time (s), irradiation dose (J), energy efficiency factor (EEF) (EEF= P × t/V, where EEF was the radiation energy required for ablation of a myoma per unit of volume, P was the output power, t was the irradiation time, and V was the volume of

Table 1 Comparison of general condition between group HIFU (group H) and group HIFU combined with ultrasound-guided intra-hysteromyoma injectionn of ethyl alcohol absolute (group E + H) (mean ± SD)

Groups	Age (years)	Body Weight (kg)	Average volume of the myomas (mm^3)
Group E + H	42.43 ± 3.92	59.15 ± 8.13	142302.12 ± 116371
Group H	43.83 ± 4.31	58.90 ± 7.15	167030.01 ± 100320
t	1.519	0.146	1.017
P	> 0.05	> 0.05	>0.05

Table 2 Comparison of the ablation indexes between group HIFU (group H) and group HIFU combined with ultrasound-guided intra-hysteromyoma injectionn of ethyl alcohol absolute (group E+H) (mean ± SD)

Groups	Irradiation time (s)	Total irradiation dose (J)	EEF (J/mm^3)
Group E + H	1166.38 ± 442.65	318031.45 ± 194579.65	4.51 ± 2.50
Group H	1444.03 ± 728.57	811941.13 ± 220277.48	5.46 ± 5.10
t	2.545	1.221	1.861
P	< 0.05	< 0.05	< 0.05

the myoma [6–7]), grey variation, pain score according to the numeric rating scale (0–10 points), and treatment complications according to the Society of Interventional Radiology classification system [8].

Statistical analysis

All computations were performed using SPSS 13.0 statistical software (SPSS, USA), and data are expressed as mean ± SD. An independent sample *t*-test was used to compare the data between group H and group E + H. A two-tailed *P*-value < 0.05 was considered statistically significant.

Results

Patients' age ranged from 34 to 47 years (mean 43.12 ± 5.88 years) and weight ranged from 41 to 78 kilograms (mean 59.03 ± 8.11 kilograms). Fifty-four patients had an anteverted uterus, and 26 had a retroverted uterus. Fifty-eight patients had intramural myomas, 29 had subserosal myomas, and 5 had submucosal myomas. Forty hysteromyomas were located in the anterior wall, 26 were located in the posterior wall, and 22 were located in the base of the uterus; the diameter of the hysteromyomas ranged from 39 to 124mm(mean 61.11 ± 16.21 mm), and the average volume was 154 587.73 mm3 (longest diameter × anteroposterior diameter × transverse diameter × 0.5233).

Two groups of patients were confirmed as satisfactory therapeutic effect by pelvic enhanced MRI after HIFU treatment,and the difference was not statistically significant.

Demographic characteristics

There was no significant difference between the two groups in average age, weight, and size of the hysteromyoma ($P > 0.05$), indicating that the treatment conditions were consistent and comparable (Table 1).

Ablation indices

The ablation indices, including the irradiation time, irradiation dose, and EEF between the two groups were statistically different ($P < 0.05$). The average irradiation time, total irradiation power, and EEF were lower in group E + H than in group H (Table 2).

Outcomes

Grey variation and the pain score were significantly different between the two groups ($P < 0.1$). The hysteromyomas of patients in group E + H were mainly shown as hyperechoic masses, and those of patients in group H were mainly shown as hyperechoic tissue (non-mass). The pain scores (Ramsay classification [8]) in group E + H were less than 4 points, which were lower than

Table 3 Comparison of gray variation and pain score between group HIFU (group H) and group HIFU combined with ultrasound-guided intra-hysteromyoma injectionn of ethyl alcohol absolute (group E + H)

Groups	Gray variation		Pain Score	
	No distinctness	distinctness	< 4	4–7
Group E + H	3	29	34	6
Group H	18	14	13	27
χ^2	3.791	1.312	1.913	3.471
P	> 0.1	< 0.25	< 0.25	< 0.1

Table 4 Comparison of complications between group HIFU (group H) and group HIFU combined with ultrasound-guided intra-hysteromyoma injectionn of ethyl alcohol absolute (group E + H)

Groups	Cases	Class A						Class C			Class C	Class D-F
		Hypog-astralgia	Sacroc-occygea/ Hip pain	Vaginal discharge	Hematuria	Lower extremity nerve irritation symptoms	Skin vesicle	Hypogas tralgia	Sacroco-ccygeal/ Hip pain	Num-bness of lower limb	Fever	
Group E + H	40	30	5	3	0	2	0	1	1	0	1	0
Group H	40	35	8	6	2	4	1	2	3	1	1	0
χ^2		2.051	0.827	1.127	2.051	0.721	1.013	0.346	1. 053	1.013		
P		> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05		

those in group H (Table 3).

Complications

The complications between the two groups were significantly different. Thirty-six patients in group E+H had complications, including 43 cases categorized as class A, 2 cases as class B, and 1 case as class C. Thirty-nine patients in group H had complications, including 63 cases categorized as class A, 6 cases as class B, and 1 case as class C. The incidence of complications was lower in group E + H than in group H (Table 4).

Discussion

As a non-invasive technology, HIFU has been widely used in the treatment of hysteromyomas in our country and abroad. Compared with the traditional treatment of hysteromyomas, such as surgery, medicine, and interventional therapy, HIFU is safe; has an outstanding curative effect; is associated with minimal trauma, less pain, and rapid recovery; preserves the uterus; causes no adverse drug reaction; and so on [9]. However, the use of HIFU for the treatment of hysteromyomas depends on the size, position, and blood supply of the myoma, T2-weighted (T2WI) high-intensity signal detected by MRI, and patient's body weight. Obesity leads to a longer irradiation time, lower treatment efficiency, increased incidence of pain and complications, and reduced compliance of patients and therapists, which restricts the clinical application of HIFU. How to improve the treatment efficiency and shorten the treatment time of HIFU has become a popular topic in research. Related studies [10-11] have shown that there are two main ways to improve the efficiency of HIFU for the treatment of hysteromyomas. The first way is to increase the output power of the HIFU transducer, and the second way is to change the acoustic properties of the target tissue and the acoustic environment in tissue (AET) to increase the energy deposition efficiency of HIFU. The increased output power of HIFU will increase the patient's pain even in the drug-induced state, making it difficult to carry out the treatment; additionally, it may lead to secondary injury or even serious complications. Thus, changing the AET using certain methods can increase the energy deposition in the target area, improve the efficiency of treatment, shorten the treatment time, and reduce or avoid the occurrence of secondary injury and complications in the condition of constant radiation parameters of HIFU. The smaller the EEF, the lower is the ultrasonic energy required for ablation of the myoma per unit of volume, which means that the energy deposition efficiency of HIFU is higher. EEF is positively correlated with the radiation time when the radiation parameters of HIFU and damage volume are constant; that is, the smaller the EEF is, the shorter the required radiation time is. This study showed that with the same output power, the irradiation time, total irradiation energy, and EEF were significantly lower in group E + H than in group H, and the difference was statistically significant. This finding indicated that the injection of absolute ethyl alcohol changed the AET of the myoma tissue and reduced the EEF needed for ablation of the myoma; thus, the radiation time was shortened, and the efficiency of treatment was improved.

Absolute ethyl alcohol, a chemical reagent, has been widely used in the chemical ablation of solid tumors, such as liver cancer. In recent years, it has been also used in the ablation of uterine fibroids, because it dehydrates and solidifies the tissue protein, denatures the tissue protein, solidifies the small blood vessels in the myomas, damages the endothelium, and embolizes the blood vessels to reduce the effect of blood cooling in the treatment of HIFU, making the myomas easier to ablate. Absolute ethyl alcohol can also reduce the threshold power of the cavitation effect on the uterine fibroid with a low ultrasonic energy of HIFU [12] and promote an increased temperature of the tissue to achieve ablation. Moreover, because of deep injection of absolute ethyl alcohol, a "sound beam barrier" forms, which increases the acoustic impedance and local heat deposition, making

it is easier and faster to detect hyperechoic masses by ultrasonography, which is in agreement with the results observed in group E + H in the present study. More sound waves are reflected by myomas in the necrotic zone, the time to myoma necrosis is shortened, energy deposition in the ectopic area is reduced, and normal tissue around the myoma is protected effectively, and at the same time, the attenuation of energy and reduction of acoustic energy in the posterior area near the myomas relieves the patient's discomfort and pain, especially for large myomas located in the posterior wall of the uterus or near the caudal tail. The present study showed that the pain score was lower in group E + H (< 4) than in group H (4–7), and the incidence of complications of all classes was significantly lower in group E + H than in group H, without serious complications.

We found that ultrasound-guided intratumoral injection of absolute ethyl alcohol is simple, safe and easy to perform; however, there are several points that require attention. (1) Due to the good mobility of the uterus and small size and hard texture of the myomas, it is easy to insert the needle into the wrong place; thus, the ultrasonographer must palpate the uterus in vitro, or transvaginal myomectomy should be performed. (2) The injection should be performed away from the endometrium as far as possible. (3) Calcified myomas should not be punctured. (4) During the puncture process, the tip of the needle should always be monitored, and it must be injected deep into the myoma. If the shallow part of the myoma is diffuse, it will affect the HIFU treatment. (5) Absolute ethyl alcohol can be easily diluted or removed from the blood, as its diffusion is related to the tissue structure and blood supply. For myomas with a rich blood supply, extension of the hyperechoic region is limited. Early injection is bound to reduce the scope of solidification and the effect on local tissue, thus reducing the synergistic effect of absolute ethyl alcohol; therefore, we injected a small dose of absolute ethyl alcohol 1 hour preoperatively, which has a synergistic effect, ensures safety, and enables preoperative localization of HIFU treatment. In addition, an excessive injection volume, rapid injection speed, puncture site without protection of the myometrium from normal contraction force, uncontrollable ablation range, and potential alcohol leakage can result in subsidiary injury to the surrounding tissue and trigger secondary infection [13].

In conclusion, the use of absolute ethyl alcohol has several advantages. It has an obvious synergistic effect, is safe, causes minimal trauma, and makes it easy to operate, which can improve the treatment efficiency, shorten the treatment time, reduce the total radiation energy of HIFU treatment, avoid energy-related adverse reactions, and complications. Thus, the use of absolute ethyl alcohol improves patients and physicians' compliance with HIFU treatment, especially in patients with a large volume of hysteromyomas in the posterior wall of the uterus, hysteromyomas with a rich blood supply, or a T2WI high-intensity signal detected by MRI, and obese patients.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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