Original Article

The safety and efficacy of add-on use of oxytocin in uterine leiomyoma patients undergoing high-intensity focused ultrasound and ultrasound-guided intratumoral ethanol injection: a randomized controlled trial

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Background: Uterine leiomyoma is one of the most common benign tumors in females. High-intensity focused ultrasound (HIFU) has been widely used in the therapy of uterine leiomyomas. However, HIFU method has a prolonged duration of operation and poor patient tolerance, which need improvement. This study sought to explore the efficacy and safety of add-on use of oxytocin in uterine leiomyomas patients who received HIFU and ultrasound-guided percutaneous anhydrous ethanol injection.

Methods: This is a randomized controlled trial. A total of 60 patients with uterine leiomyomas were included and randomly divided into study group and control group. The patients in the control group were treated with HIFU and ultrasound-guided percutaneous anhydrous ethanol injection, while the study group received oxytocin injection in addition to the treatment measures of the control group. The efficacy and safety of the treatments were assessed by using the volume ablation rate of the tumor and the Society of Interventional Radiology (SIR) Practice Guidelines, respectively.

Results: Finally, all of the 60 patients (30 in the study group and 30 in the control group) completed the treatments. There were no statistically significant differences between the 2 groups in terms of leiomyoma volume ablation rate (94.48%±2.07% *vs.* 94.91%±2.53%, P=0.36), crumb gray time (150.70±57.51 *vs.* 165.77±77.13 s, P=0.37), total treatment energy (556,835.0±202,583 *vs.* 512,610.0±158,004 J, P=0.19), and total treatment time (116.70±28.61 *vs.* 107.40±23.22 mins, P=0.14). The pain score of the oxytocin group was significantly greater than that in the control group (4.53±1.55 *vs.* 3.60±1.19, P=0.008). At 3 months and 1-year post-therapy, no statistically significant differences were observed in the residual necrotic leiomyoma volume between the 2 groups.

Conclusions: The add-on use of oxytocin in uterine leiomyomas patients undergoing HIFU and ultrasound-guided intratumoral ethanol injection could not improve treatment effect.

Trial Registration: Chinese Clinical Trial Registry identifier: ChiCTR2200058584.

Keywords: Oxytocin; high-intensity focused ultrasound (HIFU); percutaneous ethanol injection; uterine leiomyomas

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Introduction

Uterine leiomyoma is one of the most common reproductive tract benign tumors in females, usually occurs in women aged between 35–45 years old, and has a reported incidence rate of approximately 20–45% (1). It is a benign disease; however, uterine leiomyomas can cause changes in menstruation, abdominal pain, frequent urination, constipation, and other symptoms. Thus, uterine leiomyomas can severely affect women's quality of life, and necessitate appropriate treatment. The conventional treatment for symptomatic uterine leiomyoma is gynecological surgical excision. The surgery for uterine leiomyoma is the primary cause of hysterectomies and also an invasive treatment method. In recent years, high-intensity focused ultrasound (HIFU), a non-invasive thermal ablation technique, has been widely used in the treatment of uterine leiomyoma and uterine adenomyoma (2,3). Through a thermal effect, coagulative effect, and mechanical effect, HIFU can cause tumor tissue coagulation necrosis and thus achieve the purpose of treatment. It not only alleviates the symptoms but also preserves the uterus and eliminates the injury and risks associated with traditional gynecological surgery. However, HIFU treatment has a number of problems, including a prolonged duration of operation, and poor patient tolerance. Thus, the efficiency and effectiveness of the HIFU treatment needs to be safely and effectively enhanced and its treatment time shortened.

Previous reports indicated that oxytocin can selectively reduce blood flow in uterine fibroids and therefore was proposed to enhance the efficacy of HIFU treatment of uterine leiomyoma (4). Several observational studies have demonstrated the add-on use oxytocin during the HIFU procedures could improve short term outcomes of patients with uterine leiomyoma (5-7). However, the results of these studies did not reach statistical significance and RCT studies in this field are sparse.

This study sought to explore the efficacy and safety of add-on use of oxytocin in uterine leiomyomas patients who received HIFU and ultrasound-guided percutaneous anhydrous ethanol injection. We present the following article in accordance with the CONSORT reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-602/rc).

Methods

Study design and setting

This randomized controlled trial was conducted at the Daqing Oilfield General Hospital from July 2013 to July 2014. This is a two-parallel study with an allocation ratio of 1:1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Daqing Oilfield General Hospital (No. 20220310). Informed consent was obtained from all the included patients.

Study participants

Patients with uterine leiomyomas admitted to our Hospital from July 2013 to July 2014 were included in the study. All the patients had solitary lesions, and their ages ranged from 33–48 years, with an average of 40.40±3.81 years. Their leiomyoma volumes ranged from 42.25 to 251.27 cm^3, with an average of 109.78±49.29 cm^3. The patients were randomly assigned to oxytocin group and the control group; each group comprised 30 subjects. All the patients first underwent ultrasound-guided percutaneous intratumoral anhydrous ethanol injection treatment, followed by the HIFU treatment on the next day. The intravenous infusion of oxytocin was applied in the oxytocin group treated with HIFU, while the control group only received a 5% glucose intravenous drip injection. The purpose and procedure of the operation were explained in detail. Additionally, the patients were required to complete all relevant laboratory tests.

To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) be of childbearing age; (II) patients who desire to preserve the uterus and refuse to receive surgery; (III) have leiomyomas that could be clearly observed by ultrasonic examination with a clear treatment channel; (IV) have an ability to communicate with physicians easily; and (V) have no allergy to alcohol; and (VI) have signed an informed consent. Patients were excluded from the study if they met any of the following exclusion criteria: (I) were pregnant or lactating; (II) had gynecologic diseases (e.g., vaginitis, pelvic inflammation, cervical cancer, or other tumors); (III) with connective tissue disease; (IV) received abdominal high-dose radiotherapy (≥45 Gy); (V) cerebral infarction or hemorrhage within 6 months; and/or (VI) suffering from serious heart, brain, lung, kidney diseases or other systemic diseases.

Study methods

Treatment preparation

All patients underwent laboratory examinations and

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were diagnosed with uterine leiomyomas. They had no contraindications to HIFU treatment or ultrasound-guided percutaneous intratumoral anhydrous ethanol injection therapy. Before HIFU treatment, patients received catharsis, a cleaning enema, skin preparation in the treatment area, skin degreasing and degassing, and a urethral catheter. The selected patients were randomly assigned to the oxytocin group and the control group by using simple randomization method, with 30 patients in each group.

Ultrasound-guided percutaneous intratumoral anhydrous ethanol injection treatment

The ultrasound-guided percutaneous intratumoral anhydrous ethanol injection treatment was completed before the HIFU treatment. We used the GE LOGIQ E9 Color Doppler Ultrasound Diagnostic system (GE Healthcare, Milwaukee, WI, USA) for guidance, and local infiltration anesthesia was applied. Next, under the ultrasound guidance, an 18 G paracentetic needle was inserted to reach the deep surface of the uterine leiomyoma through the abdomen or vagina. Anhydrous ethanol was injected into the uterine leiomyoma by using a needle. The injection amount of anhydrous ethanol was 1/20–1/12 of the leiomyoma volume (length × width × height × 0.5233), and the maximum dose was no more than 30 mL. Finally, the needle was removed and the bleeding was stopped to finish the treatment.

HIFU treatment

We used a HIFU therapy system, specifically, a Type JC focused ultrasound tumor therapy system (Chongqing Haifu Technology Co., Ltd., Chongqing, China). The armamentarium includes a focused ultrasound treatment device that accumulates the ultrasound energy at the focal point, which causes a temperature rise effect and cavitation effect; a de-aerated water management subsystem that produces and uses the de-aerated water, and in which the ultrasound energy is coupled to the pelvic surface of the skin and the de-aerated water circulation is cooled, thus avoiding skin burns; a real-time monitoring color Doppler ultrasound subsystem; and an electric source. The specifications of the focused ultrasound transducer for the treatment subsystem were detailed as follows: the frequency was 0.8 MHz; the power of the ultrasound transmission ranged from 0–400 W (Type JC focused ultrasound tumor therapy system fixed at the 400 W for the treatment of the uterine leiomyomas); and the area of the focused ultrasound physical focal region was 1.5 mm × 1.5 mm × 10 mm. The temperature of focusing area ranged from 60 to 100 ℃, which could cause coagulative necrosis of the uterine leiomyoma tissue.

The application of oxytocin was initiated via a drip of oxytocin with the rate of injection at 20 drops/min and a dose of 0.12 U/min. The intravenous drip was administered for 15 minutes, and the HIFU treatment was then started. The control group only received an intravenous drip of 5% glucose solution.

The anesthesiologist administered doses of fentanyl and midazolam based on the patient's weight. Fentanyl 1 μg/kg and midazolam 0.03 mg/kg were given intravenously. Fentanyl 0.8 μg/kg and midazolam 0.02 mg/kg were administered intravenously 40 min later. Thereafter, the same dose of anesthetic was administrated every 40 minutes. During the treatment, the patient could tolerate the discomfort of the procedures and maintain sufficient cardiopulmonary function while still responding appropriately to speech and light touch stimuli. The HIFU treatment was performed using hierarchical point irradiation treatment under the ultrasound real-time monitoring with an irradiation power of 400 W. Based on the ultrasound gray-level change and the tolerance of the patients, the intensity and dose of the treatment were adjusted. Patients' vital signs and adverse reactions were recorded via electrocardiogram during the course of treatment.

Study outcomes

The primary endpoint was the fibroid volume ablation rate. The secondary endpoints included the postoperative pain score, surgical side effects, and changes in tumor volume at 1-year post-surgery.

Data collection and definitions

Before the treatment, all the patients underwent a gynecological ultrasound examination (with a color Doppler ultrasound diagnosis system) in a semi-quantitative way. The blood supply of the uterine leiomyoma was divided into the following 4 grades according to the level of the blood flow signal: grade 0: no blood flow and the uterine leiomyoma did not detect the signal of blood flow; grade 1: a small quantity of blood flow, the uterine leiomyoma could be detected with 1 to 3 spotty blood flow signals, and the blood vessel diameter was ≤1 mm; grade 2: a medium amount of blood flow, <4 blood vessels could be explored in the uterine leiomyoma, and the diameter of the blood vessels was ≤3 mm, or the length of a major blood vessel

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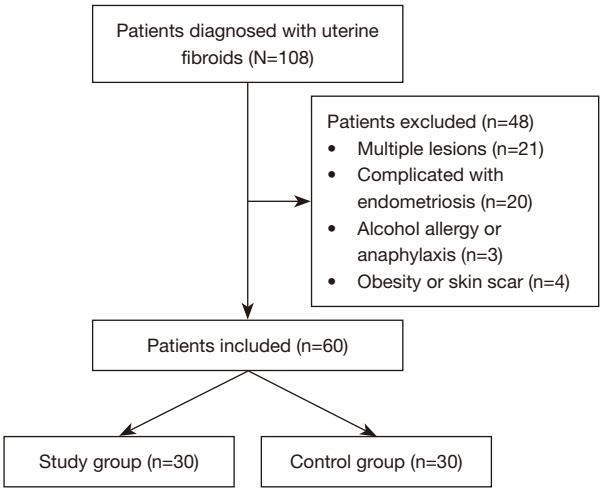

Figure 1 Patients inclusion flow chart.

exceeded the radius of the myoma; grade 3: rich blood flow, with >4 interconnected blood vessels, and the diameter of the blood vessels was ≤3 mm; and grade 4: abundant blood flow, with >4 blood vessels interconnected like a network, or Blood vessel diameter was 3mm or greater.

All patients underwent pelvic enhanced magnetic resonance imaging (MRI), and the T2-weighted image was used to discern the diameter (cm) and volume (leiomyoma length × width × height × 0.5233, $V_{\text{before treatment}}$, cm^3) of each leiomyoma. simultaneously, the shortest distance from the leiomyoma to the sacrococcyx (cm) was measured to determine the relative position of the lesion.

During the HIFU treatment the crumb gray time (s), treatment of total energy (J), and treatment of total time (min) were recorded. When the gray enhancement of the lesions appeared, the treatment passed. All patients underwent contrast-enhanced ultrasound and pelvic enhanced MRI after treatment to evaluate the therapeutic effect. The volume of the nonperfused area of the uterine leiomyoma on enhanced MRI was calculated as: leiomyoma length × width × height × 0.5233 ($V_{\text{after treatment}}$, cm^3). Next, the ablation rate of the necrotic lesion volume was calculated as: $V_{\text{after treatment}}/V_{\text{before treatment}}\times100\%$. At 3 months and 1 year after the treatment, respectively, all the patients underwent contrast-enhanced ultrasound examinations. The volume of the non-perfused area of the uterine leiomyoma on the contrast-enhanced ultrasound was re-calculated as described above.

After the treatment, based on the self-reported pain of the patients, pain scores were categorized using a scale of 0–10, on which 0 represented no pain, 1–2 represented mild pain, 3–4 represented uncomfortable pain, 5–6 represented a considerable degree of pain, 7–8 represented terrible pain, and 9–10 represented the most severe pain the patient could imagine. Additionally, the occurrence of treatment-related side effects was recorded, and according to the Society of Interventional Radiology (SIR) Practice Guidelines (8), were categorized as A–F as follows: A: no treatment is required; without adverse consequences; B: needs conventional therapy and observation; no adverse consequences; C: requires hospitalization but for <48 h; D: requires hospitalization for >48 h; E: permanent sequelae; F: death.

Statistical analysis

Patients with missing data less than 10% of the sample size were deleted, and those with more than 10% were handled with mean imputation. Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] depending on the distribution of the data and were compared by using Student's *t*-test or Mann-Whitney U, respectively. Categorical variables were expressed as number and percentage, and were compared using chi-square test or Fisher's Exact Probability Test where appropriate. A two-side P value <0.05 was considered statistically significant. All the data were analyzed using the statistical software SPSS (version 18.0).

Results

General comparison of the 2 patient groups

From July 2013 to July 2014, a total of 60 eligible patients were included in the study (30 in the study group and 30 in the control group) (*Figure 1*). The baseline characteristics of the included patients are set out in *Table 1*. Ages, average volumes of uterine leiomyoma, grades of blood flow, and the minimum distances from the deepest part of the uterine leiomyomas to the sacrococcyx did not differ significantly between the study and control groups (P>0.05). Additionally, the treatment conditions were statistically comparable between the 2 groups.

Therapeutic effects in the 2 groups

As *Table 2* shows, the necrosis rate after treatment, crumb gray-level change over time, treatment time, and treatment dose did not differ significantly between the 2 groups

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Table 1 Comparison of the baseline characteristics of the included patients

Group	Age (years)	Leiomyoma volumes (cm^3)	Blood flow grades	Distances from leiomyomas to sacrococcyx (cm)
Oxytocin group	40.70±4.16	115.67±47.96	2.00±0.53	5.31±0.83
Control group	40.10±3.46	103.89±50.70	2.10±0.55	5.24±0.95
P value	0.55	0.30	0.44	0.71

Data were expressed as mean ± SD.

Table 2 Comparison of leiomyoma necrosis rates after treatment, and crumb gray-level changes over time, the treatment energy and times, and pain scores between the oxytocin group and control group

Group	Leiomyoma necrosis rate (%)	Crumb gray-level change over time (s)	Treatment energy (J)	Treatment time (min)	Pain score
Oxytocin group	94.48±2.07	150.70±57.51	556,835.0±202,583	116.70±28.61	4.53±1.55
Control group	94.91±2.53	165.77±77.13	512,610.0±156,004	107.40±23.22	3.60±1.19
P value	0.36	0.37	0.19	0.14	0.008

Data were expressed as mean ± SD.

Table 3 Comparison of side effects between the oxytocin group and control group

SIR grade	Oxytocin group (n=30)	Control group (n=30)	P
A			
Hypogastralgia or pelvic pain	21	22	0.77
Vaginal secretion	14	13	0.79
Neurostimulation	3	3	1
Skin scalded	0	0	
B			
Severe abdominal pain	5	4	0.71
Numbness in the lower extremity	0	0	
C–F	0	0	
Total	43 (23 patients)	42 (21 patients)	0.55

SIR, Society of Interventional Radiology.

(P>0.05). However, the pain scores of the 2 groups of patients did differ significantly (P<0.05).

Comparison of side effects between the 2 groups of patients

Forty-four of the included patients developed side effects after the treatment process (23 patients in the oxytocin group and 21 patients in the control group). Under the society of Interventional Radiology system, patients experienced grade A and B side effects, but no grade C–F side effects were observed. As *Table 3* shows, there were no significant differences in side effects between the oxytocin group and the control group (P>0.05).

Follow-up of the 2 groups of patients

After the HIFU treatment, the therapeutic effects and residual volumes between the oxytocin group and the control group were compared at 3 months and 1 year, but no statistically significant difference was found between the

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Table 4 Follow-up results of the oxytocin group and control group after treatment

Project	Oxytocin group (cm^3)	Control group (cm^3)	P value
Leiomyoma volume immediately after treatment	108.93±43.99	98.87±49.19	0.35
Residual volume 3 months after treatment	58.71±23.87	52.84±25.50	0.30
Residual volume 1 year after treatment	23.89±9.80	21.53±11.36	0.31

Data were expressed as mean ± SD.

2 groups (P>0.05; *Table 4*).

Discussion

Effects of oxytocin in the HIFU treatment of uterine leiomyomas

Oxytocin, which is commonly used in gynecology and obstetrics, is a neurohypophysis hormone and a type of nonapeptide containing disulfide bonds. It primarily acts on the uterine smooth muscle and stimulates its contraction. In the clinic, it is primarily used to induce labor and control uterine bleeding (9). Oxytocin also has a weak contraction effect on the blood vessels of the kidney and skeletal muscle (10), but occasionally, it has other side effects, such as nausea, vomiting, heart rate acceleration, and cardiac arrhythmia. Large doses of oxytocin (11) (a muscle injection of 20 U for the extremum) can cause short and significant vascular smooth muscle relaxation (12), and a drop in blood pressure. At present, several researchers have suggested that oxytocin is safe to use by intravenous drip (10). Serious side effects occur very rarely; however, there remains a potential risk, and severe allergic reactions have been reported (13,14).

The traditional opinion is that oxytocin primarily causes uterine contraction during pregnancy. Researchers, such as Richer *et al.*, (15) have confirmed that oxytocin receptors are also present in the non-pregnant uterus; thus, oxytocin can also be applied in the non-pregnant uterus. Wang *et al.* (16) reported that the application of oxytocin (0.04 U/min via intravenous drip) in Uterine Myomectomy could reduce intraoperative bleeding, shorten the operation time, and reduce complications. Sun *et al.* (17) observed that oxytocin causes changes in the spectrum of nourishing blood flow in benign uterine diseases.

The application of oxytocin in the HIFU treatment of uterine leiomyomas reduces the blood supply of myoma, reduces the blood flow cooling effect, and improves the efficiency of the HIFU (18). As a way to improve the efficiency of the HIFU treatment, it has been included in the JC focused ultrasound tumor therapy system clinical manual. However, this mode of oxytocin application is not routinely used, and the dose is relatively large.

Effects of ultrasound-guided percutaneous anhydrous ethanol injection in the treatment of uterine leiomyomas with the HIFU

In recent years, as a type of minimally invasive treatment, ultrasound-guided percutaneous anhydrous ethanol injection has been used to treat uterine leiomyomas (19,20). Its mechanism of action involves the anhydrous ethanol embolization of leiomyoma blood vessels, and it directly causes tissue protein coagulation in the tumor, thus resulting in leiomyoma coagulative necrosis. This method is simple, less time consuming than surgery methods, and easy to detect the necrosis area within the tumor. Chen *et al.* (21) found that, during treatment with HIFU, anhydrous ethanol reduced the cavitation effect of the threshold value, promoted the cavitation effect, and increased the temperature in the tissue, thus improving the efficiency of the HIFU treatment.

In this study, all the patients were treated with ultrasound-guided percutaneous anhydrous ethanol injection before the HIFU treatment. Inside the uterine leiomyoma, the coagulative necrosis zone formed by the dispersion of anhydrous ethanol, followed by the HIFU treatment, produces a "damage-damage interference" effect. Thus, the formed damage has an additive effect on the damage caused by the re-applied energy. Based on these necrotic areas, all lesions showed mass gray enhancement in a short period of time, indicating coagulative necrosis in this area and gradual superposition of necrotic areas. When all lesions showed gray enhancement, treatment could be ended. Further, the injection of anhydrous ethanol can cause embolisms of flesh tumor blood vessels by blocking blood supply and reducing the blood flow cooling effect, which is helpful for HIFU energy deposition in the myoma. Yang *et al.* (22) found that treatment with HIFU and ultrasound-guided percutaneous anhydrous ethanol injection have a synergistic effect, safely

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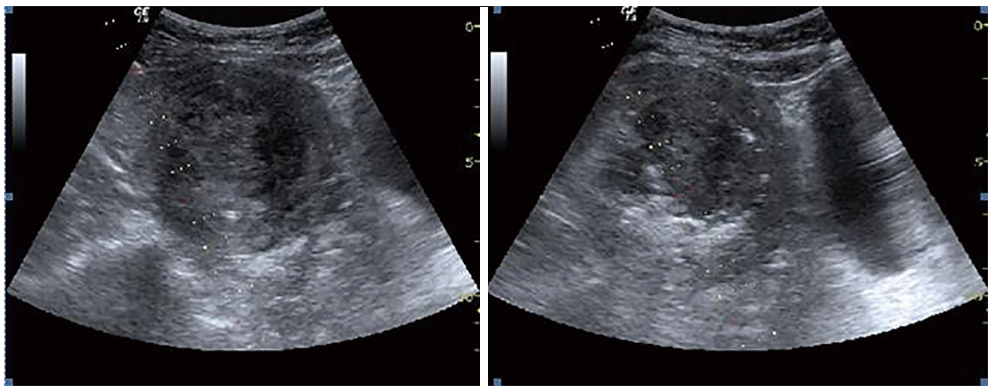

Figure 2 Ethanol injection process in patients with tumors.

and effectively improve treatment efficiency, and achieve a better therapeutic effect than HIFU alone.

Comparative analysis of treatment effects in the oxytocin and control groups

In this study, 60 patients with uterine leiomyomas were randomly divided into the oxytocin group and control group. The ages, average uterine leiomyoma volumes, grades of blood flow, and minimum distances from the deepest part of the uterine leiomyomas to the sacrococcyx of the patients in the 2 groups did not differ significantly. Thus, the treatment conditions between the 2 groups of patients were the same, and therapy effect comparison of the 2 groups of patients can be considered meaningful.

The analysis of the ultrasound guided intratumoral anhydrous ethanol injection treatment and the mechanism of action of the intravenous drip of oxytocin showed that the tumor injection of anhydrous ethanol reduced the threshold of the tissue cavitation effect and tissue coagulative necrosis, produced a "damage-damage interference effect", and simultaneously resulted in the embolism of leiomyoma blood vessels. In this study, after the ultrasound-guided intratumoral anhydrous ethanol injection treatment, the patients immediately underwent uterine ultrasound examination and the maximum volume of uterine leiomyomas showed no contrast agent perfusion status, indicating that the blood vessels were completely occluded (*Figures 2,3*).

Oxytocin binds the receptors in the uterine smooth muscle and causes smooth muscle contraction and compression in the myometrium blood vessels, thereby reducing blood perfusion (17-19). Through the uterus contrast-enhanced sonogram, patients with uterine leiomyomas in the oxytocin group that received the intravenous drip were found to have decreased blood flow and reduced blood supply. However, there is still contrast agent filling in the fibroid lesions, indicating that the blood vessels are not completely occluded (*Figures 4,5*).

In this study, the oxytocin and control groups showed no statistically significant differences in terms of the leiomyoma necrosis rate, crumb gray-level change over time, treatment time, and treatment dose. Ultrasound-guided intratumoral anhydrous ethanol injection treatment can improve the ultrasound ablation acoustic environment, and the effect is reliable. Further, the use of an intravenous drip of oxytocin had no further effect on the effects of the anhydrous ethanol injection.

The incidence of the side effects of the treatments did not differ significantly between the 2 groups of patients ($P>0.05$). Thus, the application of an intravenous drip of oxytocin did not cause serious side effects. However, the pain scores of patients in the 2 groups differed significantly ($P<0.05$). This could be because oxytocin stimulates uterine smooth muscle contraction.

Follow-up results after comparison of the 2 groups of patients

At 3 months and 1 year after the treatment, all the patients were examined by contrast-enhanced ultrasound. The results showed that uterine leiomyoma necrosis was gradually absorbed and the volume was reduced. The contrast-enhanced ultrasound results for all 60 patients revealed that the necrosis had been resolved and blood supply had been restored, and there was no evidence of

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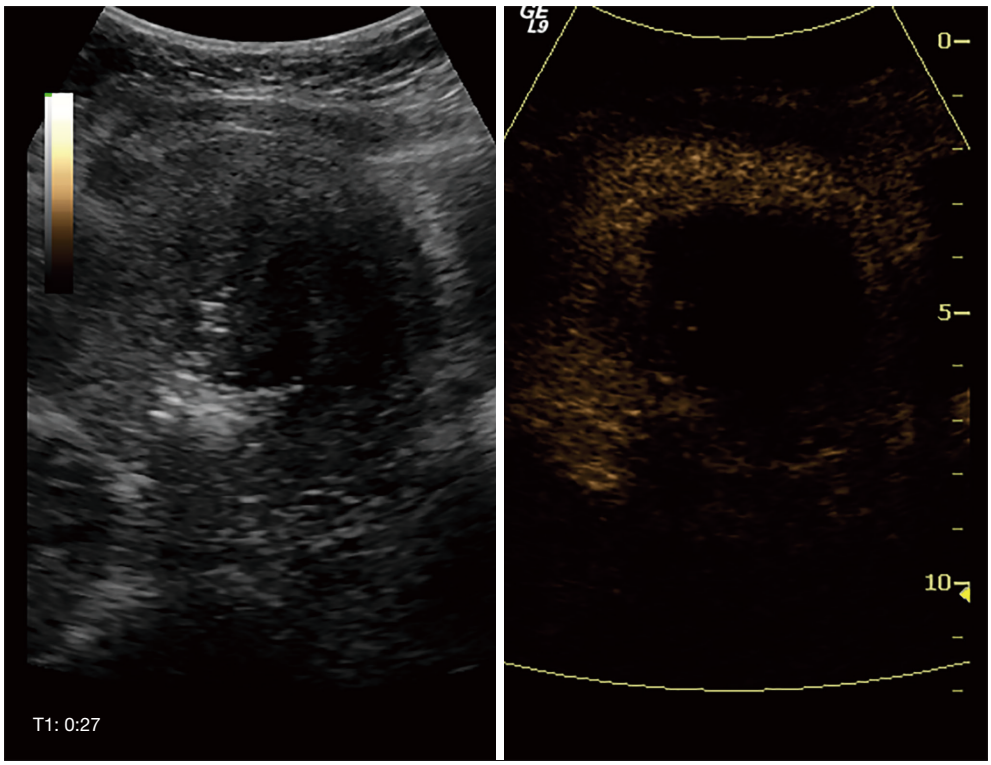

Figure 3 Contrast-enhanced sonogram of the same uterine leiomyomas after the ultrasound-guided intratumoral anhydrous ethanol injection treatment; intralesional considerable range; no contrast agent filling.

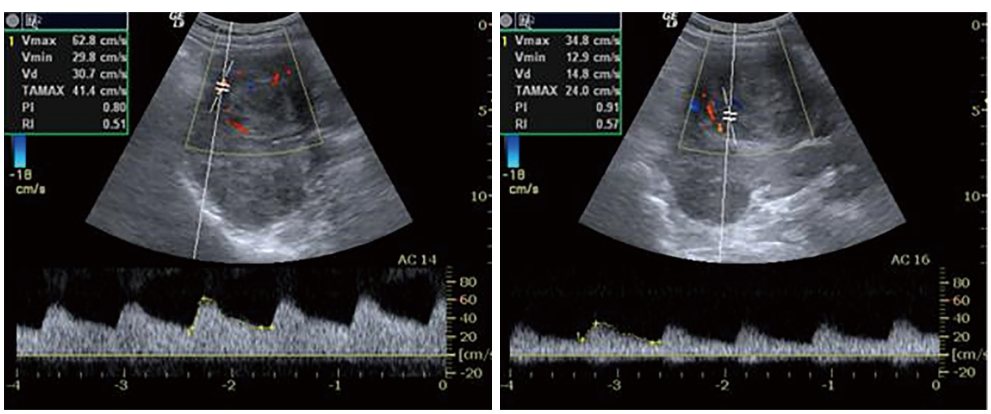

Figure 4 Change in blood flow spectrum of patients with uterine leiomyomas after the application of intravenous of drip oxytocin; blood flow velocity.

in situ necrosis recurrence. The difference in the residual necrotic leiomyoma volume was also not significant (P>0.05). HIFU combined with anhydrous alcohol injection is safe and effective in the treatment of uterine fibroids, but oxytocin has no significant effect on its efficacy.

Conclusions

In clinical practice, there are 2 different ways to improve the efficiency of the HIFU treatment (i.e., an intratumoral anhydrous ethanol injection and an intravenous drip of oxytocin). In this study, we explored the mechanism of

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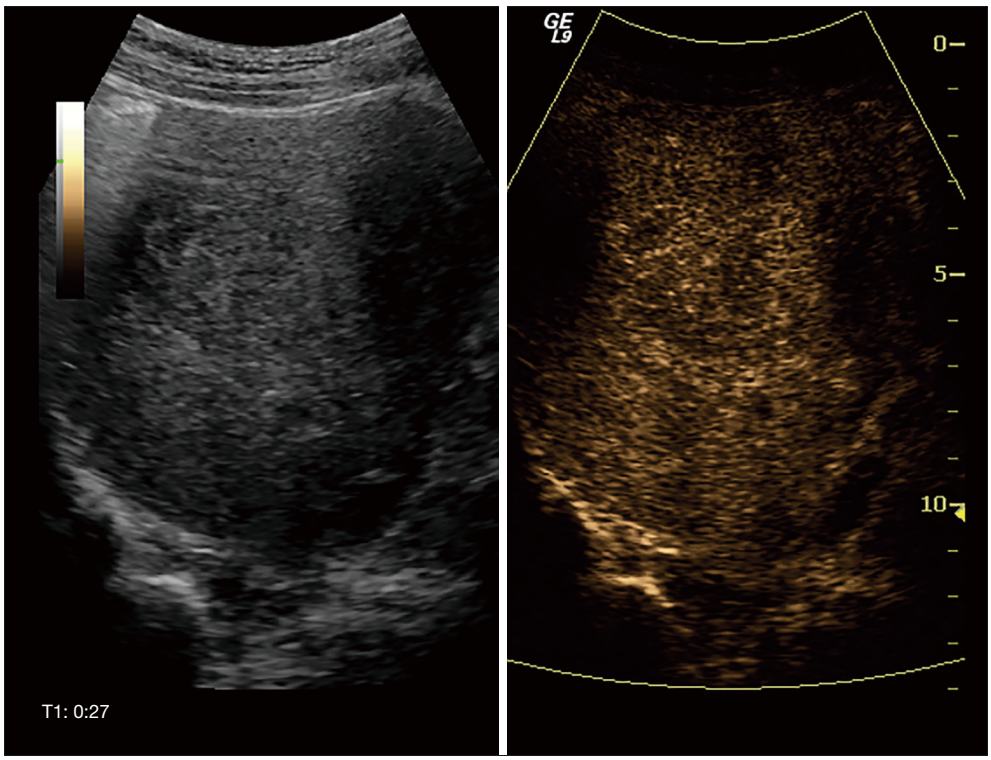

Figure 5 Contrast-enhanced ultrasound of the same leiomyomas after the application of intravenous drip of oxytocin; the lesions are still filled with the contrast agent.

the 2 methods at improving the efficiency of the HIFU treatment and performed a statistical analysis of the follow-up results of the 2 groups of patients after 1 year of treatment. We found that ethanol injection in tumors had a significant effect in improving the acoustic environment of the HIFU therapy, and the effect was precise and stable. In this situation, the intravenous infusion of oxytocin is not required, and thus the potential risk of using oxytocin can be avoided.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-602/rc

Trial Protocol: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-602/tp

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-602/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-602/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Daqing Oilfield General Hospital (No. 20220310). Informed consent was taken from all the patients.

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