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FULL PAPER

Ultrasound guided high-intensity focused ultrasound combined with gonadotropin releasing hormone analogue (GnRHa) ablating uterine leiomyoma with homogeneous hyperintensity on T_2 weighted MR imaging

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Objective: The study aimed to evaluate the safety and efficiency of ultrasound-guided high-intensity focused ultrasound (USgHIFU) combined with gonadotropin-releasing hormone analogue (GnRHa)-ablating symptomatic uterine leiomyoma with homogeneous hyperintensity on T_2 weighted MRI prospectively.

Methods: A total of 34 patients with 42 symptomatic uterine leiomyomas with homogeneous hyperintensity on T_2 weighted MRI were enrolled in our study. In the patient who had multiple uterine leiomyomas, only one dominant leiomyoma was treated. According to the principles of voluntariness, 18 patients underwent a 3-month therapy of GnRHa (once a month) before the high-intensity focused ultrasound (HIFU) treatment, while 16 patients received only HIFU treatment. Enhanced MRI was performed before and after GnRHa and HIFU treatment. Evaluation of the main indicators included treatment time, sonication time, treatment efficiency, non-perfused volume (NPV) (indicative of successful ablation) ratio and energy effect ratio; adverse events were also recorded.

Results: The treatment time and sonication time of the combination group were 102.0 min (55.8–152.2 min) and 25.4 min (12.2–34.1 min); however, they were 149.0 min (87.0–210.0 min) and 38.9 min (14.0–46.7 min) in the

simple USgHIFU group. The treatment and sonication time for the combination group was significantly shorter than that for the simple USgHIFU group. Treatment efficiency, NPV ratio and energy effect ratio were $46.7 \text{ mm}^3 \text{ s}^{-1}$ (28.5–95.8 $\text{mm}^3 \text{ s}^{-1}$), $69.2 \pm 29.8\%$ (35.5–97.4%) and 9.9 KJ mm^{-3} (4.5–15.7 KJ mm^{-3}) in the combination group, respectively; but, the lowest treatment efficiency, lowest NPV ratio and more energy effect ratio were observed in the simple HIFU group, which were $16.8 \text{ mm}^3 \text{ s}^{-1}$ (8.9–32.9 $\text{mm}^3 \text{ s}^{-1}$), $50.2 \pm 27.3\%$ (0–78.6%) and 23.8 KJ mm^{-3} (12.4–46.2 KJ mm^{-3}), respectively. Pain scores in the combination group were 3.0 ± 0.5 points (2–4 points)—significantly less than the simple USgHIFU group. There were no significant adverse reactions in either group.

Conclusion: Our data suggest that USgHIFU combined with GnRHa may be performed to ablate symptomatic uterine leiomyoma with homogeneous hyperintensity on T_2 weighted MRI.

Advances in knowledge: The conclusions indicate that GnRHa can improve the effectiveness of the USgHIFU treatment of a homogeneous hyperintense leiomyoma on T_2 weighted MRI, and combination treatment could be a promising alternative treatment for the uterine leiomyoma.

INTRODUCTION

High-intensity focused ultrasound (HIFU) can create a coagulative necrosis region by high temperature effect produced by a tightly and precisely focused high-intensity ultrasound beam, causing minimal harm to tissues outside of the focus. HIFU treatment has the advantages of less trauma, minimal pain, rapid recovery and organ preservation, and it is well received by thousands of females, especially unmarried females and childless females. HIFU remains really difficult to ablate uterine leiomyomas.

Previous studies^{1,2} have suggested that uterine leiomyoma often manifests as homogeneous hyperintense on T_2 weighted MRI and has the characteristics of lower density, higher moisture content, sparse collagen fibres and abundant cells, which result in poor energy deposit and poor efficacy in the treatment.

Oestrogen plays a role in the development of uterine leiomyoma;^{3,4} gonadotropin-releasing hormone analogue (GnRHa) can bind tightly to GnRHa receptor and

inhibit female hormone secretion by way of the hypothalamus–pituitary–gonad axis. GnRHa is used to treat uterine leiomyoma, as first reported by Filicori,⁴ and it has been widely used for a long time since then. After 3–6 months of treatment with GnRHa, the blood supply of uterine leiomyoma is reduced, and the volume of uterine leiomyoma is diminished.⁵

Therefore, it is often recommended as an effective supplemental method in the treatment of uterine leiomyoma; for example, pre-operative application of GnRHa can make uterine leiomyoma shrink, decrease bleeding during myomectomy and decrease the post-operative recurrence rate.⁶

There are no data demonstrating whether pre-treatment application of GnRHa could improve the safety and efficiency of HIFU-ablating uterine leiomyoma with homogeneous hyperintensity on T_2 weighted MRI. The objective of this study was to evaluate the safety and efficiency of ultrasound-guided high-intensity focused ultrasound (USgHIFU) combined with GnRHa for ablating symptomatic uterine leiomyoma with homogeneous hyperintensity on T_2 weighted MRI prospectively.

METHODS AND MATERIALS

Patients

The protocol was approved by the ethics committee of the First Affiliated Hospital of Xinxiang Medical University. All patients signed an informed consent form before each treatment.

A total number of 34 females with 42 symptomatic uterine leiomyomas that showed homogeneous hyperintensity on T_2 weighted MRI were prospectively analyzed between January 2013 and September 2015 at the First Affiliated Hospital of Xinxiang Medical University. In the patient who had multiple uterine leiomyomas, only one dominant leiomyoma was treated;

the mean age was 32.2 ± 6.9 (21–48) years. According to the principles of voluntariness, 18 patients underwent 3-month GnRHa therapy and then underwent USgHIFU treatment, while 16 patients received only USgHIFU treatment.

The criteria were as follows: (1) the uterine leiomyoma showed homogeneous hyperintensity on T_2 weighted MRI, defined as uniformly distributed high signal intensity equal to or slightly higher than myometrium; (2) the patients who agreed to undergo 3-month GnRHa therapy before HIFU treatment were enrolled in the combination group, and the patients who received only HIFU treatment were enrolled in HIFU group; (3) the patient ages were >18 years and <49 years; (4) the patients could easily communicate with the physician during the procedure; (5) the ultrasound was able to clearly show the location and scope of the lesion and normal tissues around the lesion; and (6) the patients had no uncontrolled critical basic diseases.

Exclusion criteria were as follows: (1) pregnant females; (2) contraindicated for MRI; (3) suspected malignant uterine tumour; (4) pelvic acute inflammatory disease; (5) could not lie in a prone position for 3 h; and (6) degeneration of leiomyoma with spontaneous non-perfused areas on contrast-enhanced MRI.

Treatment

Gonadotropin-releasing hormone analogue treatment

GnRHa Leuprorelin (Paris, France) was produced by the Ipsen Pharma Biotech Company of Paris, France. On the first day of menstrual cycle phase, 3.75 mg was administered by subcutaneous injection, and one injection was then given each following month, once a month for 3 months. Patients finished three injections and completed USgHIFU treatment 1 month after their third injection.

Table 1. The combination therapy of high-intensity focused ultrasound (HIFU) and gonadotropin-releasing hormone analogue (GnRHa) vs simple HIFU therapy

Variable	HIFU and GnRHa	Simple HIFU
Cases	18	16
Age (years)	30.6 ± 6.8 (21–39)	36.5 ± 6.7 (24–48)
BMI (kg m^{-2})	20.9 ± 3.8 (15.9–28.9)	21.5 ± 2.3 (16.6–29.1)
Leiomyoma diameter (cm)	5.5 (4.3–6.9)	5.7 (4.7–6.7)
Leiomyoma volume (cm^3)	149.2 (102.0–264.3)	155.3 (114.0–249.8)
Treatment time (min)	102.0 ^a (55.8–152.2)	149.0 ^a (87.0–210.0)
Sonication time (min)	25.4 ^b (12.2–34.1)	38.9 ^b (14.0–46.7)
Treatment efficiency ($\text{mm}^3 \text{ s}^{-1}$)	46.7 ^c (28.5–95.8)	16.8 ^c (8.9–32.9)
Energy effect ratio (KJ cm^{-3})	9.9 ^d (4.5–15.7)	23.8 ^d (12.4–46.2)
NPV ratio (%)	69.2 ± 29.8 ^e (35.5–97.4)	50.2 ± 27.3 ^e (0–78.6)

BMI, body mass index; NPV, non-perfused volume.

^a $p = 0.046$.

^b $p = 0.048$.

^c $p = 0.001$.

^d $p = 0.002$.

^e $p = 0.004$.

Ultrasound-guided high-intensity focused ultrasound treatment

The treatment was performed with a HIFU tumour therapeutic system that was guided by B-mode ultrasound Esaote MyLab™ 70 (Genoa, Italy). The transducer was 20 cm in diameter, 0.8 MHz in operating frequency, 15 cm in focal length and $1.5 \times 1.5 \times 10$ mm in the dimensions of the focal region.

All patients received careful bowel and skin preparation before treatment. Bowel preparation included fasting and a cleansing enema; skin preparation included shaving the hair of the anterior abdominal, degreasing and degassing the skin of the anterior abdominal wall. A urinary catheter was inserted into the bladder, and degassed normal saline was filled in to regulate the bladder volume. The procedure was performed under i.v. conscious sedation to relieve discomfort and prevent voluntary or involuntary movement. For detailed content about pre-operative preparation and the clinical therapy procedure and methods, the research about HIFU by Zhang et al,⁷ Zhao et al¹ and Peng et al can be referred to.⁸

Assessment of before and after treatment

Pre- and post-treatment MRIs were performed in all patients with a 1.5-T MR unit [Signa HDE; General Electric Company (Connecticut Fairfield, USA)]. Patients did not use any drugs before MRI. Axial breath-hold T_1 weighted images [repetition time (TR)/echo time (TE), 560/10; slice thickness, 9 mm; matrix size, 224×320 mm], multisection T_2 weighted fast spin-echo images (TR/TE, 4000/90; slice thickness, 6–9 mm; matrix size, 224×320 mm) and contrast-enhanced fat-saturated T_1 weighted images in axial planes (TR/TE, 5.0/2.0; slice thickness, 2.2 mm; matrix size, 192×288 mm) were acquired following the injection of gadolinium (Gd^{3+} ; 0.1 mmol kg⁻¹; Omniscan®; GE Healthcare Life Sciences, Chalfont, UK). The average times required for MRI were 25.8 min to the simple HIFU groups and 24.5 min to the combination group. All images were read by two experienced radiologists to evaluate MR signal intensity and measure the size of uterine leiomyoma. Homogeneous hyperintensity leiomyoma was defined as uniformly distributed high signal intensity equal to or slightly higher than myometrium on T_2 weighted MRI. A larger non-perfused area in the leiomyoma on contrast-enhanced MRI was defined as degeneration and was excluded from this study. The volume of fibroids and non-perfused volume (NPV) of fibroids were measured in three dimensions—longitudinal (d_1 , the maximum leiomyoma diameter parallel to the endometrium on sagittal T_2 weighted MRI), anteroposterior (d_2 , the maximum leiomyoma diameter perpendicular to d_1 on sagittal T_2 weighted MRI) and transverse (d_3 , the maximum leiomyoma diameter parallel to the abdominal wall on axial T_2 weighted MRI)—and were counted using the following equation: $V = 0.5233 \times d_1 \times d_2 \times d_3$.

Main outcome measures included treatment time (the time between the beginning and the end of the treatment), sonication time (the amount of sonication time from the beginning to the end of the sonication), treatment efficiency (the leiomyoma necrosis volume in 1-s sonication emission), NPV ratio (the NPV divided by the fibroid volume on enhanced images after USgHIFU treatment) and energy effect ratio

(the joules of energy that was needed by ablating 1 mm³ of the leiomyoma tissue).

Related adverse events such as various aches and pains (including abdomen pain, sacrococcyx pain, hip pain and radiating pain in lower limbs), burns, nerve damage and intestinal necrosis were recorded. The degree of severity of adverse effects is based on the unified standardized Society of Interventional Radiology grading system.⁹

Statistical analysis

The data were statistically analyzed using the SPSS® v. 17.0 statistical bag (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The Mann–Whitney U test, monofactor analysis of variance and χ^2 test were used for the analysis of non-normally distributed data and normally distributed data, respectively. When the p -value was <0.05 , there was a significant difference between the two groups.

RESULTS

Patients and uterine leiomyoma

A total of 18 patients with 22 leiomyomas completed 3 months of GnRHa treatment, and then they received USgHIFU treatment. A total of 16 patients with 20 leiomyomas received only HIFU treatment. In the patient who had multiple uterine leiomyomas, only one dominant leiomyoma was treated in the study. The mean age and body mass index were 30.6 ± 6.8 years (21–39 years), 20.9 ± 3.8 kg m⁻² (15.9 – 28.9 kg m⁻²) and 36.5 ± 6.7 years (24–48 years), 21.5 ± 2.3 kg m⁻² (16.6 – 29.1 kg m⁻²) in the combination group and simple USgHIFU group. The median leiomyoma diameter and volume were 5.5 cm (4.3–6.9 cm), 149.2 cm³ (102.0–264.3 cm³) and 5.7 cm (4.7–6.7 cm), 155.3 cm³ (114.0–249.8 cm³), respectively. There was no significant difference between the two groups (age, $p = 0.08$; body mass index, $p = 0.14$; diameter, $p = 0.12$; volume, $p = 0.12$) (Table 1).

Treatment outcomes

All patients receiving GnRHa underwent a plain MRI scan and enhancement a month after the end of the therapy. The sizes of their leiomyomas were smaller than they had been prior to treatment. There were significant differences between the before and after treatment (Table 2, Figure 1).

The average power of USgHIFU treatment was 400 W. The treatment time and sonication time were 102.0 min (55.8–152.2 min) and 25.4 min (12.2–34.1 min) in the combination group, which were significantly shorter than those in the simple USgHIFU group. However, treatment efficiency and NPV

Table 2. Volume change of uterine leiomyoma of gonadotropin-releasing hormone analogue pre- and post-treatment

Variable	Pre-treatment	Post-treatment
Cases	18	18
Leiomyoma volume (cm ³)	149.2 ^a (102.0–264.3)	121.1 ^a (67.8–200.0)

^a $p = 0.000$.

Figure 1. MRI of uterine leiomyoma of gonadotropin-releasing hormone analogue (GnRHa) pre- and post-treatment, high-intensity focused ultrasound (HIFU) post-treatment: A1-2, before GnRHa treatment, uterine leiomyoma shows slightly homogeneous hyperintensity on T_2 weighted MRI and regular enhancement on contrast-enhanced MRI; A3-4, 3 months after GnRHa treatment, the volume of uterine leiomyoma shrinks obviously on T_2 weighted MRI and leiomyoma shows slight enhancement on contrast-enhanced MRI compared with that of the myometrium; A5, uterine leiomyoma shows almost complete necrosis on contrast-enhanced MRI immediately after HIFU treatment.

ratios were higher in the combination group, which were $46.7 \text{ mm}^3 \text{ s}^{-1}$ ($28.5\text{--}95.8 \text{ mm}^3 \text{ s}^{-1}$) and $69.2 \pm 29.8\%$ ($35.5\text{--}97.4\%$), respectively, and the energy effect ratio was considerably lower in the combination group—it was only 9.9 KJ mm^{-3} ($4.5\text{--}15.7 \text{ KJ mm}^{-3}$) (Table 1, Figure 1).

Adverse events

The adverse reactions of GnRHa were hot flashes, decrease in sexual desire and vaginal dryness, among others. Common adverse effects during treatment included various aches and pains; for example, abdomen pain, sacrococcyx pain, hip pain and radiating pain in the lower limbs. These symptoms were generally mild and did not require medical attention (reserved for Grade A and Grade B adverse reactions according to the unified standardized Society of Interventional Radiology grading system⁹). Incidences of Society of Interventional Radiology Grad B were 4.7% vs 9.6% between groups, and there was no significant difference. The mean pain score was 3.0 ± 0.5 points (2–4 points) in the combination group and was lower than that of the simple HIFU group. In this study, no Grade C adverse reactions occurred which required hospital care (Table 3).

DISCUSSION

Previous studies¹ have suggested that homogeneous hyperintense leiomyomas on T_2 weighted MRI were harder to treat by solely depending upon the HIFU. The reason lies in their lower density, higher moisture content, sparse collagen fibres and abundant cells, among other factors.² The energy was difficult to deposit in the leiomyoma, which resulted in poor efficacy in the treatment. Homogeneous hyperintense leiomyomas on T_2 weighted MRI were more frequently seen among patients aged <40 years, and most patients had the desire of fertility. Therefore, for these patients, HIFU could be considered a better option owing to its decreased levels of trauma, rapid recovery and preservation of organs. As a result, improving the effectiveness and safety of HIFU treatment of homogeneous hyperintense leiomyomas on T_2 weighted MRI had an important clinical significance.

As an adjunct therapy, GnRHa was widely applied in the surgical treatment of uterine leiomyoma. Smart et al^{10,11} have carried out research on the efficacy of HIFU combined with GnRHa for ablating uterine leiomyomas >10 cm in diameter. Compared with simple HIFU treatment, preliminary results from that study

showed the use of a 3-month course of GnRHa therapy before HIFU improved the thermoablative treatment effect. There was an average reduction in target leiomyoma volume of 21% and 37% at 6 months and 12 months. However, distinguished from Smart et al^{10,11} study, this research focused on the uterine leiomyomas with homogeneous hyperintensity on T_2 weighted MRI—those with a diameter of 4–7 cm. A usual finding was the presence of degeneration inside fibroids >10 cm in diameter, and the research showed these leiomyomas manifested heterogeneous hyperintensity on T_2 weighted MRI and could be easily ablated by USgHIFU because they contained sparing cellularity and more fibres.¹ There was uncertainty as to whether the GnRHa and HIFU combination improved outcomes in homogeneous hyperintense leiomyomas on T_2 weighted MRI. The preliminary results in this study suggested that the treatment efficiency and NPV ratio in the combination group were significantly higher than that in the simple USgHIFU group; but, there was a lower energy effect ratio in the combination group. The possible reason was that GnRHa could attack the blood supply of uterine leiomyoma and result in avascular degeneration and necrosis,^{5,12} which was conducive to the energy deposit of HIFU in the uterine leiomyoma.⁵ One study¹³ showed that, compared with degenerated leiomyoma volume, cellular fibroid volume was significantly reduced after GnRHa treatment. This indicates that GnRHa is a more effective treatment for homogeneous hyperintense leiomyomas on T_2 weighted MRI. One published report² revealed that sparse collagen fibres and abundant cells were important biological characteristics of homogeneous hyperintense leiomyomas on T_2 weighted MRI.

In contrast, treatment time and sonication time of combination groups were significantly shorter. This is conducive to improving not only the treatment efficiency, but also the safety of the HIFU therapy, because previous research¹⁴ has shown that there is a positive correlation between the length of treatment time and the frequency of serious adverse events. It can be noted that the mean pain score in the combination group was significantly less than that in the simple USgHIFU group, signifying that GnRHa was actually beneficial to HIFU treatment.

Nevertheless, owing to biological characteristics of homogeneous hyperintense leiomyomas on T_2 weighted MRI imaging, which required difficult therapy only by simple USgHIFU, it is unclear whether combination therapy was beneficial to the therapy of these leiomyomas after HIFU treatment. Further research is needed. On the other hand, it should be noted that the small sample size and lack of long-term follow-up constituted limitations in our study.

CONCLUSION

According to our research, from a technological perspective, GnRHa can improve the effectiveness of the HIFU treatment of leiomyomas on T_2 weighted MRI. At the same time, it is also helpful in improving procedural effectiveness and patient security. USgHIFU combined with GnRHa can provide an effective alternative management of leiomyoma on T_2 weighted MRI.

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Table 3. The incidence of pain and pain score during treatment between high-intensity focused ultrasound (HIFU) and gonadotropin-releasing hormone analogue (GnRHa) group and single HIFU group

Variable	HIFU and GnRHa	Simple HIFU
Total incidence of pains (%)	88.9 (16)	91.7 (33)
Pain score (point)	3.0 ± 0.5^a (2–4)	3.6 ± 0.8^a (2–5)
Incidences of SIRB (%)	4.7 (3)	9.6 (5)

SIRB, Society of Interventional Radiology Grad B.

^a $p = 0.000$.

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