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Case Report

Real-time assessment of high-intensity focused ultrasound treatment of uterine fibroids with SonoVue: a case report with literature review

Yu-Hsuan Lin [1#], Liang-Ying Wu [2#], Li-Hsin Hsia [1], Tsung-Ho Ying [1, 3*]

[1] *Department of Obstetrics and Gynecology, Chung Shan Medical University Hospital, Taichung City, Taiwan.*

[2] *Department of Radiology, Taichung Veterans General Hospital, Taichung City, Taiwan.*

[3] *Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Chung Shan Medical University, Taichung City, Taiwan.*

[#] *These two authors contributed equally to this work.*

Uterine fibroids, which affect 30%-40% of women of reproductive age, are traditionally treated with medication or surgery. High-Intensity Focused Ultrasound (HIFU) has emerged as a noninvasive alternative. However, an immediate evaluation of the efficacy of treatment is challenging with standard magnetic resonance imaging (MRI). A 35-year-old woman with a history of uterine myomas underwent HIFU treatment, experiencing persistent anemia symptoms. Contrast-Enhanced Ultrasound (CEUS) using SonoVue was used for real-time assessment during HIFU. Grayscale changes and measurements of the non-perfused area were observed immediately post-ablation. Follow-up MRI revealed a substantial reduction in the size of the treated myoma. HIFU, known for its noninvasiveness and cost-effectiveness, lacks real-time monitoring capabilities. Traditional post-treatment evaluation involves magnetic resonance imaging, which does not provide immediate insight. CEUS with SonoVue is increasingly used during HIFU due to its ability to assess treatment responses in real time. The study reviewed the existing literature supporting SonoVue's effectiveness in detecting residual fibroid tissue during HIFU procedures. SonoVue-enhanced CEUS proves to be a valuable real-time diagnostic tool during HIFU treatment for uterine fibroids. This approach allows an immediate assessment of treatment effects, especially in challenging cases such as submucosal myomas. The safety profile of SonoVue appears favorable and the obtained results correlate well with the MRI findings, presenting a promising avenue to improve the efficiency and safety of HIFU procedures.

Keywords: Uterine fibroids, High-Intensity Focused Ultrasound (HIFU), Contrast-Enhanced Ultrasound (CEUS), sonoVue

1. Introduction

Uterine fibroids are common benign tumors with a prevalence of approximately 30%-40% among women of reproductive age (1). Traditional treatment for uterine fibroids includes medication and surgery such as myomectomy or uterine artery embolization (UAE). High-intensity focused ultrasound (HIFU) has emerged as a new non-invasive treatment for uterine fibroids (2). After HIFU treatment, follow-up magnetic resonance imaging (MRI) is used to determine the size and condition of the myoma and

* Corresponding Author: Tsung-Ho Ying
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: 886-4-24739595 ext. 200297
E-mail: ying.steve@gmail.com

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evaluate treatment by non-perfusion volume (NPV). However, the disadvantage of magnetic resonance imaging (MRI) is that it does not immediately show the effects of treatment. Therefore, if there is a better method that can immediately show the effect of treatment during the operation, it should be a good inspection method. Presently, the primary image-guided approaches for HIFU encompass magnetic resonance-guided (MR-HIFU) and ultrasound-guided (US-HIFU) methods. US-HIFU treatments achieve therapeutic precision and effectiveness by modifying echogenicity within the targeted regions (3). On the contrary, MR-HIFU treatments prioritize safety and efficacy by continuously monitoring temperature changes and offering feedback (4). The clinical use of MRgHIFU is constrained due to limited eligibility criteria, the need for a dedicated MRI device for treatment guidance, and the prolonged procedure duration. On the contrary, USgHIFU boasts a shorter treatment duration compared to MRgHIFU (5). Currently, contrast-enhanced ultrasound (CEUS) is used as a real-time diagnostic tool to evaluate treatment results during the HIFU procedure. SonoVue (Bracco SpA, Milan, Italy) is a commonly used contrast agent in CEUS. It is an intravascular microbubble composed of sulfur hexafluoride gas with a phospholipid shell. SonoVue enhances real-time visualization and assessment in USgHIFU by acting as a contrast agent. It helps detect microvascularization within the targeted tissue, allowing clinicians to monitor treatment efficacy and ensure accurate targeting for optimal outcomes(6). Additionally, SonoVue helps evaluate non-perfused areas within treated fibroids, enhancing treatment response assessment and overall procedure safety, efficacy, and precision.

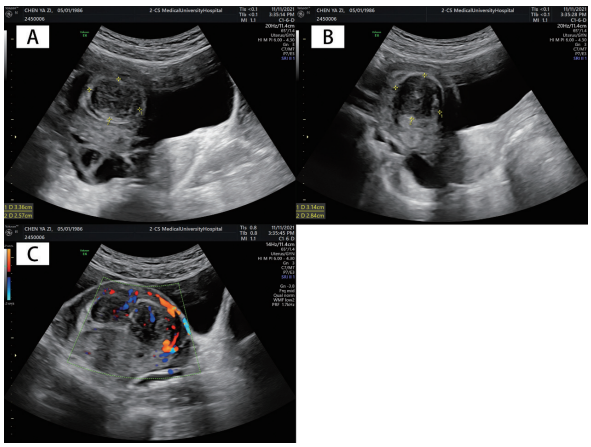


Figure 1. Under ultrasound, two round hyperechoic solid masses with internal focal hypoechoic area, (A) 3.36 × 2.57 cm and (B)3.14 × 2.84 distinctively, presence of multiple circumscribed masses, hypoechoic to myometrium with posterior refractory shadowing and multiple vessels within the mass. (C) Myomas located in the intrauterine cavity, with peripheral vascularization, suspected as submucosal myoma.

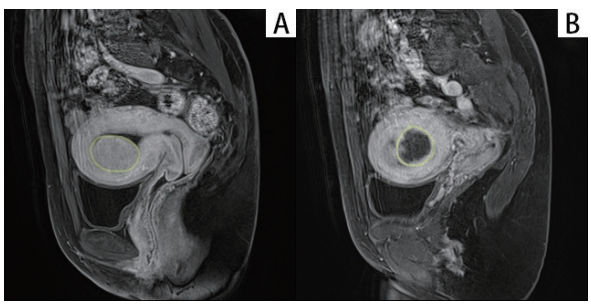


Figure 2. Fat-saturated contrast-enhanced T1-weighted MRI revealed (A) a 3.4 cm contrast enhancing mass arising from the uterine fundus that bulges out of the endometrial cavity, a suspected submucosal myoma (yellow line).
(B) A non-enhancing area in the pedunculated mass lesion with endometrial cavity, likely as a post-ablation change of previous HIFU therapy (yellow line).

2. Case Report

The patient was a 35-year-old woman, G0P0, with a medical history of uterine myomas. She had undergone HIFU 2 years earlier and was having regular follow-ups in the outpatient department (OPD). Her symptoms had been managed through HIFU surgery followed by Leuplin Depot therapy. She presented to our hospital due to persistent signs and symptoms of heavy vaginal bleeding during her menstrual cycle, along with symptoms of anemia such as irregular heartbeat and cold extremities. The results of her lab tests revealed microcytic anemia, indicated by a hemoglobin level of 8.7 g/dL and an MCV of 68.5 fl. Furthermore, no other abnormalities detected, including leukocytosis, liver dysfunction, or renal dysfunction. Sonography revealed two round hyperechoic solid masses with internal focal hypoechoic area, both presence of multiple circumscribed masses, hypoechoic to

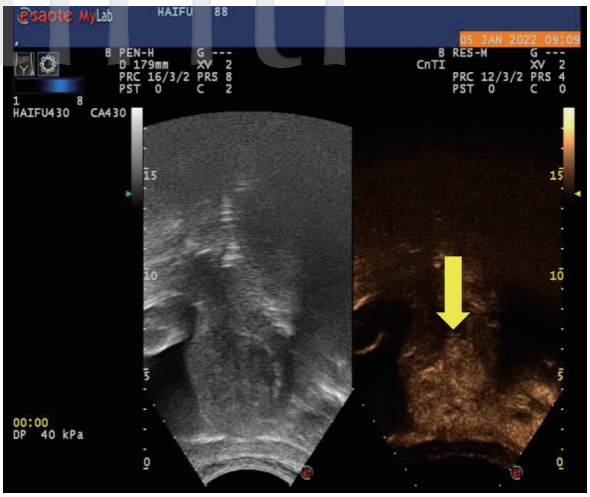


Figure 3(A). Contrast-enhanced ultrasound showing enhanced SonoVue (bold arrow) in the target region 30 seconds after SonoVue injection before HIFU ablation.

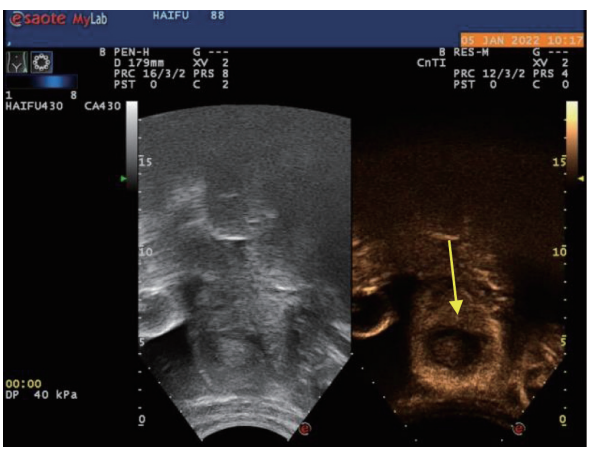


Figure 3(B). 30 seconds after SonoVue injection after HIFU ablation, contrast-enhanced ultrasound did not show enhancement surrounding the fibroid (arrow).

myometrium with posterior refractory shadowing, and multiple vessels within the mass. One measured 3.36 × 2.57 cm and the other 3.14 × 2.84 cm (Figure 1). Magnetic resonance imaging revealed a mass-enhancing contrast of 3.4 cm that bulges out of the endometrial cavity, arising from the uterine fundus, which is suspected to be submucosal myoma. Additionally, there is a non-enhancing area in the pedunculated mass lesion, likely as a myoma with a post-ablation change of previous HIFU therapy(Figure 2). Following a discussion with the patient, we administered HIFU therapy with CEUS.

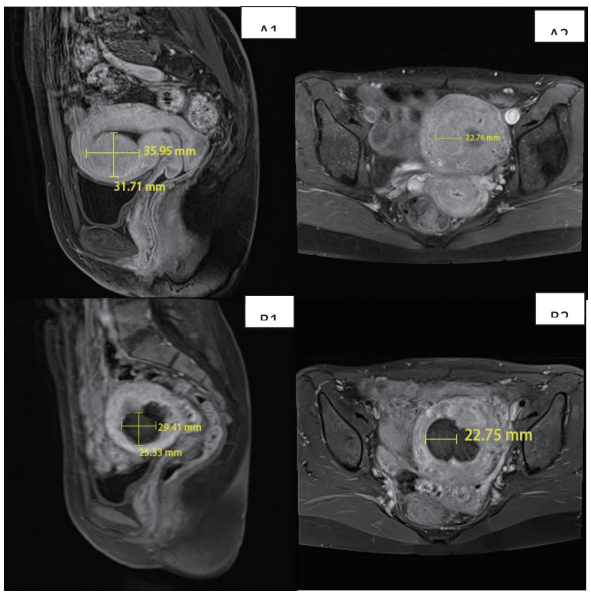


Figure 4. Fat-saturated contrast-enhanced T1-weighted MRI. (A1) and (B1) are sagittal images. (A2) and (B2) are axial images. (A) The contrast-enhanced MIR of pre-HIFU T1 showed myoma perfusion, measuring 35.95 × 31.71 × 22.76 mm. (B) Post-HIFU T1 contrast-enhanced magnetic resonance imaging showed a non-enhancing area in the left lateral wall and intracavity uterine leiomyomas, measuring 25.33 × 29.41 × 22.75 mm, compatible with post-ablation change.

We performed HIFU (JC HIFU, Chongqing Haifu Technology) and contrast-enhanced ultrasound with SonoVue, as subsequently described. Each vial of the SonoVue contrast agent contained 25 mg of lyophilized powder and 59 mg of sulfur hexafluoride gas. A 25 mg SonoVue was reconstituted with 5 ml of normal saline. Then 1.5 mL of the SonoVue solution (7.5 mg) was administered intravenously (hand vein) after a normal saline infusion. Enhancement was observed after 10 s and continued for 150 s (Figure 3A). HIFU ablation was performed after 10 min. The total treatment time was 235 s and 70500 J of energy was applied, with the average power being 300 W. We also injected 1.5 mL of the SonoVue solution immediately after HIFU ablation to assess the therapeutic response. We observed grayscale changes in the treated fibroid (Figure 3B, arrow) and a non-perfused area could be measured. During the procedure, the patient complained of pain in the treated region, which gradually relieved following pain control and rest.

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After 2 weeks, the patient returned to our OPD for follow-up where the magnetic resonance showed a decrease in the size of the treated myoma from 35.95 × 31.71 × 22.76 mm to 25.33 × 29.41 × 22.75 mm, with a non-perfused volume ratio (NPV) of nearly 99% (Figure 4). The NPV rate was defined as NPV / posttreatment fibroid volume × 100%. Subsequent laboratory analysis continued to indicate anemia, with a hemoglobin level of 9.3 g/dL and an MCV of 69.4 fl. However, it was noted that her symptoms of dysmenorrhea and menorrhagia had improved.

3. Discussion

HIFU is a noninvasive treatment option for benign uterine fibroids for patients who do not wish to undergo a myomectomy. We used HIFU because it is inexpensive, user-friendly, effective, and exhibits good real-time performance. Furthermore, it avoids exposure to ionizing radiation. However, ultrasonography is limited by its low resolution. Therefore, MRI is typically performed before and after surgery to rule out the possibility of malignancy and to monitor the size and condition of the myoma and the efficacy of treatment. However, the ablation response and the NPV ratio remain unknown during treatment.

Currently, CEUS is used as a real-time diagnostic tool to evaluate treatment results during HIFU. Immediately after ablation, we used SonoVue to compare the non-perfused area in the treated lesions before and after ablation, which presented uniform grayscale changes. The volume of the induced necrosis area observed with grayscale changes can be well correlated with the follow-up MRI results. To further substantiate our hypothesis that Sonovue functions as a secure contrast enhancement agent, helping to assess treatment responses in uterine fibroids during HIFU, we conducted a comprehensive literature search on relevant articles. We conducted searches across multiple databases, including PubMed/Medline, Cochrane Library, Web of Science/ Knowledge, and Embase. Additionally, we explored related terms in the PubMed MeSH database for "High-Intensity Focused Ultrasound" and "Sonovue." We identified 10 published studies about the Sonovue and the characteristic of the table is shown in Table 1(6-15).

Previous studies had mentioned that SonoVue is of great value in the detection of residual fibroid tissue after HIFU ablation immediately during the procedure (6, 11, 12), while most of the treated

Table 1. The characteristics of the reviewed studies and the number of patients in the comparative study of HIFU with Sonovue and HIFU alone.

Author, Year	Study type	Patient No.	Sonovue	Control (HIFU only)
Zhou, 2007	Prospective cohort study	64		
Peng, 2012	Retrospective study	291	162	129
Jiang, 2014	RCT	80	40	40
Cheng, 2015	Retrospective study	2604	1304	1300
Isern, 2015	Retrospective study	319	155	235
Orsi, 2015	RCT	33	17	16
Peng, 2015	Prospective observational study	68	68	
Cheng, 2017	RCT	143	113	30
Chen, 2018	RCT	120	60	60
Jingqi, 2018	RCT*	102	102	

Abbreviation: RCT, Randomized Controlled Trial
* This RCT compared the HIFU initiation times at 1 minute and 10 minutes after SonoVue injection.

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myomas were intramural type. The myoma in our case was submucosa type and intermediate intensity based on the T2-weighted magnetic resonance image, which was expected to be difficult to treat. Previous studies had discussed some concerns about the treatment of submucosal myoma with HIFU, concerns about vaginal expulsion of ablated tissue, longer time to complete myoma remission, and even repeated procedures for regrowth or an untreated part of myoma (16). The use of SonoVue helped us assess the ablation effect immediately during the procedure and avoid excess energy use which might cause thermal injury with necrosis of the tissue within the ablation field. Furthermore, the patient might not have to undergo HIFU again for incomplete ablation of the myoma.

Furthermore, in addition to improving the visibility of the target tissue and facilitating assessment in HIFU procedures, several studies have also reported that Sonovue contributes to treatment efficacy(6, 8, 10, 11, 13, 14). Several studies have compared the use of Sonovue during HIFU with HIFU alone. They demonstrated a higher rate of massive gray scale changes (%) in the Sonovue group (6, 8, 10, 11, 13, 14), along with a shorter sonication time required to achieve these changes(6, 8, 10, 11, 13, 14) and a lower average total energy used(10, 11). These findings indicate that SonoVue contributes to improved energy efficiency in HIFU procedures, implying that microbubbles improve the effectiveness of HIFU in the treatment of uterine fibroids.

SonoVue safety has recently been studied; the reported incidence of severe adverse effects is between 0.0086% and 0.9%. Most reported adverse effects are mild, such as pain in the treated region, skin erythema, anaphylactic shock, skin allergies, nausea, dizziness, headache, numbness, chest distress, back pain, and local reactions at the injection site (17). Some reviewed studies compared adverse events in HIFU using Sonovue with HIFU only, and the results did not show significant differences (see Table 2). Our patient had no significant discomfort or complaints after HIFU treatment.

4. Conclusion

The use of SonoVue for CEUS as a real-time diagnostic tool during HIFU allows the evaluation of the effect of treatment of difficult-to-treat myomas. It is safe and efficient, and the results were well correlated with the MRI findings. However, thorough randomized controlled clinical trials are essential to gain a deeper understanding of safety and effectiveness, assess long-term outcomes, and establish other treatment parameters.

Acknowledgements

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Table 2. Studies that compare adverse events between the Sonovue group and the HIFU treatment group only.

Author, Year	Leg pain	Sciatic pain or buttock pain	Discomfort on skin	Discomfort on skin
Peng, 2012	X	X	X	X
Jiang, 2014	C	X	X	X
Cheng, 2015	S	S	S	
Isern, 2015	X	X	X	X
Cheng, 2017	X	X	X	-
Chen, 2018	X	X	X	X

Abbreviations X, No significant difference; S, Significantly higher in the Sonovue group; C, Significantly higher in the control group (without Sonovue).

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