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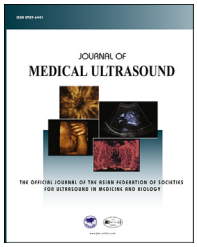

ORIGINAL ARTICLE

The Influence of Oxytocin on the Blood Perfusion of Uterine Fibroids: Contrast-enhanced Ultrasonography Evaluation

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KEYWORDS
contrast-enhanced ultrasongraphy,
oxytocin,
uterine fibroid

Abstract *Background:* High intensity focused ultrasound ablation is a new technique for the treatment of uterine fibroids. Its efficacy is influenced by the blood perfusion of the fibroids. Oxytocin is a promising drug which may decrease the blood flow to the fibroids. In this study, the alterations of blood flow to the uterine fibroids were observed using contrast-enhanced sonography (CEUS) before and after the use of parenteral oxytocin.
Methods: A total of 40 women with 42 fibroids (mean ± standard deviation, 5.8 ± 1.9 cm; range, 3.1–12.9 cm) underwent CEUS before and after intravenous infusion of oxytocin at 0.1 U/min. The CEUS time-intensity curves were drawn, the maximum signal intensity, the time-to-peak intensity and mean transit time of the fibroids were measured to observe the changes of perfusion after the use of oxytocin.
Results: After the use of oxytocin, the wash-in of microbubbles was significantly slowed down on CEUS in all patients. The maximum signal intensity of the fibroids decreased significantly and the time-to-peak intensity and mean transit time of the fibroids were prolonged significantly after the use of oxytocin in all patients ($p < 0.05$). The results suggested that the blood flow in the uterine fibroids was significantly decreased by the use of parenteral oxytocin.
Conclusion: This CEUS study demonstrated that the use of parenteral oxytocin can significantly reduce the blood perfusion of the uterine fibroids, which may help to enhance the therapeutic efficacy for high intensity focused ultrasound ablation of uterine fibroids.

Conflicts of interest: The authors have no conflict of interests to disclose.

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Introduction

Uterine fibroids are the most common benign tumors in the female genital tract [1]. About 25% of them are symptomatic which may cause menorrhagia, pelvic pain, and infertility [2]. Hysterectomy or myomectomy was the traditional treatment for symptomatic uterine fibroids. However, in the past decade, many minimally-invasive techniques have been developed for the treatment of fibroids and preservation of the uterus [3—10].

High intensity focused ultrasound (HIFU) ablation is a promising technique for the treatment of uterine fibroids. Under imaging guidance, coagulative necrosis can be induced in fibroids without damaging the overlying tissue. As treatment is repeatable and can be performed on an outpatient basis, HIFU ablation has become popular recently [8—10]. One essential factor influencing the efficacy of HIFU ablation is the perfusion mediated "heat-sink" which hampers heat deposition inside the fibroid, resulting in prolonged therapeutic time, decreased ablation volume, and irregular coagulative area [11,12]. Decreasing the blood flow to the fibroids may increase heat deposition, thereby increasing the therapeutic outcome and reducing the treatment time.

A previous study demonstrated that most fibroids had a peripheral distribution of vascular supply [13]. Methods which can induce contraction of the uterine smooth muscles may compress the peripheral vessels, reducing the blood flow to the fibroids. Oxytocin is a peptide hormone with receptors in both pregnant and nonpregnant uterus [14]. Because it can stimulate the smooth muscles of the uterus to contract, oxytocin has been used to augment labor or control postpartum hemorrhage [15,16]. We hypothesize that oxytocin may also be used to decrease the blood flow to the fibroids in a nonpregnant uterus, thereby augmenting the efficacy of HIFU ablation.

Contrast-enhanced ultrasonography (CEUS) is a new imaging technique which can depict the blood flow of the tumor in real-time, allowing for quantitative evaluation of blood perfusion parameters [17]. The purpose of this study was to use CEUS as a tool to investigate whether parenteral oxytocin can decrease the blood perfusion of the uterine fibroids.

Materials and Methods

Patients

From January 2013 to December 2014, 40 premenopausal women with 42 symptomatic uterine fibroids underwent CEUS examinations before receiving US-guided HIFU ablation in our department. The inclusion criteria were as follows: (1) the largest diameter of the fibroid $\geq$ 3 cm; (2) the number of the fibroids $\leq$ 3; (3) an acoustic pathway for HIFU ablation was present; and (4) fibroids received no treatment before HIFU ablation. The exclusion criteria were as follows: (1) pregnancy; (2) allergy to CEUS agent; and (3) contraindications to the use of oxytocin. This study was approved by the Institutional Review Committee (Chinese PLA General Hospital, Beijing, China) and informed consent was obtained in all patients at enrollment.

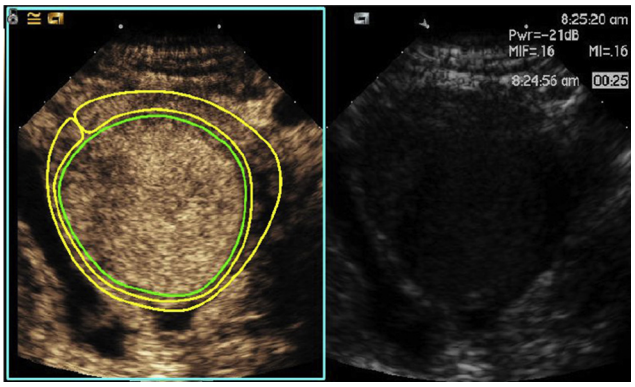

Figure 1 The region-of-interests (ROIs) are drawn in the maximum cross-sectional area of the fibroid. Using the gray-scale sonogram on the right as a reference, the ROI of the fibroid (green area) is manually set ~2 mm away from the border of the fibroid on the contrast-enhanced sonography sonogram. The ROI of the uterine wall (yellow area) is drawn in the same sonogram.

The age of the patients ranged from 29 years to 49 years (mean, 40.0 $\pm$ 6.0 years). Thirty-eight patients had a single fibroid and two patients had two fibroids. The maximum diameter of the fibroid ranged from 3.1 cm to 12.9 cm (mean, 5.8 $\pm$ 1.9 cm). Twenty-three fibroids were located intramurally, 13 fibroids were located submucosally, and six fibroids were located subserosally.

CEUS procedures

A Sequoia 512 US system (Acuson, Mountain View, CA, USA) equipped with contrast pulse sequencing software was used for CEUS. The contrast agent was SonoVue (Bracco, Milan, Italy), which was supplied as a lyophilized power and reconstituted with 5 mL of saline to form a homogeneous microbubble suspension that contains sulphur hexafluoride stabilized by a phospholipid shell. An ultrasound scan was performed with a 4V1 transducer (1—4 MHz), CEUS was performed at a mechanical index of 0.16—0.18. For all CEUS procedures, a bolus injection of a 1.0 mL SonoVue was administered via the cubital vein which was followed by a 5 mL saline flush, and the fibroids were observed continuously for at least 4 minutes. Baseline CEUS was performed first without the administration of oxytocin. Then, oxytocin (Hefeng Pharmaceuticals, Shanghai, China) was administered at a rate of 0.1 U/min with a microinjection pump via the cubital vein, and the second CEUS was performed 15 minutes later. The dose of oxytocin was chosen after consultation of experienced surgeons and pharmacologists.

CEUS was performed by one of three physicians (Y.W., D.H.R., and W.W.), each with more than 5 years' experience in CEUS. The videos were recorded digitally on a hard disc for off-line analysis. During CEUS examinations, the heart rate, blood pressure, and oxygen saturation of the patients were continuously monitored.

Analysis of CEUS was performed using a trial version of sonoliver software (TomTec Imaging Systems, Munich, Germany). The region-of-interests (ROIs) were drawn in the maximum crosssectional area of the fibroid. Using the