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

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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.

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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 ≥ 3 cm; (2) the number of the fibroids ≤ 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.

The age of the patients ranged from 29 years to 49 years (mean, 40.0 ± 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 ± 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 cross-sectional area of the fibroid. Using the...
Figure 2  The contrast-enhanced sonography changes of blood perfusion of the fibroid before and after intravenous administration of oxytocin at 0.1 U/min. (A) Before the use of oxytocin, the fibroid began to enhance 18 seconds after bolus injection of SonoVue. The green area corresponds to the location of the fibroid. The border of the uterine wall is marked by arrows. (B) The fibroid reached maximum signal intensity 20 seconds after bolus injection of SonoVue. (C) Sixty seconds after bolus injection of
The uterine wall was defined as the reference area. The Imax of the uterine wall was 100% before and after the use of oxytocin at 13.8% deviation. A p(TTP), and mean transit time (MTT) of both the fibroid and intensity (Imax) of the fibroid, the time-to-peak intensity curve was obtained by software. The maximum intensity (Imax) of the fibroid on the CEUS sonogram. The ROI of the uterine wall was manually set about 2 mm away from the margin of the fibroid on the CEUS sonogram. The ROI of the fibroid was drawn in the same sonogram (Figure 1). The time-intensity curve was obtained by software. The maximum intensity (Imax) of the fibroid, the time-to-peak intensity (TTP), and mean transit time (MTT) of both the fibroid and the uterine wall were measured.

Differences in Imax, TTP, and MTT were evaluated with Student t test. Statistical analyses were performed by using Stata software (version 7.0; Stata Corporation, College Station, TX, USA). Data were expressed as mean ± standard deviation. A p value < 0.05 was considered statistically significant.

Results

After the administration of oxytocin, the wash-in of microbubbles into the uterine wall was not slowed down on CEUS and the Imax of the uterine wall did not change significantly. However, the wash-in of microbubbles into the fibroids was significantly slowed down. On CEUS, the fibroids began to enhance from the periphery significantly later after the use of oxytocin: only a few vessels could be seen flowing slowly into the fibroids. The fibroids became significantly darker on CEUS and they reached peak enhancement much later after the use of oxytocin (Figure 2). Software analyses indicated that the Imax of the fibroids was significantly decreased by the use of oxytocin. The baseline Imax of the fibroid was 102.7 ± 59.5% (range, 13.8—242.3%), which decreased to 15.5 ± 16.9% (range, 1.2—81.6%) after the use of oxytocin (p < 0.05). The TTP and MTT of the fibroids were also significantly prolonged after the use of oxytocin (p < 0.05). The baseline TTP and MTT were 15.9 ± 4.8 seconds (range, 9.8—34.6 seconds) and 73.9 ± 35.0 seconds (range, 29.7—175.7 seconds) respectively, which were prolonged to 28.3 ± 14.0 seconds (range, 10.5—85.7 seconds) and 119.4 ± 109.2 seconds (range, 26.1—441.9 seconds), respectively after the use of oxytocin (Table 1).

The heat rate, blood pressure, and oxygen saturation did not change significantly after the administration of oxytocin in all patients. Two patients felt tolerable mild pain in the abdomen which disappeared soon after discontinuation of oxytocin infusion. No severe adverse effect was encountered during CEUS examinations.

Discussion

Minimizing the perfusion-mediated cooling effect is a promising strategy to enhance the therapeutic efficacy for HIFU ablation of uterine fibroids. A previous study showed that targeted HIFU ablation of the feeding vessel of the uterine fibroids could result in more efficient tumor necrosis and the required thermal dose could be reduced significantly [18]. However, target vessel ablation was technically difficult as it required an exact three dimensional overlay of angiography with intraoperative images. Therefore, other methods need to be developed to reduce the blood perfusion of the uterine fibroids during HIFU ablation.

Oxytocin was proposed to be a potential drug for decreasing the blood perfusion of uterine fibroids. In this study, its effect on the blood perfusion of the fibroid was observed by CEUS. After infusion of oxytocin, the Imax of the fibroid was significantly decreased and the TTP and MTT of the fibroid were significantly increased in all patients. The Imax is representative of the vascular volume and decreased Imax of the fibroid corresponded to fewer vascular volume inside the fibroid. TTP and MTT are representatives of the blood flow speed and increased TTP and MTT of the fibroid corresponded to slower blood flow inside the fibroid. These results suggested that the blood perfusion of the fibroid was significantly reduced after the use of oxytocin. Intravenous administration of oxytocin may become a safe and effective method to reduce the blood perfusion of the fibroid.

### Table 1

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<th>Fibroids&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Imax (%)</td>
<td>TTP (s)</td>
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<td>Before the use of oxytocin</td>
<td>102.7 ± 59.5</td>
<td>15.9 ± 4.8</td>
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<tr>
<td>After the use of oxytocin</td>
<td>15.5 ± 16.9</td>
<td>28.3 ± 14.0</td>
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<td>100</td>
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Imax = the maximum intensity; MTT = the mean transit time; TTP = the time to peak intensity.

<sup>a</sup> The uterine wall was defined as the reference area. The Imax of the uterine wall was 100% before and after the use of oxytocin at 0.1 U/min. The Imax of the fibroid was expressed as a percentage compared with the Imax of the uterine wall.
perfusion of the fibroids thereby enhancing the efficacy of HIFU for ablation of uterine fibroids. This study had some limitations. Firstly, the number of enrolled patients was small—the effect of oxytocin should be further tested in a larger cohort of patients. Secondly, because the CEUS software was a trial version, some parameters like the area under the curve could not be measured. Thirdly, only one dose was used in this study. The appropriate therapeutic doses need to be further investigated. Fourthly, to what extent oxytocin could enhance the therapeutic effect of HIFU ablation is unknown. We are undertaking randomized controlled trials to answer this question.

In conclusion, our CEUS study showed that the blood perfusion of uterine fibroids could be significantly reduced by the administration of oxytocin. It may have clinical implications for enhancing the efficacy of HIFU ablation for the treatment of uterine fibroids.

References