Research of dose-effect relationship parameters of percutaneous microwave ablation for uterine leiomyomas - a quantitative study

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Eighty eight patients with 91 uterine leiomyomas who underwent ultrasound-guided percutaneous microwave ablation (PMWA) treatment were prospectively included in the study in order to study the dose-effect relationship parameters (DERP) of PMWA for uterine leiomyomas and its relationship with T2-weighted MR imaging (T2WI). Based on the signal intensity of T2WI, uterine leiomyomas were classified as hypointense, isointense, and hyperintense. During ablation, leiomyomas were treated with quantitative microwave ablation (QMWA) energy of 50 w × 300 s or 60 w × 300 s. After QMWA, contrast-enhanced ultrasound (CEUS) was performed to evaluate DERP. No matter under 50 w × 300 s or 60 w × 300 s, quantitative microwave ablation volume (QMAV) of hyperintense leiomyoma was smaller than that of hypointense and isointense leiomyoma (P < 0.016). For hypointense and isointense leiomyoma, QMAV of 60 w × 300 s was larger than that of 50 w × 300 s (P < 0.05). DERP obtained by T2WI can be used to guide the treatment of uterine leiomyoma by PMWA.

Uterine leiomyomas are benign clonal tumours that arise from the smooth-muscle cells of the human uterus. Although many of them are asymptomatic, as many as 25% patients have symptoms such as abnormal uterine bleeding, dysmenorrhea, pelvic pressure, low abdominal pain and infertility. Hysterectomy has long been the main mode of therapy for leiomyomas, but it is associated with significant morbidity and guarantees infertility. Even women without a desire for future pregnancies might not wish to lose their uteruses for various reasons. However, medical technology advancements have made less invasive treatment options available, such as uterine artery embolization, high intensity focused ultrasound, and percutaneous microwave ablation (PMWA). PMWA is a minimally invasive technique for treatment of uterine leiomyomas by inducing tissue necrosis through thermal damage. Previous reports have indicated that PMWA provides a feasible, safe and reliable alternative for the treatment of uterine leiomyomas. However, until now, the dose-effect relationship parameters (DERP) of PMWA for uterine leiomyomas are still unclear. In this study, we sought to investigate the DERP of PMWA for uterine leiomyomas and the relationship with T2-weighted MR imaging (T2WI) to make the PMWA procedures quantized and to guide better clinical treatment.

Methods

The study was approved by the institutional ethics committee. Informed consent was obtained from all participants. And all experiments were performed in accordance with relevant guidelines and regulations.

Patients. From July 2012 to December 2013, 88 premenopausal women with symptomatic uterine leiomyomas who underwent PMWA treatment at PLA General Hospital were prospectively analyzed.

The inclusion criteria were as follows: (1) Patients had been diagnosed with uterine leiomyomas by ultrasonography and ceMRI in our hospital; patients had experienced one of the following symptoms for more than 1 year: menorrhagia or metrorrhagia, dysmenorrhea, lower abdominal pain, bulk pressure, or urinary frequency; (2) Patients were above 18 years of age, and in premenopausal status; (3) Patients with no reproductive needs; (4) The average diameter was ≥5 cm; (5) Patients underwent ceMRI before and after PMWA treatment within 5 days; (6) Patients had never received other treatments (such as myomectomy, HIFU, UAE, cryoablation, radiofrequency and ethanol injection) before PMWA;

Exclusion criteria: (1) menstruating, pregnant or breastfeeding women; (2) patients with pelvic infection, coagulation disorders, heart or brain diseases or malignant tumors confirmed by pathology.
Intravenous CEUS. The CEUS was performed in all patients after 50 w \times 300 s or 60 w \times 300 s ablation. Informed consent was obtained from each individual participated in this study.

Contrast agent: Sonovue (manufactured by Bracco Company in Italy). Five milliliters of physiological saline was injected into a portion of 4.98 mg frozen dry powder, fully shaken and intemriged. 2.0 ml of contrast agent was injected via elbow vein quickly, followed by 5 ml of physiological saline for washing.

The DFRs was calculated with CEUS. The non-enhanced CEUS volume after 300 s or 60 w \times 300 s ablation was defined as QMAV. The non-enhanced volume was calculated according to 4/3(\pi d^3/2) where the mean volume was 158.09 ± 127.28 cm^3 (from 65.45 to 609.13 cm^3). The mean volume of hypointense leiomyomas was 211.97 ± 193.41 cm^3 (from 65.45 to 609.13 cm^3), of isointense leiomyomas was 150.20 ± 99.71 cm^3 (from 65.45 to 448.92 cm^3), and of hyperintense leiomyomas was 148.70 ± 71.4 cm^3 (from 65.45 to 268.08 cm^3), respectively.

Table 2 | QMWLs, QMWWs, QMWHs, and QMAVs of 50 w \times 300 s in different signal intensity

| Signal intensity | Number | QMWLs (cm) | QMWW (cm) | QMWH (cm) | QMAV (cm^3) * |
|------------------|--------|------------|-----------|-----------|---------------|
| Hypointensity    | 21     | 4.82 ± 0.67| 3.91 ± 0.55| 4.34 ± 1.05| 46.48 ± 25.63 |
| Isointensity     | 12     | 4.79 ± 0.51| 4.07 ± 0.65| 4.10 ± 0.70| 44.46 ± 16.72 |
| Hyperintensity   | 14     | 3.68 ± 0.74| 3.21 ± 0.72| 3.50 ± 0.58| 23.58 ± 11.85 |

Note: *X^2 = 14.08, P = 0.001, Pairwise comparison; \*X_{hyper/isoint} = 3.97, P_{hyper/isoint} = 0.00, X_{hyper/hypo} = 4.44, P_{hyper/hypo} = 0.00.

Discussion

Uterine leiomyomas are the most common tumor in the female reproductives system. Since the first case of uterine leiomyoma treatment with PMWA was reported in 2008\(^\text{16}\) in China, a series of studies\(^\text{12} - 13\) have indicated that PMWA provides a feasible, safe and reliable alternative for the treatment of uterine leiomyomas. In these treatments, they used the DERP of MW ablation in porcine muscularurexx in vivo and hyperecho (caused by microbubbles generated during MW emission and representing roughly the ablation zone\(^\text{17}\)) to guide the ablation of leiomyom\(a\)^\(^\text{12}\). On the one hand, the DERP which was got from in vitro porcine muscle did not consider the influence of blood flow to ablation effect. Moreover, the proportion and arrangement of the cells in porcine muscle and leiomyoma are different. So the DERP of in vitro porcine muscle could not predict the DEPR of leiomyoma precisely. On the other hand, the study of Fang Wang et al.\(^\text{13}\) showed that measurements of the hyperechogenic range on ultrasonography is strongly correlated to the no enhance-
Table 3 | QMWLs, QMWWs, QMWHs, and QMAVs of 60 w × 300 s in different signal intensity

| Signal intensity | Number | QMWLs (cm) | QMWWs (cm) | QMWHs (cm) | QMAVs (cm²) *
|-----------------|--------|------------|------------|------------|----------------|
| Hypointensity   | 20     | 5.17 ± 0.88| 3.91 ± 0.64| 4.43 ± 1.34| 54.29 ± 22.46 |
| Isointensity    | 14     | 5.05 ± 0.31| 4.03 ± 0.21| 4.58 ± 0.41| 51.36 ± 8.63  |
| Hyperintensity  | 10     | 3.83 ± 0.31| 3.13 ± 0.31| 3.53 ± 0.15| 22.54 ± 2.98  |

Note: *χ² = 13.66, P = 0.001; Pairwise comparison: Zhyper/hypo = 4.06, P_hypo = 0.00; Zhyper/iso = 4.08, P.iso = 0.00.

Figure 1 | Microwave ablation range of 50 w × 300 s for hypointense leiomyomas (a) T2WI before PMWA: hypointense leiomyomas in the anterior wall of the uterus (arrowhead). (b) cEMRI: enhancement degree of leiomyomas lower than that of the myometrium (arrowhead). (c) CEUS image: microwave ablation range (“+”).

Figure 2 | Microwave ablation range of 50 w × 300 s for isointense leiomyomas (a) T2WI before PMWA: isointense leiomyomas in the anterior wall of the uterus (arrowhead). (b) cEMRI: enhancement degree equivalent to myometrium (arrowhead). (c) CEUS image: microwave ablation range (“+”).

Figure 3 | Microwave ablation range of 50 w × 300 s for hyperintense leiomyomas (a) T2WI before PMWA: hyperintense leiomyomas in the anterior wall of the uterus (arrowhead). (b) cEMRI: enhancement degree equivalent to myometrium (arrowhead). (c) CEUS image: microwave ablation range (“+”).
ment area by contrast-enhanced ultrasonography. But variations of the hyperecho needed to be monitored by real-time ultrasonography, which could not be used to predict the ablation area before treatment, so as to do treatment planning. Therefore, the study of DEPR of in vivo uterine leiomyomas is necessary.

MRI is the most accurate imaging technique for detection and evaluation of leiomyomas and therefore it has become the imaging modality of choice before and after PMWA. The study of Schwartz18 thought leiomyoma subtypes can be diagnosed accurately by MRI. It had 95% sensitivity and 72% specificity to diagnose an ordinary
uterine leiomyoma and 10% sensitivity and 100% specificity for a cellular uterine leiomyoma, respectively. Specific sequence imaging can provide some information about tissue directly and can reveal the pathological character of lesions to a certain extent. The study of Sai et al. has shown that uterine leiomyomas with T2WI hyperintensity or isointensity indicating more fiber and fewer cellular content or lesion with less blood supply. To the contrary, uterine leiomyomas with T2WI hyperintensity indicated cellular leiomyomas or vascularization. DERP of uterine leiomyoma is closely related to pathological character. Previous study found that EPVs of different T2WI signal intensity were different. MRI signal intensity of uterine leiomyomas can be used to predict PMWA energy. Therefore, we further studied the DERP of QMWA for uterine leiomyomas of different T2WI signal intensity. The study of DERP of QMWA for in vitro porcine muscle indicated that a spherical ablation shape can be created most likely, when the microwave power is 50 w or 60 w. And the two powers can be used as clinical treatment power. Therefore, in the study, a QMWA of 50 w/60 w for 300 s were performed for uterine leiomyomas of different T2WI signal intensity. And DERP was summarized and analyzed (Table 2, Table 3) in order to be used to predict PMWA energy of uterine leiomyoma before treatment and to predict the number of antennas and their placement.

The QMAVs for hypo-, iso- and hyper-intensity uterine leiomyomas under 50 w × 300 s were respectively 46.48 ± 25.63 cm3, 44.46 ± 16.72 cm3 and 23.58 ± 11.85 cm3; the QMAVs for hyper-intensity uterine leiomyomas under 60 w × 300 s were respectively 54.29 ± 22.46 cm3, 51.36 ± 8.63 cm3, 22.54 ± 2.98 cm3. No matter for 50 w × 300 s or 60 w × 300 s, QMAVs of hyperintense leiomyomas were smaller than that of hypointense and isointense leiomyomas. These were statistically significance difference. This study analyzed the ceMRI characteristics for hypointensity, isointensity and hyperintensity uterine leiomyomas, which indicates that uterine leiomyomas of hypointensity are mainly slight or inhomogeneous enhancement and uterine leiomyomas of hyperintensity were mainly homogeneous enhancement, between which there was statistical significance. According to Harman’s study, increased contrast enhancement of leiomyoma is presumably indicative of a lesion with increased vascularity. As high perfusion decreases heat accumulation through the vascular cooling effect, more abundant blood supply, more heat will be taken away during the ablation process, smaller microwave ablation region will be obtained. In our study, hyperintense leiomyomas enhanced better than that of hypointense leiomyomas, which was consistent with Swe’s study. And the QMAV of uterine leiomyomas with T2WI hyperintensity is smaller than that of hypointensity.

For hypointense and isointense leiomyomas, QMAVs of 60 w × 300 s were larger than that of 50 w × 300 s, with statistically significant difference. Comparing with 50 w × 300 s, 60 w × 300 s may extend the ablation range. For larger leiomyomas, treatment with 60 w × 300 s is more time-saving than 50 w × 300 s.

The ablation EPVs for hypo-, iso- and hyper-intensity uterine leiomyomas under 50 w × 300 s were respectively 381.91 ± 120.74 J/cm3, 393.00 ± 171.86 J/cm3, 843.80 ± 592.09 J/cm3. The ablation EPVs for hypo-, iso- and hyper-intensity uterine leiomyomas under 60 w × 300 s were respectively 373.79 ± 119.26 J/cm3, 368.54 ± 49.26 J/cm3, 807.81 ± 102.87 J/cm3. EPVs of 50 w × 300 s is greater than that of 60 w × 300 s, but the difference was not statistically significant. In the study, we can not conclude that treatment with 60 w × 300 s is more energy-saving than that with 50 w × 300 s.

In conclusion. This research prospectively studied the DERP of PMWA for uterine leiomyomas, and compared the QMAVs and EPVs in different T2WI signal intensity. The parameters obtained can be used to guide treatment planning. This can effectively reduce the unnecessary microwave radiation time, increase the MW ablation safety and promote the widespread utilization of MWA technique for uterine leiomyomas in clinical.

| Table 4 | Comparison of QMAVs (cm³) of 50 w × 300 s and 60 w × 300 s in different signal intensity |
|---|---|---|---|---|
| Energy | QMAVs of hypointensity* | QMAVs of isointensity* | QMAVs of hyperintensity* |
| 50 w × 300 s | 47 | 46.48 ± 25.63 | 44.46 ± 16.72 | 23.58 ± 11.85 |
| 60 w × 300 s | 44 | 54.29 ± 22.46 | 51.36 ± 8.63 | 22.54 ± 2.98 |

Note: *Z = −2.089, P = 0.037, †t = −2.145, P = 0.043.

| Table 5 | Comparison of EPVs (J/cm³) of 50 w × 300 s and 60 w × 300 s in different signal intensity |
|---|---|---|---|---|
| Energy | EPVs of hypointensity * | EPVs of isointensity* | EPVs of hyperintensity* |
| 50 w × 300 s | 47 | 381.91 ± 120.74 | 393.00 ± 171.86 | 843.80 ± 592.09 |
| 60 w × 300 s | 44 | 373.79 ± 119.26 | 368.54 ± 49.26 | 807.81 ± 102.87 |

Note: *Z = −0.539, P = 0.606, †t = 0.553, ‡Z = −0.273, P = 0.815.
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**Author contributions**

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**Additional information**

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