Reduction in the Vascular Bed Volume of Uterine Fibroids after Hormonal Treatment: Evaluation with Dynamic Double-Echo R2* Imaging

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Purpose: To demonstrate the reduction in vascular bed volume (VBV) of uterine fibroids after administration of gonadotropin-releasing hormone analogue (GnRHa) using magnetic resonance (MR) imaging including dynamic double-echo R2* imaging (DDE-R2*I) and to assess the value of DDE-R2*I as a predictor of such reduction.

Methods: Twenty-one women with uterine intramural fibroids underwent MR imaging including DDE-R2*I before GnRHa treatment. DDE-R2*I was acquired using a single-section, double-echo, fast spoiled gradient recalled acquisition in the steady state (SPGR) sequence. We calculated the area under the curve (AUC) of the signal intensity on R2*I within a 3×3-cm² region of interest that served to represent the VBV. We repeated MR imaging after 2 administrations of GnRHa and repeated image analyses. We statistically analyzed correlations between (A) pre-treatment AUC (AUC(pre)) and AUC reduction and (B) AUC(pre) and volume reduction.

Results: The interval between the 2 MR studies ranged from 56 to 119 days (mean: 80.4 days). The average volume of the fibroids before GnRHa treatment was 647.8 mL compared with 463.4 mL after the therapy (decreased by an average of 28.5; P<0.0001). Meanwhile, measured AUC was reduced by 55.3 (483.4 vs. 206.5; P<0.0001). AUC(pre) correlated with volume reduction (r=0.68), but not AUC reduction.

Conclusions: We confirmed reduction in the VBV of fibroids using DDE-R2*I. The measurement of AUC(pre) on DDE-R2*I aids prediction of fibroid volume reduction but correlates poorly with the percentage of AUC reduction.

Keywords: drug response, hormonal therapy, magnetic resonance imaging, uterine fibroid, vascularity

Introduction

Uterine fibroids are the most common pelvic tumor in women; reported incidence is 20 to 25% during reproductive years.1 Uterine fibroids can cause abnormal uterine bleeding, and treatment is considered for women with clinically severe symptoms. Traditional treatments include hysterectomy or myomectomy; less invasive techniques, such as uterine artery embolization (UAE) and focused ultrasound (FUS), have recently been introduced.2,3 Observations that maintenance and growth of uterine fibroids require estrogen and that uterine fibroids express estrogen and progesterone receptors led to the hypothesis that gonadotropin-releasing hormone analogue (GnRHa) might alleviate fibroid-related symptoms.4 Fibroid vasculature diminished significantly in patients treated with GnRHa.5 However, we believe the change in vascular bed volume (VBV) after GnRHa treatment has not been reported.

Gadolinium-enhanced magnetic resonance (MR) imaging is widely used and accepted for the detection and characterization of tumors and inflammatory processes on T1-weighted imaging (T1WI). In addition, T1WI dynamic studies have been utilized for the semiquantification of tissue vascularity in analyzing signal intensity (SI) time series.6 However, SI changes on T1WI after gadolinium ad-
ministration reflect a mixture of shortened $T_1$ and $T_2^*$ relaxation and are also the product of both VBV and vessel permeability. Dynamic double-echo MR imaging enables the generation of $R_2^*$ ($T_2^*$ relaxation rate, $1/T_2^*$) images (DDE-$R_2^*$I), which are not confused by $T_1$ shortening and, so, reflect the VBV of tissue. DDE-$R_2^*$I is suitable for evaluating VBV and has been successfully applied in previous research.

Our aims were to demonstrate the reduction in VBV of uterine fibroids after GnRHa administration using DDE-$R_2^*$I and to evaluate the value of DDE-$R_2^*$I as a predictor of such reduction.

Materials and Methods

Patient population

Our institutional review board approved this study, and we obtained written informed consent from all patients. Between January 1 through December 31, we recruited 23 patients referred to our Department of Obstetrics and Gynecology for myomectomy. We excluded from study patients with fibroids demonstrating myxoid degeneration exceeding 50% in volume that showed very high signal intensities on T2-weighted images because such patients are reported less responsive to GnRHa; as well, inaccurate estimation could result from inclusion of an area of avascularity resulting from cystic change in the region of interest used to assess VBV. After the pretreatment MR examination, GnRHa (leuprorelin acetate, 1.88 mg) was administered twice to all patients.

MR scan protocol

All MR scans were obtained on a 1.5-tesla clinical scanner (SIGNA HD, GE Healthcare, Waukesha, WI, USA) using a pelvic-array coil as receiver. Image data were acquired before and after GnRHa treatment. First, T2-weighted imaging (T2WI) in the axial and sagittal planes was acquired using a fast spin echo sequence with parameters: repetition time (TR), 4000 ms; effective echo time (TE), 100 ms; echo train length (ETL), 20; image matrix, $512 \times 512$; and number of excitations (NEX), 3. Second, T1-weighted axial imaging (T1WI) was performed using a fast spin echo sequence with parameters: repetition time (TR), 400 ms; TE, 8 ms; ETL, 2; image matrix, $256 \times 256$; NEX, one).

After acquisition of T2WI and T1WI, we performed gadolinium-enhanced dynamic study using an in-house, single-section, double-echo, fast spoiled gradient recalled acquisition in the steady state (SPGR) sequence. Parameters were: TR, 13 ms; TE1/TE2, 3.5/8.6 ms; flip angle, 20°; bandwidth, 16.63 kHz; matrix size, $128 \times 128$; NEX, one; field of view (FOV), 24 cm; and thickness, 10 mm. Sets of images for each TE were obtained every 1.5 s during the 2-minute scan, which included 20 sets of baseline images. When multiple fibroids were present, we targeted the largest. We chose a single sagittal plane for acquisition of images with the largest cut surface of the uterine fibroid. The contrast agent (Omniscan; gadodiamide hydrate, 0.15 mmol/kg) was injected at a rate of 4 mL/s 30 s after the start of image acquisition and followed by a 15-mL saline solution flush.

$R_2^*$I generation

$R_2^*$ images were generated using the equation:

$$R_2^* = \ln [S(TE1)/S(TE2)]/(TE2 - TE1),$$

in which TE1 and TE2 reflect the first and second TE, and S(TE1) and S(TE2) are the signal intensities of the images acquired at the first and second TE.

To measure signal, we identified a region of interest (ROI) with a $16 \times 16$ voxel matrix ($3 \times 3 \text{ cm}^2$) placed in the center of the fibroid on the $R_2^*$I. We plotted the time series of the signal intensity (SI) in the ROI and generated the fitted gamma curve using all data points. We calculated the area under the curve (AUC) for the fitted signal curve on $R_2^*$I, excluding the recirculation of the contrast agent following the first pass.

Volume measurement

To measure the volume of the fibroid, we manually traced its margins on the sagittal T2WI with commercially available software on a workstation (Advantage Workstation, GE Healthcare, WI, USA). We calculated the percentage of reduction (with standard deviation) of the AUC as:

$$\text{% reduction of AUC} = (\text{AUC(pre)} - \text{AUC(post)}) \times 100/\text{AUC(pre)} \ (2)$$

and that of volume as:

$$\text{% reduction of volume} = (\text{volume(pre)} - \text{volume(post)}) \times 100/\text{volume(pre)}, \ (3)$$

where “pre” indicates before GnRHa treatment and “post” indicates after the treatment. Data are presented as the mean ± standard deviation (SD).

Statistical analysis

We performed all statistical analyses using Prism 4 software (version 4.02, GraphPad Software Inc., La Jolla, CA, USA). We used paired t-tests to compare the volume and AUC of fibroids before and after GnRHa treatment. We used paired t-tests to
compare the volume and AUC of fibroids before and after GnRHa treatment. $P < 0.05$ was considered statistically significant. Pearson’s coefficient was also used to determine the relationships between (A) the AUC(pre) and fibroid volume reduction percentage and (B) the AUC(pre) and AUC reduction percentage.

**Results**

We recruited 23 women for the study and excluded two whose fibroids contained more than 50% cystic degeneration by volume; we enrolled the remaining 21 for study (aged 23 to 44 years; average age, 35.7). $R_2^*$ I was successfully obtained from all patients. The interval between the 2 MR imaging studies ranged from 56 to 119 days (mean ± standard deviation: 80.4 ± 19.2 days). Figure 1 shows typical images of a uterine fibroid before and after treatment, and Fig. 2 shows the time courses of the $R_2^*$ values in the selected ROI with the fitted gamma curves before and after treatment.

Following treatment, mean fibroid volume was reduced from $647.8 ± 330.1$ mL to $463.4 ± 255.7$ mL, a statistically significant average reduction of $28.5 ± 9.7\%$ ($P < 0.0001$). The mean AUC value before GnRHa treatment was $483.6 ± 302.0$ and after, $206.5 ± 143.8$. The mean reduction of AUC was $55.3 ± 32.5\%$. Statistical difference was observed between AUC values before and after GnRHa treatment ($P < 0.0001$) (Fig. 3).

We observed correlation between AUC(pre) and the percentage of reduction of fibroid volume ($r = 0.68$) (Fig. 4) but none between AUC(pre) and per-
Fig. 2. The time course of the $R_2^*$ values in the selected region of interest (ROI) (shown in Fig. 1) before (filled circles) and after (squares) the treatment with gonadotropin-releasing hormone analogue (GnRHa), plotted with the gamma-fitted curves. We calculated the area under the curve (AUC) excluding the flat signal portion of the curve after the signal peak, which corresponds to the second circulation of the contrast agent and measured the AUC as 411.0 before treatment and 254.4 after. The reduction percentage of the AUC was calculated as 38.1% in this case.

Fig. 3. Graphs show the differences in (a) fibroid volume and (b) area under the curve (AUC) before and after GnRHa treatment in 21 patients. Data are represented as box plot with median and 25th to 75th percentiles (boxes). There is a significant difference between the values of the AUC as well as the volume before and after treatment ($P<0.0001$).

Fig. 4. A scatterplot with linear regression fit and 95% confidence intervals (dotted lines) comparing the area under the curve (AUC)(pre) and the percentage reduction in fibroid volume after treatment. We observed significant correlation between these values (Pearson’s correlation, $r=0.68$). The regression equation was calculated as $y=0.875x+17.89$ ($P=0.0007$).
Fig. 5. Graph shows relationship between area under the curve (AUC(pre) and AUC reduction percentage after treatment with gonadotropin-releasing hormone analogue (GnRHa). No significant correlation was observed ($r = 0.10$). AUC increased in 2 patients (arrow; +14%, +15%).

percentage reduction of AUC ($r = 0.10$). AUC values increased by 15% in one woman with 17% shrinkage of fibroid volume after GnRHa treatment and by 14% in one woman with 29% shrinkage after treatment (Fig. 5).

Discussion

GnRHa has been widely used to decrease volume and vascularity of uterine fibroids before surgery, but the reduction in fibroid VBV after GnRHa administration is not well demonstrated. In this study, we used DDE-R$_2^*$I to compare AUC and fibroid volume before and after GnRHa treatment in each patient and observed an average 55% reduction in AUC after treatment. This result is consistent with a previous histological investigation that observed that the average diameter of intramyomatous arteries was 24% smaller (that is, there was a 42% reduction in the cross-sectional area of these arteries) in subjects receiving GnRHa compared with those receiving placebo. $^{14}$ GnRHa is used clinically to reduce operation time and intraoperative bleeding, thus there is significant value to demonstrate the reduction of volume as well as VBV in the current study. AUC increased in 2 patients, but GnRHa was clinically effective because of fibroid shrinkage.

In a study using Doppler ultrasonography, elevations in the resistance index (RI) and pulsatility index (PI) were observed before fibroid volume reduction. $^{15}$ The authors concluded that reduced flow of myometrial blood is the first significant effect of GnRHa in the process of uterine volume shrinkage; low estrogen concentration in the blood induced by GnRHa would work to reduce fibroid vascularity. This theory could explain the relationship between AUC(pre) and the percentage of reduction of fibroid volume, which is also consistent with a previous report. $^{16}$ However, the entire process of fibroid shrinkage after GnRHa administration has not been explained. Direct activation of the GnRH receptors on fibroids is presumed to be involved in fibroid shrinkage. $^{17}$ Crow and colleagues suggested that response to GnRHa treatment is affected by other histopathological features, including rate of cell proliferation, degree of inflammatory cell infiltration, and density of estrogen receptors. $^{18}$ These factors may work to change vascularity as well as volume of the fibroid, which could make it more difficult to predict AUC reduction. The detection of GnRH and estrogen receptors on fibroids may facilitate the more accurate estimation of fibroid change in the future.

The parameters of Doppler sonography are also reported useful for predicting GnRHa efficacy. $^{19}$ In addition, 3-dimensional (3D) power Doppler ultrasonography currently provides induces of vascularity and flow. $^{20,21}$ These parameters are more informative than RI and PI for the evaluation of tissue vascularity. Few studies using these sonographic techniques for uterine fibroids are reported, but active investigations that include comparison between MR and 3D Doppler ultrasonography are underway. Currently, MR has an advantage because a correlation has been established between the semi-quantitative analysis of DDE-R$_2^*$I and the vessel density of histopathological specimens. Therefore, DDE-R$_2^*$I is suitable for observing changes in the VBV after GnRHa treatment. $^{22}$

Limited presurgical assessment of uterine fibroids demonstrating typical benign features can be performed using non-contrast MR imaging; additional use of contrast material would increase medical costs and risk to patients of potential side effects. However, DDE-R$_2^*$I is useful for predicting GnRHa efficacy and providing insight into tumor vascularity, which should have implications for patient care. Further research is needed to determine whether these advantages overcome the drawbacks of additional use of contrast material.

Our study has several limitations. The number of patients was relatively small, and our results should be confirmed in additional study of more patients. Another limitation was the wide range of time intervals between the 2 MR studies. We also measured only the signal in a 3 × 3-cm$^2$ ROI placed in the center of the fibroid at a single location, so we did
not assess the entire signal change in the fibroids. Resolution of this point requires the development of an MR sequence with multi-location capability. Finally, our use of a semi-quantitative analysis of VBV might have caused scattering in the plot of the AUC versus fibroid volume reduction (Fig. 5). Quantitative analysis that incorporates the arterial input function might improve our measurements in future studies.

In summary, we have shown that VBV in uterine fibroids can be evaluated using DDE-R²*Ia and semi-quantitative analysis. We observed a mean reduction in AUC of 55.3% in volume, of 28.5%. GnRHa is effective in reducing VBV as well as fibroid volume. AUC(pre) is a predictive factor for volume reduction but correlates poorly with the percentage of AUC reduction.

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