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Can an apparent diffusion coefficient of uterine fibroid before uterine artery embolization predict potential fibroid response?

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ABSTRACT

Objectives: ACOG guidance confirms the use of uterine artery embolisation (UAE) as an alternative to hysterectomy or myomectomy.

The main objective of this article is to evaluate the ability of preoperative magnetic resonance ımaging (MRI) to study the relationship between uterine fibroid reduction and diffusion coefficient (ADC) value after UAE. This is a relevant topic with the growing interest in using ADC as a noninvasive imaging biomarker for monitoring tissue changes and predicting uterine fibroid response to UAE over the past years.

Material and methods: In this prospective controlled non-randomized trial; uterine fibroid volume, fibroid diameter, uterine volume, fibroid ADC and normal myometrium ADC were recorded before and after UAE. Wilcoxon test was used in the analysis of the dependent quantitative data. Pearson correlation coefficients were calculated between post-UAE uterine volume, fibroid volume, and average fibroid diameter reduction and the patient's age, parity, gravidity, fibroid ADC and myometrial ADC before UAE.

Results: The mean fibroid volume reduction was 36.0% (range between 17.3–77.7%). Mean fibroid diameter, fibroid volume, uterine volume, and myometrium ADC values after UAE were significantly lower than before the procedure ($p = 0.002$, < 0.001, 0.001, 0.006 respectively), but the decrease in fibroid ADC is not significant. As a result decrease in fibroid volume was greater as pre-UAE fibroid ADC values increased, and that finding may contribute to the selection of the patients for the procedure.

Conclusions: The ADC value before UAE was positively correlated with fibroid volume reduction.

Keywords: embolization; gynecology; myoma; uterine artery

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INTRODUCTION

Uterine artery embolization (UAE) has been used as a non-surgical treatment option for symptomatic fibroids [1]. Atlantic Canada Oncology Group (ACOG) guidance confirms the use of UAE as an alternative to hysterectomy or myomectomy [2]. The goal of UAE is to permanently occlude the uterine arterial branches that supply leiomyomas and eventually lead to the myomas' devascularization and infarction [3]. Magnetic resonance imaging (MRI) is the choice of radiological technique for determining patient eligibility and for assessing the possible procedural risk. It is a useful tool for evaluating potential treatment outcomes and for diagnosing complications after UAE [4, 5].

The efficacy of UAE is determined by symptom relief of the patient and the symptom is heavy menstrual bleeding or dysmenorrhea caused by intramural fibroids. Most patients (73 to 90 percent) report improvement or disappearance of heavy menstrual bleeding symptoms up to 10 years after the treatment [6, 7]. In the embolization versus hysterectomy randomized trial 62% of patients in the UAE group reported that menorrhagia had completely resolved at two years. At five years 83% of the patients reported no menorrhagia. The cumulative secondary hysterectomy rate after the UAE procedure was 24% at two years, 28% at five years, and 35% at 10 years respectively [6, 8, 9]. Uterine artery embolization also affects lower abdominal pain and dysmenorrhea symptoms

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of uterine fibroids in up to 80% of patients. In the EMMY study, UAE compared with the hysterectomy group; 85 and 78% at least moderate improvement in terms of dysmenorrhea at two years were found respectively [8]. Another study, the Ontario Uterine Fibroid Embolization Trial was a multicenter prospective study that reported after bilateral UAE there is an improvement of dysmenorrhea in 77% of 538 patients [10]. When we look at the pelvic pressure and bulk-related symptoms in large cohort studies it is found that up to 90% of patients reported improvement in bulk-related complaints and in the EMMY trial compared with hysterectomy the improvements found as 66 vs 69% respectively [8, 11, 12].

In meta-analyses of randomized trials comparing UAE with surgeries such as myomectomy, hysterectomy, and laparoscopic uterine artery occlusion; UAE resulted in the faster resumption of daily activities, lower rates of blood transfusions odds ratio (OR) 0.07, 95% CI 0.01–0.52], lower risks of major complications [risk ratio (RR) 0.45, 95% CI 0.22–0.95] and higher risks of minor complications (RR 1.65, 95% CI 1.32–2.06) [13, 14].

Some of the existing literature emphasizes the utility of diffusion-weighted imaging (DWI) sequences in MRI [15]. DWI is a functional imaging technique that could reflect the varying tissue cellularity and it is a noninvasive imaging modality that does not require the administration of contrast agents [16]. The apparent diffusion coefficient (ADC) which was calculated from DWI, can characterize tumor architecture like cellularity, cell membrane integrity, and vascularity [17]. Fibroids that show high signals on T1W images and low vasculature before embolization are likely to respond poorly to UAE [4, 18].

Ideal candidates for UAE include premenopausal patients that have heavy menstrual bleeding or dysmenorrhea due to uterine fibroid and who have no desire for future pregnancy. It is important to identify patients who will benefit from this procedure before the UAE. This benefit may be objectively assessed by a reduction in uterine and fibroids volume/size or clinical improvement. In this study, we investigated whether myometrial ADC and fibroid ADC examined by MRI before UAE were associated with fibroid shrinkage potential.

MATERIAL AND METHODS

This prospective self-controlled nonrandomized trial was approved by the institutional review board and a waiver of consent was granted. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Eighteen patients diagnosed with uterine fibroids were included in the study for two years. Fifteen of them refused surgery, and three could not be operated on because the operation was risky due to cardiac causes. All the patients who want UAE and refuse/could not have an operation are accepted to the study, which is why there is not any bias in choosing the cases. All UAE patients are included to the study during those two years in our clinic.

Lower abdominal conventional MRI and DWI examinations were performed using an 8-channel body coil with a 1.5 Tesla superconducting MRI device (Signa HDxt, GE Medical Systems, Milwaukee, Wisconsin, USA). In all investigations, sagittal T2A, axial T1A FSE, fat-printed axial T2A FRFSE, coronal STIR, axial and sagittal contrast images, and DAG images are obtained. Diffusion-weighted imagings are obtained by using b = 0 and b = 800 values. Apparent diffusion coefficient maps are created on a separate workstation (Advantage Workstation 4.4-GE Medical Systems) using the software program (Functool). Measurements were performed using the ROI to include 80% of the fibroids on the ADC map. In addition, ADC values were measured from normal myometrium without fibroids.

During ADC calculations, all fibroids greater than 4.7 cm were included and largest fibroid was chosen for the calculations. Before and after UAE, fibroid and uterus volumes, using an ellipsoid formula [$4/3*pi(\pi)*r^1*r^2*r^3$ (r = radius)], were measured on axial and sagittal T2 weighted images. Before and after the UAE, fibroids volume, mean fibroids diameter, uterine volume, fibroids ADC and normal myometrium ADC were recorded.

Embolization technique

Under fluoroscopy, first the internal iliac and then the uterine artery is catheterized with a microcatheter through a macrocatheter. After uterine arteriography, embolic material was injected into the uterine artery till the occlusion of all vessels of the fibroid has achieved. According to the size of the uterine artery, bead block microspheres were injected in the form of 100–300 or 300–500 particles. All patients experienced mild-to-severe ischemic pain requiring parenteral analgesia but pain severity gradually decreased after the first 24 hours. Tramadol 50 mg IV infusion was given for the first 24 hours, and oral non-steroid anti-inflammatory analgesic (NSAID) was given for 72 hours after discharge. No complications were observed during or after the procedure.

Statistical analysis

All statistical analyzes were calculated SPSS version 16 for Windows. Descriptive statistics were used to describe the content and frequencies. Wilcoxon test was used in the analysis of the dependent quantitative data. Pearson correlation coefficients were calculated between post-UAE uterine volume, fibroid volume, and average fibroid diameter reduction and the patient's age, parity, gravidity, fibroid ADC and myometrial ADC before UAE.

Table 1. The demographical features of the patient

Characteristics	Value
Age [years] mean ± SD	41.1 ± 8.8
Gravida, median (min–max)	1.5 (0–6)
Parity, median (min–max)	1.5 (0–4)
Multipl myom, n	2
Single myom, n	16
Fibroid volume [cc^3] mean ± SD (min–max)	272.7 ± 240.1 (29–730)
Fibroid volume reduction, mean (min–max)	36.0% (17.3–77.7%)

SD — standard deviation

Table 2. Uterus volume, fibroid volume, fibroid apparent diffusion coefficient (ADC) and myometrium ADC; mean standard deviation (SD) and p values

		Mean ± SD	p value
Average myom diamater			
	Before UAE	74.5 ± 22.7	
	After UAE	64.8 ± 24.1	0.002[w]
Uterine volume			
	Before UAE	655.0 ± 410.2	
	After UAE	473.1 ± 289.2	0.000[w]
Fibroid volume			
	Before UAE	272.7 ± 240.1	
	After UAE	197.3 ± 212.4	0.001[w]
Fibroid ADC [× 103]			
	Before UAE	0.82 ± 0.39	
	After UAE	0.57 ± 0.52	0.352[w]
Myometrium ADC [× 103]			
	Before UAE	1.00 ± 0.42	
	After UAE	0.42 ± 0.52	0.006[w]

[w]Wilcoxon test; UAE — uterine artery embolisation

RESULTS

The mean age of the patients included in the study was 41.1 ± 8.8, and the median gravidity and parity were 1.5 (0–6) and 1.5 (0–4), respectively (Tab. 1). Multiple myomas in two patients and single myomas in other patients were present. Fibroid volumes ranged from 29 to 710 cc^3. Uterine volume was over 1000 cm3 in four patients. Duration between UAE and follow-up MRI was 90 days.

Mean myoma diameter, uterine volume, fibroid volume, and myometrium ADC values after UAE were significantly lower than before the procedure ($p = 0.002$, $p < 0.001$, $p = 0.001$, $p = 0.006$ respectively), but the decrease in fibroid ADC was not significant. The mean fibroid volume reduction (VR) was 36.0% (range 17.3–77.7%) in the follow-up MRI. Table 2 shows the average myoma diameter, uterine volume, fibroid volume, fibroid ADC and myometrium ADC which were calculated by the Wilcoxon test before and after the UAE procedure.

Table 3. Pearson correlation analysis results

		UVR	FVR	AFDR
Age	r	0.07	–0.46	–0.62
	p	0.77	0.86	0.82
Gravity	r	0.06	–0.32	–0.21
	p	0.83	0.22	0.44
Parity	r	0.06	–0.24	–1.18
	p	0.83	0.36	0.50
Pre-UAE fibroid ADC	r	0.11	0.61	0.06
	p	0.65	0.01	0.98
Pre-UAE myometrial ADC	r	0.15	0.41	0.13
	p	0.56	0.11	0.63

UVR — uterine volume reduction, FVR — fibroid volüme reduction; AFDR — average fibroid diameter reduction; ADC — apparent diffusion coefficient

According to Pearson's correlation analysis, there was a significant positive correlation between pre-UAE fibroid ADC and fibroid volume reduction but not with myometrium ADC. Age, gravidity, parity, uterine volume before UAE, and fibroid volume were not correlated with volume reduction.

Table 3 shows the correlation of age, gravidity, parity, pre-UAE fibroid ADC and pre-UAE myometrial ADC with uterine volume reduction, fibroid volume reduction, and average fibroid diameter reduction calculated by Pearson analysis.

DISCUSSION

Uterine artery embolization treatment of fibroids has been performed worldwide since it was introduced for the treatment of symptomatic fibroids in 1995 [19, 20]. There are many options for treatment, including hormonal therapy, myomectomy, and hysterectomy. Uterine artery embolization provides a minimally invasive and uterine-sparing treatment option. Ideal candidates for UAE include premenopausal women who had no desire for future pregnancy and who have heavy menstrual bleeding or pelvic pain caused by intramural fibroids. Good prognostic factors that have been described are heavy menstrual bleeding (rather than other symptoms), smaller leiomyoma size, and submucosal location [21]. Larger fibroids and more numerous fibroids predict symptom recurrence [22]. Hypervascular fibroids before UAE predict a high regrowth-free interval [23].

In this study, significant reductions in uterine and fibroid volume and fibroid size were detected after the UAE procedure. The primary aim of our study was to investigate the

factors that may be associated with the reduction of myoma size. We found that diameters and volumetric shrinkages were not significantly correlated with age, gravidity, or parity. Only fibroid ADC values before UAE were significantly correlated with the reduction in myoma diameter and volume. ADC provides functional information about the cellular microscopic water molecule motions associated with cellularity, water content, and microvascular perfusion [8–10].

There is some research related to ADC of uterine fibroid as a predictor of the potential response to UAE and ADC value is significantly related to volume reduction [24–26]. In a study by Hecht et al, researchers found a positive correlation between pre-UAE ADC and fibroid volume reduction after UAE [24]. They found that using a threshold of 0.875×10^{-3} mm^2/s, ADC could predict > 50% VR with sensitivity and specificity of 70% and 83%, respectively at 207 days follow-up MRI. Indeed in our study, we found that the mean fibroid VR was 36.0%.

Cao et al. [27] reported that VR was 58.9% at the end of 6 months, and fibroid ADC was positively correlated with VR after UAE. The total number of fibroids was 16. The mean ADC of fibroids was 1.37×10^{-3} mm^2/s (range 1.05×10^{-3}–2.32×10^{-3} mm^2/s) before UAE [27]. Similarly, Lee et al. [9] found that the rate of fibroid VR was 44.1% and that ADC and fibroid VR were significantly associated.

In our study, although the uterine fibroid volume was above 1000 cm^3 in four patients, there were not any complications. Smeets et al. in their studies on the relationship between fibroid volume and complications reported that in women with a dominant fibroid of >10 cm and/or a uterine volume of > 700 cm^3 before UAE, they found no increase in the risk of serious complications [28]. However, Hysterectomy or Percutaneous Embolisation for Uterine Leiomyomata (HOPEFUL) study showed a 2.6% incidence of septicemia after uterine fibroid embolization, with 1.1% of the women requiring emergency hysterectomy [29].

A systemic review and meta-analysis which included 11 studies showed that there is no correlation between baseline ADC values and leiomyoma VR at approximately six months ($r = 0.40$; 95% CI from –0.07 to 0.72; $I^2 = 69.7\%$) [30]. Heterogenicity in this topic may be due to variations in technical factors, DWI assessment and sequencing methods used, biological characteristics of uterine leiomyomas, and embolization techniques.

There were some limitations of our study. First, the small sample size is a major limitation of this study but in the literature, there are two prospective studies with 11 samples and 49 samples so this study is also important in terms of contribution to literature; the main reason for less sample size is the techniques itself is not so commonly chosen by the patients. More accurate results will be achieved by increasing the number of fibroids. We also follow the patients after UAE for three months (in the literature there are some six months followed up studies but generally they are retrospective studies; on the other hand prospective studies have the follow-up period in the literature is similar to our study and is limited to three months as well) but the decrease in size may continue up to 12 months. Evaluating during a longer follow-up period might be more useful in determining VR. Thirdly, we did not consider the localization of the myoma; but categorization of myoma localization and calculation through those categories would be more accurate.

CONCLUSIONS

In conclusion, ADC derived from DWI, a functional imaging technique on MRI, reflects hypervascularity and cellularity [9]. The decrease in fibroid volume was greater as the pre-UAE fibroid ADC value increased. This finding may be useful in determining which patients will benefit more from this procedure. Eventually, with the help of more studies in this field, it would be easier to choose the right patient for the UAE procedure. Heterogeneity in the literature about this topic may be overcome by the standardization of ADC calculation and interpretation approaches.

Article information and declarations

Data availability statement

All the data are available and can be achieved by authors via email.

Ethics statement

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Local ethical committee approval has been taken and written informed consent forms from the patients were collected.

Author contributions

All authors work for data collection. Ceren Turan Bektaş: do the embolization; Özgür Uzun: do the statistics; Ahmet Birtan Boran: supervisor, article writting; Sezgi Güllü Erciyestepe: article writting, interpretation, literature search.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

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