GYNECOLOGY

Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis

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BACKGROUND: Uterine fibroids are a common problem for reproductive-aged women, yet little comparative effectiveness research is available to guide treatment choice. Uterine artery embolization and magnetic resonance imaging–guided focused ultrasound surgery are minimally invasive therapies approved by the US Food and Drug Administration for treating symptomatic uterine fibroids. The Fibroid Interventions: Reducing Symptoms Today and Tomorrow study is the first randomized controlled trial to compare these 2 fibroid treatments.

OBJECTIVE: The objective of the study was to summarize treatment parameters and compare recovery trajectory and adverse events in the first 6 weeks after treatment.

STUDY DESIGN: Premenopausal women with symptomatic uterine fibroids seen at 3 US academic medical centers were enrolled in the randomized controlled trial (n = 57). Women meeting identical criteria who declined randomization but agreed to study participation were enrolled in a nonrandomized parallel cohort (n = 34). The 2 treatment groups were analyzed by using a comprehensive cohort design. All women undergoing focused ultrasound and uterine artery embolization received the same postprocedure prescriptions, instructions, and symptom diaries for comparison of recovery in the first 6 weeks. Return to work and normal activities, medication use, symptoms, and adverse events were captured with postprocedure diaries. Data were analyzed using the Wilcoxon rank sum test or χ^2 test. Multivariable regression was used to adjust for baseline pain levels and fibroid load when comparing opioid medication, adverse events, and recovery time between treatment groups because these factors varied at baseline between groups and could affect outcomes. Adverse events were also collected.

RESULTS: Of 83 women in the comprehensive cohort design who underwent treatment, 75 completed postprocedure diaries. Focused ultrasound surgery was a longer procedure than embolization (mean [SD], 405 [146] vs 139 [44] min; $P < .001$). Of women undergoing focused ultrasound (n = 43), 23 (53%) underwent 2 treatment days. Immediate self-rated postprocedure pain was higher after uterine artery embolization than focused ultrasound (median [interquartile range], 5 [1–7] vs 1 [1–4]; $P = .002$). Compared with those having focused ultrasound (n = 39), women undergoing embolization (n = 36) were more likely to use outpatient opioid (75% vs 21%; $P < .001$) and nonsteroidal antiinflammatory medications (97% vs 67%; $P < .001$) and to have a longer median (interquartile range) recovery time (days off work, 8 [6–14] vs 4 [2–7]; $P < .001$; days until return to normal, 15 [10–29] vs 10 [10–15]; $P = .02$). There were no significant differences in the incidence or severity of adverse events between treatment arms; 86% of adverse events (42 of 49) required only observation or nominal treatment, and no events caused permanent sequelae or death. After adjustment for baseline pain and uterine fibroid load, uterine artery embolization was still significantly associated with higher opioid use and longer time to return to work and normal activities ($P < .001$ for each). Results were similar when restricted to the randomized controlled trial.

CONCLUSION: Women undergoing uterine artery embolization have longer recovery times and use more prescription medications, but women undergoing focused ultrasound have longer treatment times. These findings were independent of baseline pain levels and fibroid load.

Key words: focused ultrasound, leiomyoma, randomized controlled trial, uterine artery embolization, uterine fibroid

Uterine fibroids (myomas or leiomyomas) are common and debilitating in reproductive-aged women, yet little high-quality evidence exists to guide treatment decisions.[1] Most randomized controlled trials (RCTs) of fibroid therapies have been performed outside the United States,[2-10] and those performed in the United States for the related problem of heavy menstrual bleeding have faced recruitment challenges.[11-14]

The Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) study is a National Institutes of Health–funded RCT to evaluate the efficacy of 2 minimally invasive fibroid treatments: uterine artery embolization (UAE) and magnetic resonance imaging–guided focused ultrasound surgery (MRgFUS) (clinical registration number NCT00995878; clinicaltrials.gov).[15] The aim of the FIRSTT study is to examine the safety, efficacy, and economics of these therapies and the ovarian reserve after treatment.

In addition to the RCT participants, women who met identical enrollment criteria but declined randomization were recruited into a parallel cohort (PC1). Analysis of FIRSTT trial baseline data showed that using a comprehensive cohort design (CCD), combining the

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RCT and PC1 participants, yields valid results and provides additional power.[16,17] The current report summarizes the treatment parameters, recovery trajectory, and adverse events (AEs) of patients during the first 6 weeks after treatment, using both RCT and CCD analyses.

Materials and Methods

Overview

The design and baseline data from the FIRSTT study have been previously reported.[15,16] The Institutional Review Boards at Mayo Clinic (Rochester, MN), Duke University (Durham, NC), and the University of California, San Francisco, approved the same study protocol. Briefly, UAE and MRgFUS were performed according to the clinical standard of care, with follow-up for up to 36 months.

Study population and randomization

All participants were premenopausal women with symptomatic uterine fibroids who were not actively seeking pregnancy and had uteri smaller than 20 gestational weeks. Full enrollment criteria have been reported previously.[15,16] Enrollment began April 29, 2010, for the RCT and March 24, 2011, for the PC1 group. All study procedures were performed by Aug. 1, 2014. A study gynecologist screened all participants, and treating physicians at each site were experts in these therapies.

Multiple general and disease-specific quality-of-life measures, including the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) instrument, were recorded at baseline.[15,18] Randomization was stratified by site and by calculated uterine volume ($\geq$700 vs $<$700 cm^3) and performed using a Web-based, dynamic allocation application.[19] Neither participants nor investigators were blinded to study assignments.

Standardized treatment and recovery protocols

Both UAE and MRgFUS were performed using standardized protocols. The treating physician captured key treatment variables on the day of treatment, including whether a complete treatment was achieved. This result was not disclosed to the patient. Identical standardized instructions and postprocedural prescriptions were used for both procedures.

UAE protocol

For UAE, a standardized protocol that allowed for some variation among sites was used, which included moderate sedation and antiinflammatory and antiemetic agents.[20] Prophylactic antibiotics were used at all sites; at 1 site, oral antibiotics were continued for another 5 days.

UAE was performed, along with arteriography, to evaluate for collateral ovarian blood supply to the fibroids. Trisacryl gelatin microspheres (500–700 μm) were used; if necessary, 700–900 μm spheres were also used until near-stasis was achieved. After the procedure, patients were admitted overnight to a hospital-based observation unit.

MRgFUS protocol

Treatments were performed with a clinical MRgFUS system (ExAblate 2000; InSightec, Haifa, Israel) with moderate conscious sedation.[21] T2-weighted magnetic resonance images were acquired, and the sonication plan was developed. Sonication pulse duration was generally 12–24 seconds, with an interpulse interval of 45–90 seconds to allow for tissue cooling. At the conclusion, gadolinium contrast was administered, and T1-weighted images were acquired for visualization of nonperfused volume (NPV). After MRgFUS treatment, women were typically observed for 1 hour and discharged with an escort. Two sites allowed 2 sequential treatment days.

For both treatment groups, baseline image analysis was performed using Vitrea 3 Software (Vital Images, Inc, Minnetonka, MN). For the MRgFUS group, the NPV ratio (ie, the ratio [percentage] of NPV to the total fibroid load) was analyzed similarly.

Data safety monitoring board

The data safety monitoring board comprised 2 fibroid experts, 1 gynecologist, and 1 radiologist in addition to the study statistician (A.L.W.). The National Institutes of Health project officer also reviewed safety-related issues.

Postprocedure medications and instructions

For both procedures, women received identical prescriptions and instructions for medication usage; slight variations among sites and modifications were allowed in the case of allergies or known prior medication use. Women were typically provided with a prescription for oxycodone (5 mg, 40 tablets), ibuprofen (600 mg, 30 tablets, 2 refills), ondansetron (4 mg, 6 tablets, 1 refill), and docusate sodium (100 mg, 10 tablets, 2 refills).

Women also received written instructions that acetaminophen could be taken with the study medications. Medications taken during the study period were to be recorded in the study diaries. The postoperative instructions outlined the goal that pain should be as close as possible to 0 on a 10 point pain scale. Contact information for the site investigator and the study coordinator was provided.

Postprocedure diaries

Women received 3 single-page, color-coded diaries with stamped return envelopes at the time of hospital discharge. Each diary covered 2 weeks of recovery and included a pictorial representation of a 10 point pain scale. Information recorded in the diaries included medication use, functional status after surgery, bleeding, pain, and common symptoms. The study coordinator called women on the weekday nearest to the date of expected diary completion and reminded them to return their current diary and start the next one.

Adverse events

Data on AEs were obtained via clinic or hospital notes, review of the diaries, and telephone calls with study staff. Characterization included severity (eg, mild, moderate, or severe) based on the Common Terminology Criteria for Adverse Events. Relatedness to the procedure (eg, definitely, probably, possibly, unlikely, or unrelated) was determined

by the site investigator, and the patient's outcome was recorded.

We further classified the AEs using both the Society of Interventional Radiology (SIR) classification system, which grades events on a scale from A (no therapy, no consequences) to F (death),[22] and the American College of Obstetricians and Gynecologists system, which characterizes morbidity indicators such as fever, hemorrhage, unintended procedures, life-threatening events, and readmission.[23]

Data management and statistical analysis

Data were analyzed using both a CCD and an RCT design.[16] Demographic and baseline characteristics, day-of-treatment parameters, and post-procedure recovery measures were summarized and reported using standard descriptive statistics: frequency (percentage) for categorical variables and mean (SD) or median (interquartile range) for continuous variables. Comparisons between treatment arms (MRgFUS vs UAE) were evaluated using the χ^2 test or Fisher exact test for categorical variables and the 2-sample *t* test or Wilcoxon rank sum test for continuous variables.

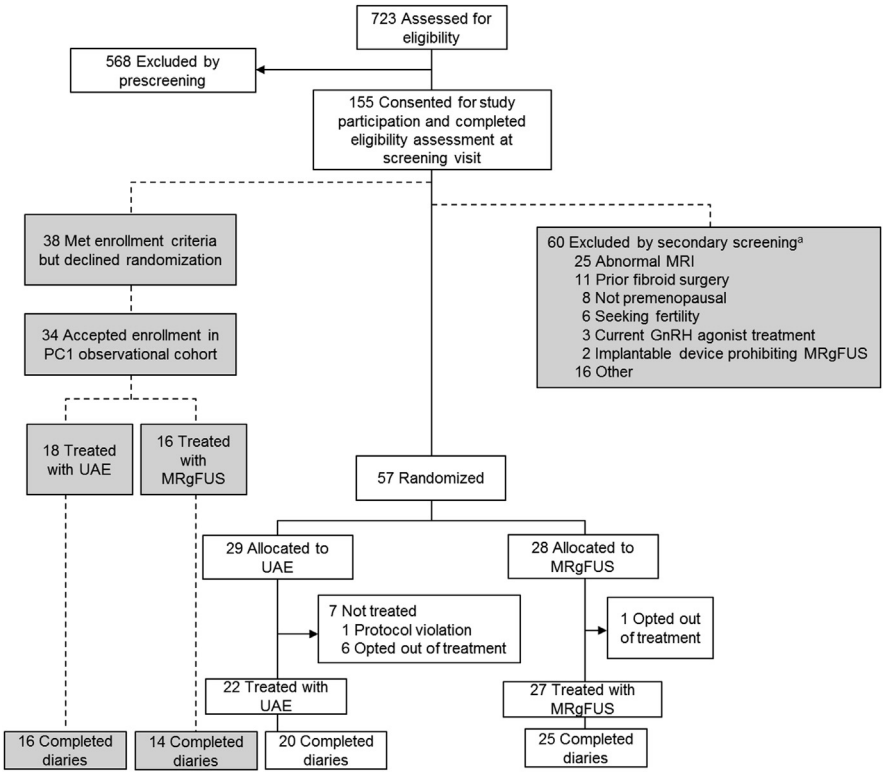
Because pain and total fibroid load can substantially affect recovery parameters and there was a differential loss of participants in the UAE arm after randomization,[16] a multivariable regression analysis was used to assess the independent effect of treatment group on posttreatment recovery measures after adjustment for pain levels and total fibroid load at baseline.

Adjusted odds ratios were obtained using logistic regression for the rare (<10%) binary outcome (AE SIR classes C–E), adjusted risk ratios were obtained using Poisson regression with a robust error variance for the common binary outcomes (opioid use and any AE), and linear regression was used to estimate the average difference in days for the continuous outcomes (recovery time in days).[24]

In these models, logarithmic transformation was applied to the recovery time continuous outcome measures (natural log) and total fibroid load (log base 2) because of the skewed data. Model results were back-transformed to obtain adjusted estimates and confidence intervals in the original scale of the outcome variable.

All calculated *P* values were 2 sided, and $P < .05$ was considered statistically significant. Analyses were performed using SAS version 9.3 software (SAS Institute Inc, Cary, NC).

FIGURE
Flow diagram of the study



Flow diagram for the selection, enrollment, and randomization of the participants in a comprehensive cohort design. *Solid lines* and *unshaded boxes* show disposition of randomized controlled trial participants. *Dashed lines* and *shaded boxes* indicate flow of participants who entered PC1 or were excluded by screening. The superscript letter a indicates that 11 patients had 2 exclusion criteria. Adapted, with permission, from AbdElmagied et al.[16]

GnRH, gonadotropin-releasing hormone; *MRgFUS*, magnetic resonance imaging–guided ultrasound surgery; *MRI*, magnetic resonance imaging; *PC1*, parallel cohort 1; *UAE*, uterine artery embolization.

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Results

Baseline demographics

Of the 83 women who underwent treatment in the CCD cohort (43 MRgFUS, 40 UAE), 75 completed the postprocedure diaries (Figure). Baseline parameters were similar between women undergoing UAE and MRgFUS in both the RCT and CCD analysis (Table 1).[16] The remainder of the data presented refer to the CCD cohort, unless otherwise specified.

Women in the study were predominantly white and overweight. Calculated median (interquartile range) uterine volumes were similar between treatment arms (UAE, 540 [382-837] vs MRgFUS, 586 [395-707] cm^3). However, women undergoing UAE had a larger mean (SD) fibroid load than women in the MRgFUS group (362.5 [292.3] vs 249.2 [159.9] cm^3; $P = .03$), and the number of fibroids larger than 3 cm was higher in women undergoing MRgFUS.

Participants in both arms had similar fibroid symptoms and substantially

TABLE 1
Baseline characteristics, day-of-treatment measures, and adverse events of treated study participants

Characteristic	RCT			CCD		
	MRgFUS (n = 27)	UAE (n = 22)	*P* value	MRgFUS (n = 43)	UAE (n = 40)	*P* value
Demographic data						
Age at treatment, y, mean (SD)	44.0 (4.3)	44.3 (5.2)	.84	44.0 (5.0)	44.9 (5.0)	.45
Race, n, %			.22			.41
White	18 (67)	18 (82)		28 (65)	31 (78)	
Black	3 (11)	4 (18)		5 (12)	4 (10)	
Asian	1 (4)	0 (0)		4 (9)	1 (3)	
Hispanic or Latina	3 (11)	0 (0)		4 (9)	1 (3)	
Other	2 (7)	0 (0)		2 (5)	3 (8)	
BMI, kg/m^2, mean (SD)	27.4 (5.7)	30.1 (5.1)	.09	26.7 (5.5)	27.8 (6.4)	.41
Age at fibroid diagnosis, y, mean (SD)	39.6 (7.2)	39.5 (7.8)	.97	39.9 (7.1)	40.9 (7.1)	.49
Uterine characteristics						
Number of fibroids ≥3 cm, n, %			.17			.17
0	2 (7)	1 (5)		2 (5)	1 (3)	
1	11 (41)	13 (59)		18 (42)	21 (53)	
2	1 (4)	5 (23)		4 (9)	11 (28)	
3	8 (30)	1 (5)		11 (26)	3 (8)	
≥4	5 (19)	2 (9)		8 (19)	4 (10)	
Calculated uterine volume, cm^3, median (IQR)	549 (334–693)	540 (402–690)	.82	586 (395–707)	540 (382–837)	.90
Total fibroid load, cm^3, mean (SD)[a]	225.0 (125.1)	365.4 (233.2)	.01	249.2 (159.9)	362.5 (292.3)	.03
Baseline validated measures						
MPQ total score, median (IQR)	11.0 (6.0–20.0)	7.5 (3.0–16.0)	.19	10.0 (6.0–17.0)	7.0 (2.0–12.0)	.08
VAS pain score, median (IQR)[b]	48.0 (27.0–71.0)	27.0 (5.0–52.0)	.03	38.0 (21.0–66.0)	24.5 (4.5–54.0)	.08
UFSQOL						
Symptom severity score, mean (SD)	54.6 (21.6)	53.0 (17.7)	.79	53.9 (19.8)	53.1 (19.8)	.85
Health-related quality of life, mean (SD)	50.6 (19.2)	51.7 (19.3)	.85	52.5 (18.4)	51.0 (23.0)	.76
Day-of-treatment measures						
Total treatment time, min, mean (SD)[c]	390 (138)	137 (47)	<.001	405 (146)	139 (44)	<.001
Pain rating, median (IQR)[d]						
On arrival to recovery area	3.0 (1.0–5.0)	5.0 (1.0–7.0)	.14	1.0 (1.0–4.0)	5.0 (1.0–7.0)	.002
On discharge from recovery area	2.0 (1.0–4.0)	3.0 (2.0–5.0)	.16	1.0 (1.0–4.0)	4.0 (2.0–6.0)	<.001
Adverse events, n, %						
Any	12 (44)	9 (41)	.80	20 (47)	16 (40)	.55
Any SIR class C–E	2 (7)	2 (9)	>.99	3 (7)	4 (10)	.71

BMI, body mass index; *CCD*, comprehensive cohort design; *IQR*, interquartile range; *MPQ*, McGill Pain Questionnaire; *MRgFUS*, magnetic resonance imaging–guided ultrasound surgery; *RCT*, randomized controlled trial; *SIR*, Society of Interventional Radiology; *UAE*, uterine artery embolization; *UFSQOL*, Uterine Fibroid Symptom and Quality of Life questionnaire; *VAS*, visual analog scale.

[a] Total fibroid load was calculated based on all fibroids >1 cm; [b] Scale of 0, no pain, to 100, worst pain possible; [c] Total treatment time was calculated using both days of treatment, when applicable; [d] Scale of 0, no pain, to 10, worst pain possible.

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TABLE 2
Six week postoperative measures of disability of treated patients

Measure	RCT (n = 45)			CCD (n = 75)		
	MRgFUS (n = 25)	UAE (n = 20)	*P* value	MRgFUS (n = 39)	UAE (n = 36)	*P* value
Outpatient medication use						
Any use, n, %						
Opioids	6 (24)	14 (70)	.002	8 (21)	27 (75)	<.001
NSAIDs	17 (68)	19 (95)	.02	26 (67)	35 (97)	<.001
Tylenol/aspirin	16 (64)	6 (30)	.02	23 (59)	14 (39)	.08
Nausea medication	3 (12)	8 (40)	.03	3 (8)	16 (44)	<.001
Bowel medication	8 (32)	17 (85)	<.001	11 (28)	29 (81)	<.001
Alt/comp medication	10 (40)	11 (55)	.32	13 (33)	19 (53)	.09
Total days used among users, median (IQR)						
Opioids	9 (2–40)	3 (2–5)	.23	4 (2–26)	2 (2–4)	.43
NSAIDs	8 (3–19)	10 (7–13)	.68	7 (2–19)	9 (6–13)	.58
Tylenol/aspirin	5 (3–9)	3 (2–6)	.39	5 (3–9)	3 (2–6)	.23
Alt/comp medications	7 (2–24)	3 (1–13)	.64	10 (2–24)	6 (2–13)	.63
Day of last use among users, median (IQR)						
Opioids	37 (5–42)	3 (2–5)	.049	27 (4–41)	3 (2–5)	.03
NSAIDs	32 (18–37)	14 (9–40)	.29	32 (19–38)	13 (6–36)	.04
Tylenol/aspirin	16 (5–31)	4 (2–6)	.03	18 (5–36)	3 (2–6)	.004
Return to normal activities, median (IQR)						
First day back to work	5 (3–8)	8 (5–14)	.08	4 (2–7)	8 (6–14)	<.001
First day totally back to normal	11 (10–16)	15 (10–24)	.23	10 (10–15)	15 (10–29)	.02
Other reported symptoms, n, %						
Fatigue	20 (80)	17 (85)	.72	33 (85)	31 (86)	.86
Hot flashes	11 (44)	11 (55)	.46	15 (38)	18 (50)	.32
Fever	3 (12)	4 (20)	.68	4 (10)	9 (25)	.09
Discomfort urinating	12 (48)	11 (55)	.64	18 (46)	19 (53)	.57
Passage of fibroid tissue	10 (40)	10 (50)	.50	19 (49)	17 (47)	.90
Vaginal discharge	16 (64)	16 (80)	.24	27 (69)	26 (72)	.78
Constipation	18 (72)	16 (80)	.73	28 (72)	28 (78)	.55
Diarrhea	8 (32)	10 (50)	.22	12 (31)	18 (50)	.09

Alt/comp, alternative/complementary; *CCD*, comprehensive cohort design; *IQR*, interquartile range; *MRgFUS*, magnetic resonance imaging–guided ultrasound surgery; *NSAID*, nonsteroidal anti-inflammatory drug; *RCT*, randomized controlled trial; *UAE*, uterine artery embolization.

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impaired fibroid-specific quality of life based on the UFS-QOL. Baseline pain scores tended to be higher in women undergoing MRgFUS, and the difference in visual analog scale for pain (VAS) scores reached significance in the RCT (MRgFUS, 48.0 [27.0–71.0] vs UAE, 27.0 [5.0–52.0]; $P = .03$) (Table 1).

Day-of-treatment parameters

In the UAE group, 36 of the 40 procedures (90%) were done with a unilateral puncture; all were performed in 1 day, with a mean (SD) fluoroscopy time of 42.0 (19.2) minutes (Supplemental Table 1). Total blood loss was minimal, and 100% of the treatments were deemed complete. The majority of the procedures used fentanyl (85%) and midazolam (93%).

Among the 43 women undergoing MRgFUS, 23 (53%) underwent a second day of treatment (Supplemental Table 2). The number of fibroids sonicated ranged from 1 to 9, with 19 patients (44%) having 1 fibroid treated. Mean (SD) NPV ratio was 46.1% (24.8%)

(Supplemental Table 2). The treating physician judged that 39 women (91%) had complete MRgFUS treatment. Similar to UAE, most procedures were performed using intravenous opioids (93%) and midazolam (98%).

Women undergoing MRgFUS had significantly lower self-rated post-procedural pain than women undergoing UAE (1.0 [1.0−4.0] vs 4.0 [2.0−6.0]; $P < .001$) (Table 1). All UAE patients remained overnight as inpatients, and all MRgFUS patients were discharged on the day of the procedure.

Six week recovery trajectory

Women undergoing UAE were more likely than those in the MRgFUS group to use outpatient opioid medication (75% vs 21%; $P < .001$) (Table 2). However, among the opioid users, the last day of opioid use occurred later in the MRgFUS group than the UAE group (day 27 [4−41] vs day 3 [2−5]; $P = .03$). In particular, in the RCT group, 2 women who underwent MRgFUS took opioid pain medication for the entire 6 week follow-up period.

Nonsteroidal antiinflammatory drug use was also higher in UAE patients than MRgFUS patients (97% vs 67%; $P < .001$), although the total days of use did not significantly differ between treatment arms (7 [2−19] vs 9 [6−13] days; $P = .58$). Antiemetic and stool softener use was also significantly more frequent in the UAE patients (both $P < .001$) (Table 2).

Women undergoing the UAE procedure took longer to return to work than did women in the MRgFUS group (8 [6−14] vs 4 [2−7] days; $P < .001$). The day of the week the treatment was scheduled did not affect this parameter (data not shown). The first day on which participants felt they were totally back to normal also occurred later in the UAE group (15 [10−29] vs 10 [10−15] days; $P = .02$). No significant differences were observed in hot flashes and passage of fibroid tissue from the vagina.

Adverse events

A total of 36 patients (20 MRgFUS, 16 UAE) experienced 49 AEs; rates overall and rates of severe AEs (SIR class C−E) did not differ between treatment arms ($P = .55$ and $P = .71$, respectively) (Table 1).

The AEs are described in detail in Table 3. Most AEs (42; 86%) required only observation or nominal treatment, and none led to permanent adverse sequelae (class E) or death (class F). Two patients in the MRgFUS arm underwent second procedures within the first 6 weeks, 1 electing UAE and 1 choosing hysterectomy; both were deemed to have had incomplete MRgFUS treatment. Three patients in the UAE arm required readmission to the hospital for severe pain, which was associated with post-embolization syndrome in 2. Only 8 AEs qualified for reporting using the American College of Obstetricians and Gynecologists classification.

TABLE 3
Number of AEs by SIR class for all patients in the CCD

SIR class and AE category[a]	MRgFUS (n = 43)	UAE (n = 40)
Class D (major therapy, unplanned increase in level of care, prolonged hospitalization)	2	2
Surgical treatment within 6 wks	2	0
Rehospitalization (≥48 h)	0	1
Postembolization syndrome	0	1
Class C (required therapy, minor hospitalization)	1	2
Rehospitalization (<48 h)	0	2
Other (urinary retention requiring catheterization)	1	0
Class B (nominal therapy, observation, no consequences)	11	13
Postembolization syndrome	0	2
Severe/prolonged pain	3	1
Vaginal passage of leiomyoma tissue	1	3
Peripheral nerve injury (sacral neuropathy)	2	0
Urinary tract infection	3	1
Allergic reaction/rash	1	2
Other	1	4
Class A (no therapy, no consequences)	13	5
Severe/prolonged pain	2	0
Vaginal passage of leiomyoma tissue	1	0
Peripheral nerve injury	3	0
Upper/lower extremity tingling	2	
Sacral neuropathy	1	
Urinary tract infection	1	0
Allergic reaction/rash	2	0
Other	4	5

AE, adverse event; *CCD*, comprehensive cohort design; *MRgFUS*, magnetic resonance imaging−guided ultrasound surgery; *SIR*, Society of Interventional Radiology; *UAE*, uterine artery embolization.

[a] No AEs of class F (death) or E (permanent adverse sequelae) occurred in the CCD cohort.

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Multivariable analysis

UAE treatment was significantly associated with a higher likelihood of opioid use and a longer time to return to work and normal activities (all $P < .001$), even after adjusting for baseline pain levels and fibroid load using multivariable

TABLE 4
Multivariable analysis of treatment and recovery parameters

Outcome	Predictor[a]	RCT			CCD		
		Adjusted RR/OR/mean[b]	95% CI	*P* value	Adjusted RR/OR/mean[b]	95% CI	*P* value
Binary outcomes							
Opioid use[c]	UAE	4.28	1.94–9.42	<.001	4.57	2.51–8.33	<.001
	VAS score	1.14	1.03–1.28	.02	1.12	1.05–1.20	.001
	Fibroid load	1.01	0.80–1.29	.93	1.02	0.89–1.18	.74
Any AE[c]	UAE	1.22	0.59–2.51	.59	0.99	0.58–1.70	.96
	VAS score	1.11	0.98–1.25	.10	1.12	1.03–1.23	.01
	Fibroid load	0.93	0.69–1.25	.64	0.94	0.76–1.17	.59
AE SIR class C–E[d]	UAE	1.40	0.11–17.48	.80	0.87	0.10–7.48	.90
	VAS score	1.42	0.89–2.27	.15	1.55	1.05–2.29	.03
	Fibroid load	2.30	0.54–9.84	.26	2.76	0.89–8.62	.08
Continuous outcomes[e]							
First day fully back to work	UAE	2.01	1.28–3.14	.004	2.13	1.51–2.99	<.001
	VAS score	1.24	1.15–1.34	<.001	1.18	1.11–1.25	<.001
	Fibroid load	1.04	0.88–1.23	.64	1.07	0.94–1.22	.30
First day totally back to normal	UAE	2.71	1.49–4.93	.002	2.50	1.59–3.93	<.001
	VAS score	1.23	1.11–1.36	<.001	1.15	1.06–1.24	.001
	Fibroid load	1.02	0.82–1.28	.84	1.04	0.87–1.23	.67

AE, adverse event; *CCD*, comprehensive cohort design; *CI*, confidence interval; *MRgFUS*, magnetic resonance imaging–guided ultrasound surgery; *OR*, odds ratio; *RCT*, randomized controlled trial; *RR*, risk ratio; *SIR*, Society of Interventional Radiology; *UAE*, uterine artery embolization; *VAS*, visual analog scale for pain.

[a] All predictors were measured at baseline; [b] For UAE, MRgFUS is the reference treatment group. For the VAS score, the value is per 10 unit increase in baseline pain on a scale of 0, no pain, to 100, worst pain possible. For fibroid load, the value is per doubling of fibroid load in cm^3; [c] Values are adjusted RRs; [d] Values are adjusted ORs; [e] Values are adjusted means.

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analysis (Table 4). After adjusting for treatment group and fibroid load, women with higher baseline VAS scores were more likely to use opioid medication ($P = .001$), experience an AE ($P = .01$), and take longer to return to work and normal activities (both $P \leq .001$) (Table 4). Results were similar when restricting analysis to the RCT group, except that the association between VAS score and AEs was attenuated.

Comment

In this study, women undergoing either UAE or MRgFUS were typically able to return to work within 1–2 weeks. However, women undergoing MRgFUS had significantly longer treatment times, with about half undergoing 2 sequential days of treatment, and 9% had incomplete treatment.

Substantial differences in recovery trajectory were also observed between treatment groups, with women undergoing MRgFUS reporting lower levels of immediate postprocedure pain, using fewer outpatient pain medications, and fully returning to work sooner than patients undergoing UAE. These differences in recovery parameters persisted, even with adjustments for 2 key confounders (baseline pain and fibroid load), both of which were different between treatment arms despite similar uterine volumes, the parameter on which randomization strata was predicated.

Although these differences may be due to chance, it is notable that more women in our RCT declined to proceed with treatment after random assignment to UAE. This is particularly relevant when women declining randomization but consenting to be in an observational cohort chose the 2 procedures in more equal numbers. We suspect that this occurred because women were specifically seeking MRgFUS, which was less likely to be covered by insurance and was supported within the confines of the RCT. This possible subversion of the allocation process on the part of participants also supports the use of a CCD analysis.

These results on postprocedural recovery are consistent with previous case series and with differences in the mechanism of tissue destruction between UAE and MRgFUS.[25-27] UAE is a uterine-directed therapy, in which specific fibroids are not targeted for treatment; in contrast, MRgFUS, like myomectomy, is a fibroid-specific therapy.[27] Thus, UAE

may result in increased volume of devascularized tissue.

In addition, UAE works via ischemic necrosis, whereas MRgFUS induces coagulative necrosis, which may account for the differences in pain. It will be important to ascertain whether these differences correlate with long-term outcomes of these therapies.

It is worth noting that both UAE and MRgFUS have substantially shorter recovery times than hysterectomy.[28] Although minimally invasive hysterectomies and enhanced recovery protocols have decreased inpatient stays considerably, most women undergoing hysterectomy still stay longer than 1 inpatient day.[29,30] Differences are magnified when comparing time to return to work.

In our study, MRgFUS and UAE patients returned to work a median of 4 and 8 days after treatment, respectively. In contrast, recent studies of hysterectomy report average time to return to work of 3.8 weeks for laparoscopic-assisted vaginal hysterectomy and 5.9 weeks for total abdominal hysterectomy.[31] The loss of productivity while convalescing from traditional surgical approaches for uterine fibroids can be a major economic burden for women and their employers; thus, minimally invasive alternatives to hysterectomy could have substantial benefits.

Our findings also highlight the importance of assessing baseline pain levels because greater pain was found to be an independent risk factor for prolonged recovery and AEs. Chronic pain after hysterectomy has been reported in up to 32% of women, and studies have shown that preoperative pain predicts postoperative pain.[32]

Although some studies have linked chronic pelvic pain to higher cumulative rates of hysterectomy, our study is the first to link preoperative pain to the incidence of AEs.[33] Further research is needed comparing hysterectomy with minimally invasive options in women with chronic pelvic pain to assess the preferred treatment for this population.

Strengths of our study include implementing a standardized treatment protocol and providing patients in both treatment groups with the same post-procedure instructions and prescriptions. Comparing the recovery trajectory for UAE and MRgFUS treatments is an important and understudied research area. An RCT offers the highest level of evidence, and our study offers the added benefit of increased power and generalizability gained by including similar nonrandomized patients in a parallel cohort via a CCD analysis.

Our study has several important limitations. We could not recruit as many participants as we wanted; thus, some analyses may be underpowered, such as the assessment of safety parameters. Some group differences were also present at baseline; although we controlled for these differences using statistical analysis, a larger sample size may have made that unnecessary. The only blinded study aspect was the analysis of postprocedural imaging. In addition, the system used for MRgFUS in this study (ExAblate 2000) is older than that currently used (ExAblate 2100), and thus, the completeness of the treatment and the NPV seen in this study may be lower than those currently achieved.

Finally, a key limitation of our study is the small number of black women who were enrolled, despite having a study site devoted specifically to black women and key outreach measures at other sites. Understanding how to optimize recruitment of black women to fibroid RCTs is an important research goal. Other than this limitation, we recruited a representative cohort with significant symptomatic burden based on validated measures and consistent with other studies.

The critical question for these therapies, however, is whether there are differences in long-term outcomes. Long-term studies evaluating comparative effectiveness for symptom relief, economic utilization, and ovarian reserve after treatment will be forthcoming from the FIRSTT study. This will be beneficial information to empower women and their physicians to choose the correct treatment for uterine fibroids and improve overall quality of life on an individual basis. ■

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SUPPLEMENTAL TABLE 1
Day-of-treatment parameters for UAE cohort

Parameters relevant to UAE	Study design	
	RCT (n = 22)	CCD (n = 40)
Arterial puncture entry site, n, %		
Unilateral	21 (95)	36 (90)
Bilateral	1 (5)	4 (10)
Fluoroscopy time, min, mean (SD)	36.6 (20.5)	42.0 (19.2)
Use of microcatheter, n, %	22 (100)	40 (100)
Vials of embolic agents, median (IQR)		
500–700 μg vials	3.8 (3.0–4.0)	4.0 (3.0–4.0)
700–900 μg vials	1.3 (0.0–2.5)	1.0 (0.0–3.0)
Aortography, n, %	8 (36)	15 (40)
Ovarian arteries seen supplying fibroids, n, %	2/20 (10)	3/35 (9)
Total blood loss, mL, mean (SD)	9.0 (5.1)	10.9 (15.9)
Treatment deemed complete, n, %	22 (100)	40 (100)

CCD, comprehensive cohort design; *IQR*, interquartile range; *RCT*, randomized controlled trial; *UAE*, uterine artery embolization.
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SUPPLEMENTAL TABLE 2
Day-of-treatment parameters for MRgFUS cohort

Parameters relevant to MRgFUS	Study design	
	RCT (n = 27)	CCD (n = 43)
Treatment days, n, %		
1[a]	14 (52)	20 (47)
2	13 (48)	23 (53)
Fibroids sonicated, n, %		
1	11 (41)	19 (44)
2	5 (19)	6 (14)
3	6 (22)	8 (19)
4	3 (11)	4 (9)
≥5	2 (7)	6 (14)
Sonications, mean (SD)	108.5 (56.5)	121.7 (57.4)
Treatment deemed complete, n, %	23 (85)	39 (91)
T2 signal intensity of dominant fibroid, n, %	(n = 26)	(n = 42)
Bright	4 (15)	7 (17)
Dark with minimal heterogeneity	16 (62)	25 (60)
Dark with substantial heterogeneity	6 (23)	10 (24)
Estimated average power, W, mean (SD)	128.5 (36.9)	130.1 (37.3)
Average energy, J, mean (SD)	2556.8 (701.4)	2568.9 (734.5)
Total NPV, cm^3, mean (SD)	108.4 (79.1)	119.3 (83.3)
NPV ratio, %, mean (SD)	42.9 (24.8)	46.1 (24.8)

CCD, comprehensive cohort design; *MRgFUS*, magnetic resonance imaging–guided ultrasound surgery; *NPV*, nonperfused volume; *RCT*, randomized controlled trial.

[a] Six of these women were treated at a center that did not offer a second day of treatment.

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