



Effects of High-Intensity-Focused Ultrasound Treatment on Benign Uterine Tumor

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In this study, the effects of high-intensity-focused ultrasound (HIFU) treatment on benign uterine tumor patients were examined. A total of 333 patients diagnosed with fibroids or adenomyosis using diagnostic sonography, treated with HIFU between February 4, 2010 and December 29, 2014 at a hospital in Korea, and followed up for three or six months were selected for this study. Their benign uterine tumor volume was measured, and the effects of HIFU treatment on the volume were analyzed according to age, disease, fertility, and treatment duration. The volume of benign tumors of the uterus changed by age in all age groups after conducting HIFU treatment for 3 and 6 months, respectively. The rate of decrease in individuals' in their twenties was the largest, at 64.9%. When the decreasing volume of benign tumors of the uterus was analyzed by type of disease, the treatment efficacy for adenomyosis was the best, with a decrease of 164.83 cm³ after 6 months. Myoma had the fastest decreasing rate, at 68.5%. When evaluated on the basis of fertility, the volume of benign tumors of the uterus continued to decrease until 6 months after completing all procedures. The volume has continued to decrease for 6 months after all procedures. This study showed that HIFU treatments for uterine fibroid and adenomyosis is an effective non-invasive therapy via reducing the benign uterine tumor volume. Therefore, the HIFU method might replace other conventional treatment methods.

Keywords: High-Intensity-Focused Ultrasound; Benign Uterine Tumor; Treatment Effects

INTRODUCTION

The uterus, which is associated with sex and childbirth, has been socioculturally recognized as a symbolic organ of mature women (1). According to the 2011 in-depth analysis of the results of a patient survey in South Korea, 329.6 in every 100,000 women had undergone hysterectomy, the highest rate among the OECD countries (2). Fibroids and adenomyosis are the most common indications of hysterectomy, accounting for approximately 30% and 20% of the total, respectively (3). According to the National Health Insurance Service of South Korea, 237,000 patients were diagnosed with fibroids in 2009, and the number increased to 293,000 in 2013 for a mean annual increase of 5.5%. The number increased in all age groups except the 20s or younger (4).

The fundamental method of benign uterine tumor treatment is hysterectomy or myomectomy, but it requires general anesthesia, hospitalization, and a long recovery period. Furthermore, women who want pregnancies or want to preserve their uterus require non-invasive treatments (5). High-intensity-focused ultrasound (HIFU) is a non-invasive and non-hazardous method of preserving organs. It can be used repeatedly and is not affected by the lesion size. The treatment process can be monitored in real time for evaluation of its performance. Physical trauma can be minimal because no incision or resection of tumors is

performed. The normal functions of the uterus could be maintained (6,7). However, few fundamental studies on HIFU treatments have been conducted in South Korea.

In this study, the effects of HIFU on fibroids and adenomyosis patients treated in a Hospital in South Korea were analyzed.

MATERIALS AND METHODS

Study subjects

Of the 1,168 patients diagnosed with fibroid or adenomyosis (546 fibroids patients and 622 adenomyosis patients) 333 patients (141 fibroid patients and 192 adenomyosis patients) who underwent HIFU treatment between February 4, 2010 and December 29, 2014, and followed for three- and six-month follow-ups were selected for this study. To enhance the accuracy of the volume measurements, the subjects were followed up for up to six months.

HIFU treatments and the tumor volume measurement method

Before HIFU treatment, the size and location of the fibroids and adenomyosis were confirmed using transvaginal ultrasound, and the feasibility of the HIFU procedure was assessed through simulation. The strength of the ultrasound was adjusted from

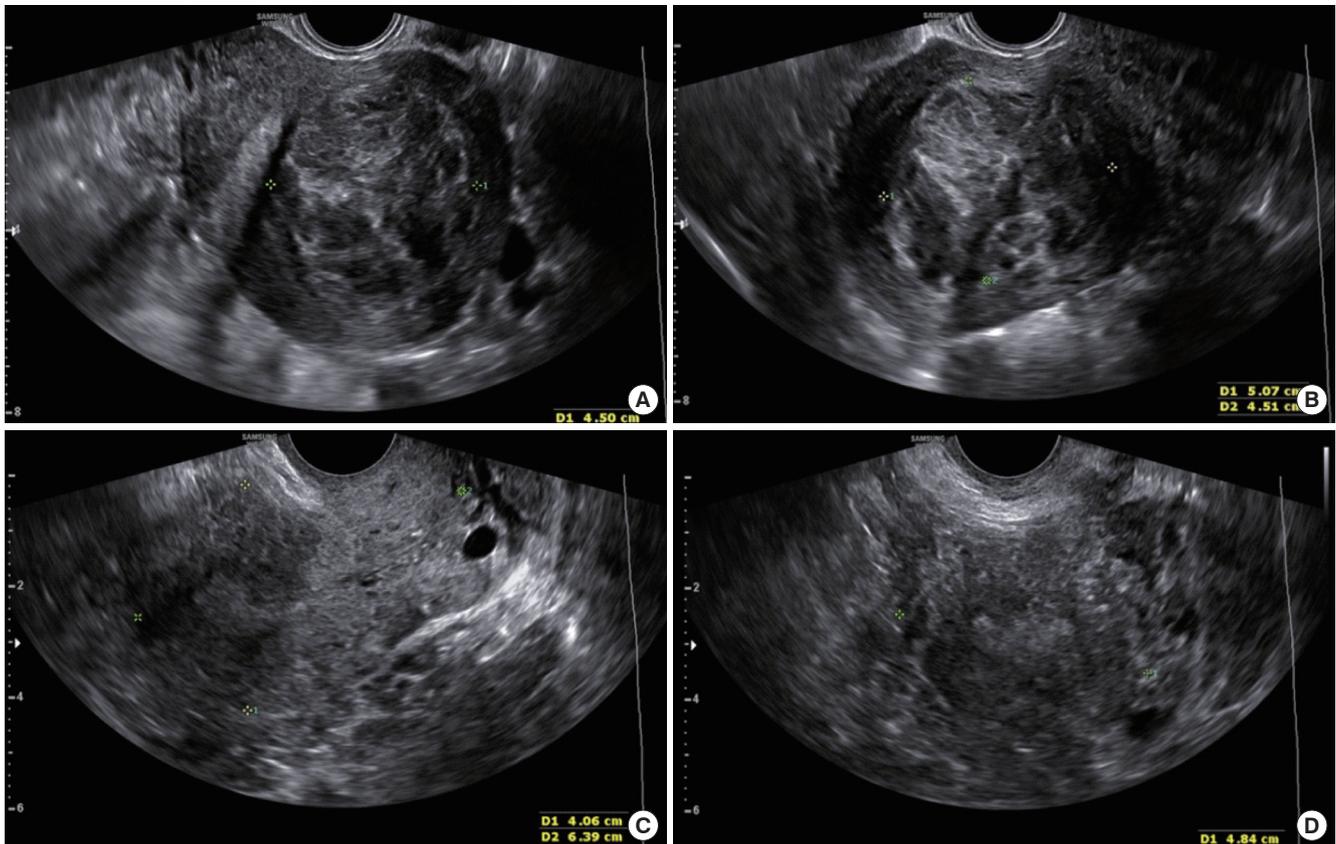


Fig. 1. Measurement of the adenomyosis by ultrasound scanning. (A) Horizontal & vertical length. (B) Longitudinal length. (C) Horizontal and vertical length. (D) Longitudinal length.

300 W to 400 W considering the subject's pain level and the transmutation level of the fibroid and adenomyosis shown in the ultrasound. The clinician determined the treatment duration. The median room time was 102 minutes, and mean time for sonication was 20 minutes 11 seconds.

ACCUVIX V10 (Samsung Medison, Seoul, Korea) was used to measure the tumor volume. A single gynecologist measured the horizontal, vertical, and longitudinal lengths of the fibroids and adenomyosis using the transvaginal ultrasound method before the HIFU procedure was performed, and the process was repeated three and six months later (Fig. 1). In patients with two or more fibroids or adenomyosis, the largest one was measured, and their volume was calculated using the following ellipsoid volume equation.

$$\text{Volume} = \pi/6 \times H \times V \times L \text{ ----- Equation 1}$$

H: Horizontal Length, V: Vertical Length, L: Longitudinal Length

SPSS ver. 18.0 was used for the statistical analyses. ANOVA was used for the analyses according to the subject's age, fertility, and treatment duration, and the independent *t*-test was used for the analysis by disease. The significance test was used to verify the significance of the volume reduction and the reduction rate of the fibroids and adenomyosis. Statistical significance was accepted at $P < 0.05$.

Ethics statement

The study protocol was approved by the institutional review board of Incheon Christian Hospital (2015-01), and written informed consent was provided by all subjects.

RESULTS

Treatment effects according to the subject's age

In all age groups of the subjects who underwent the HIFU procedure, decreases in the benign tumor volume were measured. The 30s group showed the greatest reduction of 158.36 cm³, but the differences among all age groups were statistically insignificant. In terms of the reduction rate of the benign uterine tumor volume, all age groups showed changes three and six months after HIFU treatment. The 20s groups showed the highest reduction rate of 64.9% six months later, but the difference was statistically insignificant (Table 1).

Treatment effects according to the subject's disease

The adenomyosis volume decreased by 164.83 cm³ six months later, which was the most statistically significant treatment effect. The myoma showed a statistically significant 68.5% volume reduction rate (Table 2).

Table 1. Changes in the benign uterine tumor volume according to the subject's age

Period	Age group, yr	No.	Volume (cm ³) Mean ± SD	P value	Reduction rate (%) Mean ± SD	P value
Before treatment	20-29	22	249.35 ± 211.45	0.733		
	30-39	134	277.91 ± 188.05			
	40-49	154	256.59 ± 159.93			
	50-59	23	260.54 ± 144.57			
3 months after	20-29	22	114.95 ± 107.57	0.606	57.02 ± 10.73	0.194
	30-39	134	136.16 ± 94.28			
	40-49	154	124.81 ± 83.44			
	50-59	23	123.13 ± 74.60			
6 months after	20-29	22	103.25 ± 113.32	0.443	64.86 ± 14.47	0.188
	30-39	134	119.55 ± 86.36			
	40-49	154	104.44 ± 78.05			
	50-59	23	104.33 ± 63.00			

SD, standard deviation.

Table 2. Changes in the reduction rate of the benign uterine tumor volume according to the subject's disease

Period	Disease	No.	Volume (cm ³) Mean ± SD	P value	Reduction rate (%) Mean ± SD	P value
Before treatment	Myoma	141	218.23 ± 175.50	< 0.001		
	Adenomyosis	192	299.28 ± 165.12			
3 months after	Myoma	141	97.77 ± 91.85	< 0.001	57.35 ± 13.39	< 0.001
	Adenomyosis	192	151.25 ± 79.73			
6 months after	Myoma	141	77.74 ± 81.90	< 0.001	68.54 ± 13.50	< 0.001
	Adenomyosis	192	134.45 ± 75.86			

SD, standard deviation.

Table 3. Changes in the reduction rate of the benign uterine tumor volume according to the subject's fertility

Period	Fertility	No.	Volume (cm ³) Mean ± SD	P value	Reduction rate (%) Mean ± SD	P value
Before treatment	0	147	295.85 ± 201.77	0.001		
	1	49	253.21 ± 141.72			
	2	124	222.60 ± 130.49			
	3	13	364.15 ± 216.05			
3 months after	0	147	140.33 ± 98.89	0.036	53.08 ± 12.42	0.176
	1	49	128.29 ± 82.31			
	2	124	110.89 ± 70.19			
	3	13	166.24 ± 130.66			
6 months after	0	147	126.36 ± 97.61	0.005	59.56 ± 16.45	0.811
	1	49	105.30 ± 65.88			
	2	124	90.47 ± 60.83			
	3	12	140.14 ± 114.03			

SD, standard deviation.

Treatment effects according to the subject's fertility

The reduction of the benign uterine tumor volume was statistically significant up to six months after treatment in all fertilities. The volume reduction rates were sustained for up to six months after treatment, but the difference was statistically insignificant (Table 3).

Benign uterine tumor change according to the treatment duration

In all treatment durations, the benign uterine tumor volume decreased with statistical significance up to six months post-operatively. The volume reduction rate were unchanged up to six months after treatment, so the difference was statistically in-

significant (Table 4).

DISCUSSION

Most recently, HIFU has been widely applied in clinical cases, and an increasing number of hospitals are using HIFU equipment. HIFU is recognized as a more conservative and safe method with a faster recovery time than surgical methods, thereby drawing the attention of patients with benign uterine disease. However, its treatment effects and safety have not yet been adequately studied.

In previous studies, only the reduction rates of fibroids and adenomyosis--no other factor of the benign uterine tumor size-

Table 4. Changes in the reduction rate of the benign uterine tumor volume according to the subject's treatment duration

Period	Minute	No.	Volume (cm ³) Mean ± SD	<i>P</i> value	Reduction rate (%) Mean ± SD	<i>P</i> value
Before treatment	0-30	7	78.55 ± 40.10	< 0.001		
	31-60	71	150.55 ± 87.66			
	61-90	127	229.37 ± 121.51			
	91-120	79	330.24 ± 165.33			
	121-150	37	382.91 ± 178.35			
	151-	12	633.99 ± 223.60			
3 months after	0-30	7	37.96 ± 26.40	< 0.001	59.27 ± 19.64	0.178
	31-60	71	81.10 ± 55.45			
	61-90	127	108.19 ± 65.13			
	91-120	79	156.44 ± 83.36			
	121-150	37	190.46 ± 96.32			
	151-	12	304.67 ± 117.69			
6 months after	0-30	7	34.90 ± 24.94	< 0.001	62.96 ± 20.86	0.778
	31-60	71	69.39 ± 56.85			
	61-90	127	94.19 ± 60.79			
	91-120	79	136.63 ± 84.13			
	121-150	37	148.79 ± 89.76			
	151-	12	278.67 ± 104.65			

SD, standard deviation.

-were investigated (8,9). In addition, the factors of the treatment effects according to the patient's age, disease, fertility, and HIFU treatment duration were not investigated. In this study, the effects of HIFU treatments according to the patient's age, disease, fertility, and treatment duration were examined.

During HIFU treatment, the necrotized benign tumor is absorbed via the nearby micro-blood flow. Thus, this study was conducted to prove the hypothesis that younger patients with an active blood flow experience better treatment effects. In our results, the treatment effects in the 20s age group were the greatest, and those in the 30s age group were the lowest, but the benign uterine tumor volume reduction and its reduction rates did not show a statistically significant difference among the age groups.

In this study, the volume reduction and the volume reduction rate of fibroids and adenomyosis were statistically significant. In a previous study on the changes in fibroids and three, six, and 12 months after completion of HIFU treatment, the volume was reduced by 58.1%, 66.2%, and 77.6%, respectively. Regarding adenomyosis, reduction rates of 44.0%, 47.0%, and 54.0% were observed, respectively (10). Ren et al. (11) reported the reduction rates of 27.2%, 47.9%, and 50.3% at 3, 6, and 12 months, respectively (11), and Wang et al. (8) showed 46.7%, 68.2%, 78.9%, and 90.1% at 3, 6, 12, and 24 months, respectively.

Since pregnancy and childbirth cause hormonal changes, fertility was thought to have affected the changes in the fibroid and adenomyosis. In this study, the subjects who had given birth three times experienced the greatest treatment effects, and those who had given birth only once experienced the least treatment effects. The volume reductions according to fertility were statistically significant, but no statistically significant reduction rate result was obtained. The volume reductions according to the

treatment duration were statistically insignificant; but as a result of ANOVA on the volume reduction rate, statistically significant results were obtained. What was unique about the treatment duration was that the subjects with 31-60 minutes and 121-150 minutes experienced lesser treatment effects three months later, but at six months post-operatively, they showed a greater reduction than the subjects with any other treatment duration. This study had the following limitations. Although some patients were followed up to 12 months after HIFU treatment, this study contains only short-term treatment (6 months) effect. The discrimination based on the contrast-enhancement ultrasound using microbubbles might be more meaningful than the method used in this study. In the case of two or more fibroid or adenomyosis, only the largest one was used for the analysis of treatment effect. In addition, patients who underwent HIFU treatment only at a Hospital were targeted. In future studies, patients from various hospitals may be targeted. Considering the size of the benign uterine tumor, would be decreased up to 24 months after completion of HIFU treatment, a longer follow-up period might be needed. Next, HIFU can also cause complications but data related to HIFU complications were not collected in this study. For HIFU treatment, however, it is known that the general complications are as follows: subcutaneous edema can occur on the patient's skin. In addition, pain similar to that experienced due to a slight burn can occur. Although HIFU treatment does not cause bleeding because it is an extracorporeal treatment, it can cause damage to the surrounding organs (i.e., heart, stomach, and intestine). In cases of liver cancer, there is a low possibility of nerve damage. However, if nerves exist in adjacent regions like uterine myoma, some transitional disabilities have been reported. There is also the possibility of infection in the tissues with coagulation necrosis (12). In cases of uterine myo-

ma, the follow-up observation of 7 pregnant women who experienced unplanned pregnancies showed that all women had a full term delivery and did not have any specific complications related to the pregnancy within 1 year (range: 5-32 weeks, average: 20 ± 8.85 weeks) after receiving HIFU treatment. Although it is considered safe for women to get pregnant 1 year after HIFU treatment, the need for a large-scale study on the topic has been mentioned (13). However, Bohlmann et al. (14) mentioned that there has yet to be any prospective research on the effects of HIFU treatment on pregnancy; therefore, they recommend that HIFU treatment be conducted selectively only for the following types of patients: patients at high risk of undergoing surgery, patients who refuse surgery, or infertile patients. Complications observed have been predominantly of Society of Interventional Radiology class A (no medical intervention required), with a small number of Society of Interventional Radiology class B (nominal therapy, no consequence). Class A adverse effects have included abdominal pain, mild sciatic/buttock pain, genital bleeding/increased discharge, and a prolonged next period (15). Zhang et al. (9) reported a slightly increased frequency of abdominal pain (64% vs. 71%) and skin reaction (0.8/2.4%) in patients with diffuse adenomyosis compared with those with focal disease. In their recent large analysis of 346 cases, Lee et al. (10) reported a range of more unusual complications, including foot drop (one case), transient unilateral leg weakness (one case), tumor lysis syndrome with transient acute prerenal failure (one case), sleep apnea due to a sedative agent (one case), first degree skin burn (five cases), second degree skin burn (three cases), and transient hematuria (ten cases) (10). Research on HIFU complications is planned in the future.

HIFU is a relatively effective method of treating benign uterine tumors. It can be used for patients who cannot undergo the conventional surgical methods due to their poor medical condition. In conclusion, HIFU might replace existing methods of treating benign uterine tumors.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Concept and design: Park J, Lee JS, Cho JH, Kim S. Data collection and analysis: Park J, Lee JS, Cho JH. Interpretation of the data and critical review: Park J, Lee JS, Cho JH, Kim S. Revision: Park J, Lee JS, Cho JH, Kim S. Approval of final manuscript and agreement of submission: all authors.

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