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Using microbubble sonographic contrast agent to enhance the effect of high intensity focused ultrasound for the treatment of uterine fibroids

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ABSTRACT

Objective: To evaluate the effects of the ultrasound contrast agent SonoVue in enhancing the ablative effects of Ultrasound-Guided high-intensity focused ultrasound (HIFU) on different sub-types of uterine fibroids.

Materials and methods: In this study, 390 fibroids from 319 patients were retrospectively evaluated, among which 155 were treated with SonoVue and 235 were without SonoVue during HIFU ablation. The efficacy of HIFU was evaluated using magnetic resonance scanning (MRI) in all patients.

Results: The total ablation time to achieve the same non-perfused volume was significantly shortened with SonoVue. The average energy used and the acoustic energy for treating 1 mm^3 (EEF) was less when SonoVue is used as enhancing agent. The non-perfused volume (NPV) was measured by post-HIFU MRI and the mean fractional ablation was calculated. Mean NPV was 74% (range: 15%–100%) in the HIFU-only group and 75% (range: 17%–100%) in the HIFU+ SonoVue group. However, for T2 MRI low intensity signal fibroids, NPV in the SonoVue group reached 83% (range: 20%–100%) that was significantly higher than in the HIFU-only group, which was 76% (range: 15%–100%). No differences in adverse events were observed between the two groups.

Conclusions: Our observations demonstrate that the use of therapeutic SonoVue during the HIFU procedure can significantly decrease the ablation time and the energy requirement for the treatment of the same fibroid volume in all types of fibroids.

1. Introduction

Since the introduction of the HIFU therapy for the treatment of uterine fibroids, one of the goals to achieve is to derive a faster and more effective therapy for the types of fibroids with low response rate to HIFU alone, either due to their high volume or their physical characteristics.

Funaky et al [1,2] were the first to describe a correlation between the response of fibroids to HIFU and the signal intensity in T2-weighted images on MRI. They noted very low nonperfused volumes in Type III fibroids that corresponded to poor clinical response. Zhao et al [3] sub-classified Funaky Type III fibroids according to the homogeneity of the T2 signal, and noted a poor response of fibroids presented hyper-intensive and slightly homogeneous T2 signals. Kim et al [4] observed a poor response in fibroids with high vascularisation using dynamic contrast-enhanced magnetic resonance imaging. Other less important factors, which also affect treatment outcome, have been reported, such as the heterogeneity of the signal in the MRI [5], the time of the menstrual cycle in which the treatment is performed, and Doppler flow characteristics in ultrasound examination [6].

To improve the performance of the ablation, in particular on cases that may have low response to HIFU ablation, different strategies have been put forward. Smart [7,8] proposed the pre-treatment use of GnRH analogues with the intention to reduce fibroid size, and also observed that the use of GnRH agonists potentiated the thermal effects of MRgFUS. However, Funaky [2] described worse clinical outcomes in the group of patients previously treated with GnRH analogues. During treatment, several procedures have been tested. Huang [9] proposed the infusion of oxytocin, concluding that its use could significantly decrease the energy required for ablation, shorten treatment time and improvement of the

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treatment efficiency. A technique described by Voogt [10] focused the treatment primarily on locations where supplying vessels entered the fibroid, through previous identification of these feeding vessels by contrast enhanced T1-weighted magnetic resonance angiography. Unfortunately only two cases have been reported. Also, an experimental study of Li [11] showed that the iodized oil injection prior to sonication induced major changes in the gray scale of myoma associated with an increased tissue necrosis.

Recently Yang [12] reported the effects of ethanol injection into the fibroid the day before HIFU treatment. It showed that HIFU combined with sonographically guided intratumoral ethanol injection required less treatment time and a lower dose than stand-alone HIFU treatment, and significantly reduced the pain and side effects commonly experienced by patients.

Since the report of experimental studies [13–15] showing that the use of SonoVue (a microbubble contrast agent) decreased the time required for other tissue ablation procedures, some groups have reported the use of SonoVue during HIFU treatment to enhance the effects of ultrasound ablation and monitoring the efficacy of HIFU. Peng et al [15] published in 2012 the first clinical study of the use of SonoVue during HIFU treatment to monitor the ablated area. He unexpectedly found that the sonication time to achieve massive gray scale changes was shorter with SonoVue than without it. No major complications were observed in any patients. More recently Jiang et al [16] found, in a randomized controlled trial of SonoVue infusion, that the sonication time to reach massive gray scale changes was shorter and the acoustic energy necessary to treat 1 mm [3] were significantly less in the SonoVue group. They also reported a higher nonperfused volume ratio in the SonoVue group.

Given the promising experience with SonoVue reported in the literature, our group decided to study the effects of SonoVue during HIFU ablation therapy in our common clinical practice and to assess its effects on different types of fibroids. In our study, we evaluated the non-perfused area, as it is the measure that best correlates with clinical outcomes [18].

2. Materials and methods

2.1. Baseline characteristics of patients

This study was done in accordance with the Ethics Research Committee of the Mutua Terrassa University Hospital. The inclusion and exclusion criteria were defined on the basis of previous studies [8–19]. Specifically, the inclusion criteria were: (1) patients older than 18 years; (2) diagnosis of uterine fibroids made by clinical exploration and confirmed by ultrasound or MRI examination, or made directly by image exploration; (3) the maximum diameter of fibroids smaller than 13 cm; (4) clinical symptoms attributable to fibroids; and (5) treatment plan accepted by the patient. The exclusion criteria were: (1) pregnancy; (2) patients with uterine or cervical malignancy or pre-malignancy; (3) patients with more than three fibroids; and (5) adenomyosis, diffuse or focal, and adenomyomas. All patients signed a written informed consent before the treatment. The total number of fibroids evaluated was 390 (Tables 1 and 2). From May 2008 to 2012, 195 patients underwent HIFU ablation without using SonoVue, whereas from 2012 to January 2014, 124 patients underwent HIFU ablation using SonoVue. The average age of the patients in the two treatment cohorts was comparable [HIFU alone: 40 ± 6 (26–54) yrs; HIFU+ SonoVue: 41 ± 6 (25–53) yrs].

Table 1
Demographic characteristics of the patients treated with and without SonoVue.

Variables	HIFU	HIFU+ SonoVue
Number of patients	195	124
Age (years)	40 ± 6 (26–54)	41 ± 6 (25–53)
GnRH n[a] (%)	107 (55)	75 (60)
GnRH[b] (months)	2.6 ± 1.1 (1–7)	2.3 ± 1.0 (1–6)
Total number of fibroids	235	155
Patients with solitary fibroid n (%)	157 (81)	102 (82)
Patients with 2 or 3 fibroids n (%)	38 (19)	22 (18)

No significant difference was observed between the two groups.
[a] Number of patients with previous GnRH analogues treatment (n) and percentage (%).
[b] Mean duration of the treatment with GnRH analogues.

Table 2
Characteristics of the treated fibroids.

Variable	HIFU	HIFU+ SonoVue	p value
Number of fibroids	235	155	
Volume of the fibroids[a] (cm^3)	127 (2–736)	87 (2–982)	0.007
MRI T2 signal intensity of the fibroids n[a] (%)			
Low	115 (49)	85 (55)	0.003
Medium	87 (37)	34 (22)	
High	33 (14)	36 (23)	
MRI T1 gadolinium-enhanced signal of the fibroids n[a] (%)			
Low	36 (15)	43 (28)	0.003
Medium	92 (39)	48 (31)	
High	107 (46)	64 (41)	

[a] Significant difference was observed in the distribution between the two groups, $p < 0.05$.

2.2. Pre-treatment evaluation

Clinical evaluation and examination were performed on all patients. We assessed the risk of malignancy or pregnancy and, if necessary, we performed additional tests including cervical cytological smear and endometrial biopsy.

All patients underwent a Gadolinium enhanced pelvic MRI, in order to evaluate the number, volume and localization of the fibroids and the features of the T2-weighded signals. The enhancement after the administration of gadolinium allowed us to functionally classify the characteristics of vascularisation for each fibroid. The size of fibroids was measured in three dimensions (longitudinal (d1), anteroposterior (d2) and transverse (d3) diameters), and the volume was calculated with the formula $V = 4/3\pi r^3$, where $r = (D1 + D2 + D3/3) \times 0.5$. The fibroids were classified into high, medium or low intensity in MRI T2 signal using the criteria as described in our previous studies [1,2]. The vascularisation of each fibroid was defined in relation to the uterus enhancement signal as high, medium or low degree. Patients with high T2 signal, high vascularisation and fibroids bigger than 7 cm in diameter received a three-month pre-treatment with GnRH analogues.

Blood tests for assessing the number of haemoglobin, hematocrit, electrolytes, and renal function were performed. In cases with suspicion of malignancy, the level of LDH isoenzymes was also measured for the detection of malignancy in uterine nodules.

2.3. Pre-treatment preparation

Prior to HIFU treatment, specific bowel preparation was required in order to reduce the presence of intestinal gas. Patients underwent a three-day specific diet, fasting on the previous day and an enema on the day of the treatment. In HIFU unit, specialized nurses prepared the skin by shaving the lower abdomen and performed the procedure to remove air bubbles from the surface of the skin. A three-way urinary catheter was inserted to control the bladder volume during the treatment.

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