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Does the phase of menstrual cycle affect MR-guided focused ultrasound surgery of uterine leiomyomas?☆

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Abstract

Purpose: To determine whether the phase of menstrual cycle at the time of MR-guided focused ultrasound surgery (MRgFUS) treatment for uterine leiomyomas affects treatment outcome.
Methods: We enrolled all patients participating in a prospective phase III clinical trial from our center who completed 6 months of clinical and imaging follow-up. Patients with irregular cycles and those on oral contraceptives were excluded. Data prospectively documenting the date of the last menstrual period (LMP) at the time of treatment, length and duration of cycle, and raw symptom severity score (SSS) from the Uterine Fibroid Symptom and Quality of Life questionnaire, at baseline and 6 months were collected. Proliferative phase patients were determined retrospectively as those who were treated within less than 14 days from LMP; secretory phase patients were classified as those who were treated greater than 14 days from LMP.
Results: A total of 58 patients were enrolled. There was no significant difference in the mean SSS at baseline and mean SSS at 6 months between patients treated in the proliferative versus secretory phase of the cycle. No significant difference in the SSS change from baseline to 6 months was seen between the two groups.
Conclusions: Menstrual cycle phase does not influence MRgFUS treatment outcome. Symptomatic improvement occurs with treatment during either phase of the menstrual cycle. Thus, the scheduling of MRgFUS treatment need not be based upon the phase of the menstrual cycle.

Keywords: Menstrual cycle; MRgFUS; Focused ultrasound; Fibroids; Leiomyomas

1. Introduction

Symptomatic leiomyomas, the most common benign female tumor, may result in a range of clinical symptoms from severe bleeding and abdominal bulk symptoms to minor discomfort [1]. It is a significant cause of morbidity, estimated to affect 20–40% of women of reproductive age. The direct costs of this disease exceed one billion dollars in the U.S. alone [2]. A wide range of treatment options exist: medical therapy with GnRH agonists, uterine artery embolization, myomectomy and hysterectomy. Percutaneous interstitial laser therapy and cryoablation have also been investigated as potential minimally invasive treatments [3–5]. MR-guided focused ultrasound surgery (MRgFUS) is a new, non-invasive method of thermal ablation for treating women with symptomatic uterine leiomyomas [2,6,7].

The potential surgical application of focused ultrasound originated more than 50 years ago [8]. Using this technique, a focused ultrasound beam can penetrate soft tissue and is localized to a target site causing high temperatures (55–90 °C), inducing necrosis within a few seconds through molecular vibrations. The added application of real time MR guidance allows for precise targeting and localization of tumors, and through temperature sensitive sequences, focal temperature elevations are detected, ensuring effective thermal doses [8–11].

Clinical feasibility has been demonstrated with uterine leiomyomas and benign and malignant tumors of the breast [6,12–14]. The adequacy of target thermal doses are substantiated by real-time temperature sensitive MR imaging and post-

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treatment necrosis with T1-weighted imaging with intravenous gadolinium contrast showing decreased perfusion in the ablated tissue [9,15]. In treatment of uterine leiomyomas, successful treatment outcome has been previously defined by an improvement in symptom severity score (SSS) [7,16], which is part of a standardized uterine fibroid symptom-quality of life (UFS-QOL) questionnaire [17].

As the availability of MRgFUS as a treatment choice increases, it will become vital to further define what treatment parameters can be used to predict a successful clinical outcome. The normal uterus demonstrates differences in signal intensity within the myometrium in response to a variety of physiological effects, including menstrual cycle, hormonal effects, and sustained contractions [18–20]. During the proliferative phase, myometrium is low in T2 signal intensity. During the secretory phase, the signal intensity of the outer myometrium increases [20]. Change in myometrial signal intensity is caused by transient increase or decrease in blood volume, which is related to the water content of the myometrium [10,21]. Thus, high signal intensity during the secretory phase relates to high water content of the myometrium. It is also known that leiomyomas can be quite heterogeneous on both MRI and pathological evaluation. The purpose of this study was to determine if the phase of menstrual cycle at the time of MR-guided focused ultrasound surgery (MRgFUS) treatment for uterine leiomyomas affects treatment outcome.

2. Materials and methods

This was a prospective study of patients who had completed at least 6 months of follow-up after MRgFUS treatment of symptomatic leiomyomas. All patients analyzed in this report were enrolled from a single center as part of a multi-center, prospective phase III clinical trial studying the treatment of uterine fibroids with MRgFUS. The study was approved by our institutional review boards, and all patients gave informed consent after the nature of the MRgFUS procedure was explained to them. The study was performed using the ExAblate 2000 and sponsored by the device manufacturer Insightec Inc. (Haifa, Israel).

3. Pre-treatment

Eligibility criteria for procedure enrollment included: premenopausal women (age greater than 18 years) with symptomatic uterine leiomyomas, a uterine size of less than 20 weeks, and no dominant leiomyoma larger than 10 cm in diameter. Patients with irregular menstrual cycles and those on oral contraceptives were excluded from the study.

All patients completed a UFQoL questionnaire detailing the number and severity of clinical symptoms at baseline and 6 months. The UFQoL questionnaire consists of eight symptom questions and an additional 29 health-related quality of life questions. The eight symptom questions was determined using a five-point Likert scale, with responses ranging from “not at all” to “a very great deal”, with a possible score ranging from 8 to 40. All patients enrolled were required to have a raw SSS of at least 21 using the 8 symptom questions. The raw SSS is what is being reported in this study.

All patients then underwent pre-treatment MR imaging at 1.5 T (GE Signa, General Electric Healthcare, Milwaukee, WI), using an external phased array coil and a standardized imaging protocol including multiplanar T2W imaging and T1W imaging before and after the intravenous administration of gadopentetate dimeglumine (dose, 0.1 mmol per kg of body weight) (Magnevist; Berlex Laboratories, Wayne, NJ). MR images were used to confirm the presence of leiomyomas, exclude adenomyosis or other pathologies, and define the leiomyomas for size, volume, and location. MR images were then used for surgical planning to evaluate the planned focused ultrasound beam path. Images were also evaluated for possible obstacles in the beam path that may preclude treatment, such as loops of bowel, bladder and bone between the leiomyoma and the anterior abdominal wall.

4. Treatment

On the night prior to treatment, patients were instructed to fast from midnight and to shave any hair on the anterior abdominal wall to the pubic crest. On the day of surgery, all patients had a urine pregnancy test, which was required to be negative before the patients were to be treated. The patient’s LMP date and length and duration of cycle were obtained. Informed consent was obtained for the use of intravenous conscious sedation (intravenous Versed and Fentanyl). According to hospital guidelines, prior to the procedure all patients had an intravenous line and Foley catheter. Heart rate, blood pressure, and oxygen saturation levels were monitored throughout the procedure.

All patients were positioned on the MR table overlying a water tank and transducer. Multiplanar, T2W images were acquired for treatment planning of the FUS beam path. A region of treatment within the leiomyoma was drawn by the radiologist. The maximum number of sonications to safely ablate the leiomyoma without causing damage to other structures was then determined. Each sonication targeted a 0.5 cm^3 cigar shaped region. Total treatment time was limited to 3 h and treatment volume was limited to a maximum of 100 cm^3 per leiomyoma and 150 cm^3 per treatment. Most patients underwent a single leiomyoma treatment, however treatment of multiple leiomyomas were allowed within the treatment time and volume limitations. Each sonication was monitored by the radiologist with real-time MR for localization and temperature mapping.

5. Post-treatment

Immediately post-treatment, patients underwent MR imaging, post-administration of IV gadolinium, to evaluate the area of non-perfusion or necrosis (Figs. 1 and 2). The patients were discharged and returned within 1 week for a follow-up clinic visit. At the follow-up visit, patients were evaluated by the obstetrician/gynecologist and any complications were noted. Six months post-treatment, patients returned for a follow-up visit, MR imaging and completed the UFQoL questionnaire. The raw