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Clinical Efficacy of Non-invasive Magnetic Resonance Guided Focused Ultrasound Therapy in Treatment of Multiple Uterine Fibroids

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Abstract The purpose of this study was to evaluate the efficacy and outcome of magnetic resonance guided, focused ultrasound (MRgFUS) therapy in the treatment of women with symptomatic multiple uterine fibroids. As MRgFUS is a noninvasive, nonsurgical method and can be done as a day-care procedure, this was more acceptable for these women. In this single-site study, 40 Malaysian women with a mean age of 43.8 + 7.8 years who were candidates for surgical intervention due to symptomatic multiple uterine fibroids were recruited. The women had a minimum of two and a maximum of five uterine fibroids. Only the largest intramural fibroid (mean, 8.08 + 2.3 cm) was targeted for treatment. Fibroid size and volume were measured by magnetic resonance imaging before and 6 months after treatment. MRgFUS related adverse events that occurred during and within 1 week after treatment were monitored and recorded. Menorrhagia and pressure symptoms improved in 28 women (70%) at follow up. There was reduction in fibroid volume; with a mean difference of 79.3+51.7 cm3 (22%, $p < 0.0001$) 6 months after treatment. Hysterectomy was performed in seven (18%) patients who had persistent menorrhagia and five (12%) patients who had persistent menorrhagia responded to hormones, with improvement of symptoms within 6 months. The long-term efficacy of this promising non-invasive approach in the treatment of multiple uterine fibroids is being followed up. MRgFUS has a good safety profile, and no major adverse events were noted in this study. The symptoms of the women who were treated improved, with a moderate reduction in fibroid volume. Thus, the need for surgical intervention was avoided in most cases.

Keywords Focused Ultrasound Therapy, Magnetic Resonance Imaging, Multiple Uterine Fibroid, Leiomyoma

1. Introduction

Uterine fibroids are the commonest benign tumors of the female genital tract, and 20–40% of uterine fibroids occur in women of reproductive age group. Common symptoms are menorrhagia, dysmenorrhoea, pelvic pain and bulk-related symptoms such as urinary frequency and a feeling of heaviness.[1,2] Multiple uterine fibroids essentially cause more morbidity, especially in nulliparous women, who, when offered hysterectomy as the only definitive treatment, have permanent regret in their lives. Thus, women either delay or choose no treatment due to the invasiveness of surgery and the economic impact, and continue to suffer with their symptoms.[3,4,5]

For many years and in present hysterectomy was the most definitive and curative treatment available for women with multiple uterine fibroids. This procedure is effective, but it is not suitable for women who wish to remain fertile. In view of the growing tendency of women to postpone pregnancy into the late thirties and the morbidity represented by multiple uterine fibroids, alternative treatments, which are non-invasive, with shorter recovery times and with retention of childbearing potential have recently received much attention.[6,7]

Uterine-sparing treatments such as myomectomy and uterine artery embolization (UAE) are limited with respect to the number, size and location of fibroids that can be treated. In various locations of multiple fibroids, removal of fibroids which are located close to the cervix, submucosal fibroids or at the entrance of the fallopian tubes can lead to to increased scarring or tubal blockage following removal by myomectomy. Myomectomy is also suboptimal in such situations, as the cumulative uterine fibroid recurrence rates increases with time and has been reported to be 27–51% . In a study of outcome and resource use associated with myomectomy, Subramanian et al. reported repeated surgeries in 16.5% of women within 2 years of myomectomy.[22]

Uterine artery embolization is associated with postoperative fever and pain, post-treatment hospital stay for

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2.5 days lengthy time off work for 7 days and suspension of normal activities during recovery.[23] MRgFUS is a novel noninvasive technique that is capable of producing coagulative necrosis at a precise focal point within the body. The ability of ultrasound energy to interact with biologic tissues and to cause a rise in tissue temperature was recognized long ago since 1927.[8] The ultrasound beam carrying a high level of energy is brought to a focus and is rapidly converted into heat. The temperature at the targeted spot can be raised to more than 55℃ causing denaturation of proteins resulting in coagulative necrosis and cell death.[9,10,11,12] Many results have shown that MRgFUS ablation for uterine fibroids is feasible and safe. [13.-16] Although the ablation volume may represent only a small fraction of the targeted fibroid, patients have reported at least partial improvement in their symptoms.[17-19] With the exception of hormonal therapy, MRgFUS appears to be the least invasive therapy for uterine fibroids.[20,21]

At University Malaya Medical Center in Malaysia, MRgFUS has recently been added as a treatment option for symptomatic uterine fibroids. The aim of this study was to determine the efficacy of this technique in the treatment of women with symptomatic multiple uterine fibroids.

2. Materials and Methods

This was a prospective study for one year beginning from January 2010. Before the study was initiated, the protocol for use of MRgFUS for the treatment of uterine fibroids was approved by the ethics committee of University Malaya.

Inclusion criteria were as follows: (1) a diagnosis of multiple uterine fibroids by clinical examination and ultrasound imaging; (2) women aged > 20 years but premenopausal, with fibroids<10 cm in diameter; (3) symptomatic fibroids requiring treatment; (4) able to communicate with a nurse or physician during the procedure and agreed to undergo pre and post treatment Magnetic Resonance imaging(MRI).

2.1. Exclusion Criteria

Pregnancy, more than five fibroids, standard MRI contraindications, suspected or confirmed uterine malignancy or extensive abdominal scarring that could not be avoided by redirection of the beam or scar patch. The other exclusion criteria are as listed below.

2.2. Patient Exclusion Criteria

1). Hemoglobin <10 mg/dL

2). Patient has hemolytic anemia

3). Patient has unstable cardiac status including:

a. Unstable angina pectoris on medication

b. Documented myocardial infarction within six months of protocol entry

c. Congestive heart failure requiring medication (other than diuretic)

d. Currently taking anti-arrhythmic drugs

e. Presence of cardiac pacemaker

4). Severe hypertension (diastolic BP>100 on medication)

5). Patient has severe cerebrovascular disease (within six months)

6) Patient is on anti-coagulation therapy or has an underlying bleeding disorder

7) Evidence of uterine pathology other than leiomyoma

8) Patient has an active pelvic infection

9) Patient has an undiagnosed pelvic mass outside the uterus.

10) Patient's weight >110 kg

11) Patient with extensive longitudinal abdominal scarring in an area of the abdomen directly anterior to the treatment area.

12) Patient with standard contra-indications for MRI such as non-MRI compatible implanted metallic devices.

13) Individuals who are not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 h.)

14) Hyperintense, non-enhancing fibroids, or calcified fibroids were also excluded from treatment.

Forty women with symptomatic multiple uterine fibroids, who met the inclusion criteria were recruited. All patients provided written, informed consent, after the nature of the procedure was explained to them. Patients were seen first by a gynecologist who obtained an informed consent, then underwent a screening MRI to confirm that fibroids were present and could be treated and that no other disease process (such as an ovarian tumor) was present to preclude treatment. All patients underwent pre-treatment MR imaging with a standardized protocol. MR images helped to define the number, size, volume, location and enhancement after administration of gadolinium of the fibroids.

The MRI-guided focused ultrasound therapy system used in this study (ExAblate 2000, InSightec) integrates fully with a 1.5-T MRI system to enable focused ultrasound therapy to be planned directly with MR images and to give a real-time MR thermometry feedback of each sonication. Each therapeutic sonication is preceded by imaging of the treatment area and followed by temperature feedback, which allows the interventional radiologist to increase power if necessary to optimize effective tissue coagulation or to decrease it to prevent injury to adjacent normal tissue.[11, 12]

The ExAblate 2000 is integrated with a 1.5-T MRI scanner (GE Medical Systems, Milwaukee, WI), and provides real-time thermal imaging during the treatment phase of the procedure. This Exablate 2000 was installed in university Malaya since November 2008. Prior to treatment, hair is shaved from the umbilicus to the pubis to ensure acoustic coupling. The patient lies prone on the treatment table, with her abdomen lying on a gel pad situated directly above the ultrasound transducer.

The patient is pre-medicated with light conscious sedation (diazepam 5 mg PO, pentazocine 15 mg IV, and hydroxyzine hydrochloride 25 mg IV) to relieve anxiety, prevent movement, and to minimize discomfort. Light sedation allows patients to communicate with the medical staff

throughout the procedure. In addition, patients were given a ‘‘stop button’’ so that they can immediately stop the energy pulse in the event of pain or discomfort. The largest intramural fibroid was targeted for treatment and the contour of the entire targeted fibroid is drawn on the MR image using ExAblate System software. The system computes the energy and the sonications required to completely treat the defined region based on tumor volume and depth.

The interventional radiologist optimizes the plan to cover as much fibroid volume as possible to achieve maximum tumor ablation. Fibroids with more than 50% of their volume within the maximum focus and the largest intramural fibroid were generally excluded. Patients with fibroids which do not fit into the above criteria were excluded from the study.

A maximum treatment time from first to last sonication was limited to 180 min. Following treatment, the patient generally remains in the MRI suite for one hour to recover from the sedation. Then they are discharged and accompanied home by their spouse or a relative. All patients were prescribed with some post-procedure analgesics. Patients were provided with the contact phone number of the gynecologist should they need any assistance after discharge. The patients were asked to report any discomfort after discharge, and a structured interview was used to ensure that common or expected adverse events were identified and recorded. The pain and discomfort as reported by patients immediately after treatment before they were discharged home were assessed on a categorical scale, with 0 = none, 1 = mild, 2=moderate, and 3=severe. The patients were followed up at 1, 3 and 6 months and were asked about subjective relief of symptoms, and additional treatment was given as necessary. Data are reported as the mean ± SD. Paired t-test was used for statistical comparisons of fibroid volume between baseline and 6 months after MRgFUS treatment. A p value below 0.05 was considered significant.

3. Results

In total, 40 patients were treated by a single interventional radiologist .The mean age was 43.8 + 7.8years. Among the races treated 60% were Malays, 17.5% were Chinese, 17% were Indians and 2% were others. Menorrhagia was present in 36 (90%) women and 4 (10%) had pressure symptoms in the form of heaviness in the pelvis with some difficulty in passing urine with no acute retention. Among the forty women recruited 39 women had 3 fibroids and one woman had a maximum of 4 fibroids.

By the 6-month follow up, there was a significant reduction in the fibroid volume with a mean volume difference of 79.3+51.7 cm3 (22%, $p < 0.0001$) 6 months after treatment . Hysterectomy was performed in seven (18%) patients who had persistent menorrhagia not responding to medical treatment and were not keen for embolization. Five (12%) patients who had minor bleeding; were started on hormonal therapy, and their symptoms had improved within 6 months.

In this study the procedure was aborted in 2 patients after 20 minutes due to technical failure. These 2 patients were excluded from this study. Immediately after the treatment 8 (20%) patients complained of mild lower abdominal pain, and 3 (7%) had moderate pain, when questioned after the procedure. No serious adverse events were reported. There was one hospitalization on the third day following the procedure for persistent fever and was treated with antibiotics for urinary tract infection on the third day following treatment and made a full recovery after one week.

There were 3 device related adverse events out of which one patient developed skin burns with formation of seroma of 2 x3 cms size which regressed after 2 weeks. She was treated with antibiotics for one week as it got infected. It took 4 weeks for complete healing of skin with no scar formation .Two patients developed mild first degree skin burns with pain and redness over a birth mark on the abdomen.

One patient had a Pfannensteil scar and had an uneventful procedure with no complications. Three patients had persistent vaginal discharge for a week which spontaneously reduced without any medication. Three patients developed fever for 2 to 3 days following the procedure and were treated with oral paracetamol.

Seven patients had hysterectomy as the symptoms of bleeding persisted for 3 months after the procedure and prior to the decision of hysterectomy they were treated with Oral progestogens but the response was poor. One patient developed intermenstrual bleeding following 5 months and was noted to have a benign endometrial polyp which was removed by hysteroscopy. One patient had a successful pregnancy after treatment. She was a 36years old lady,with one previous spontaneous vaginal delivery was treated with intramural fibroid volume of 454 cm3. The estimated conception date was 5 months after the treatment. Her pregnancy course was uneventful and she is being followed up.

4. Discussion

Treatment of multiple uterine fibroids with MR imaging-guided focused ultrasound treatment appears to be feasible and safe, which can still produce significant reduction in the fibroid volume and provide a short term relief of symptoms. This may not be the appropriate treatment, for example, subserosal leiomyomas associated with uterine bleeding instead of compression symptoms to adjacent organs. Hence it is now recommended that sonications are performed at least 4 cm from bony structures to minimize the amount of heating of the bone ,which can in turn heat the fat surrounding the nerves and lead to stimulation or potentially damage of the nerve. Such stimulation of the adjacent sacral nerves may result in incomplete treatment with reduced efficacy of the procedure if the pain is severe. Patients with a significant proportion of the fibroids mass not more than 12 cm depth away from the

skin line (which is the maximum depth of penetration of the sound) are deemed technically suitable for MRgFUS[24]

The ease of treatment in this study was determined by the fibroid that was chosen, and an attempt was made to target only one and the most dominant fibroid that was most likely to cause symptoms. Selecting the fibroid for treatment was based on relevance of the fibroid(s) to the patient's symptoms. Complete coagulation of all the fibroids was not the goal of the this study; rather, treatment was to induce coagulative necrosis safely within an operator defined portion of the targeted tumor. As MR imaging can provide excellent guidance for therapeutic planning, accurate tissue targeting causing localized thermal changes in the sonicated tissue without causing damage to surrounding structures, a significant reduction in fibroid volume was achieved safely without any side effects.

In this study four cases of adverse events were reported after the treatment. All were known adverse events that can occur after MRgFUS, and are similar to those observed in previous studies. Women suffering from multiple uterine fibroids of>5 are invariably advised to undergo hysterectomy as it is a definitive treatment and in this study eventhough only a single and the largest fibroid was treated still they were benefitted as the severity of the symptoms reduced. MRgFUS holds the promise of being completely noninvasive, low-risk therapy and can cause significant reduction in the overall fibroid volume. The patients who were recruited in this study are still being followed up to ascertain the long term outcome of this procedure. Few studies have proved that MRgFUS is consistent and reproducible but we need more expanded treatment guidelines on the volume and the number of fibroids treated especially in women suffering from multiple uterine fibroids .

In conclusion, MRgFUS is an effective fascinating treatment alternative with a good safety profile for women who defer surgery and who wish to preserve fertility.

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