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Magnetic resonance guided focused ultrasound surgery of uterine fibroids—The tissue effects of GnRH agonist pre-treatment

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Abstract

Objective: The purpose of this study was to determine the ablative effect of magnetic resonance guided focused ultrasound (MRgFUS) on fibroid tissue following the administration of gonadotrophin releasing hormone (GnRH) agonist.

Study design: Fifty women with clinically symptomatic uterine fibroids were treated. Those with uterine diameter of 10 cm or greater were given 3 months pre-treatment with GnRH agonists. Data regarding number of ultrasound sonications, Joules of energy delivered and volume of thermal destruction was recorded.

Results: Twenty-seven subjects were given GnRH agonist therapy before MRgFUS and 23 women underwent MRgFUS without pre-treatment. All patients in both study groups completed MR guided FUS as an outpatient procedure with no device related adverse events reported. In the group of women who received GnRH agonists, the volume of ablation was significantly larger than that in the control group (0.06 cm³ versus 0.03 cm³, $P < 0.05$), per Joule of energy applied.

Conclusion: The use of GnRH agonists potentiates the thermal effects of MRgFUS in women undergoing treatment of uterine fibroids.

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Keywords: Fibroids; Focused ultrasound; GnRH agonist

1. Introduction

Magnetic resonance guided focused ultrasound has emerged as an entirely non-invasive method of accurately ablating tissue at depth within the body.

Using high intensity ultrasound waves, targeted within a small focal volume, a localised rise in temperature sufficient to cause lethal cell damage can be created, with minimal heating only to adjacent tissues [1]. By combining focused ultrasound technology with the properties of magnetic resonance imaging, a system has been developed (ExAblate 2000) which enables precise targeting within tissues. In addition, temperature sensitive MR sequences provide real time feedback of focal rises in temperature to ensure safe delivery of an effective thermal dose [2].

The potential uses for this novel type of therapy are numerous. Technical feasibility of an MRI guided system was established over 10 years ago [3]. Although studies have been carried out in many different areas including breast, brain, and liver tumours [4–6], the largest body of work, to date, has taken place in women with symptomatic uterine fibroids. Following initial safety and feasibility studies [7,8], phase III efficacy trials have been carried out and results from 109 women demonstrate a significant symptomatic improvement in over 75% of those treated with this technique [9].

Exclusion criteria for these earlier studies dictated a maximal uterine diameter of 10 cm. This arbitrary cut off point aimed to keep patient treatment times, which are volume dependent, to a maximum of 180 min. A significant proportion of women seeking therapy for fibroid related symptoms will have uteri that exceed this size. Therefore, in order to offer MRgFUS effectively to this population with large fibroids, we set out to explore a way in which tumours in excess of 10 cm in diameter could be fully ablated without increasing treatment times. We have postulated that the administration of subcutaneous gonadotrophin releas-

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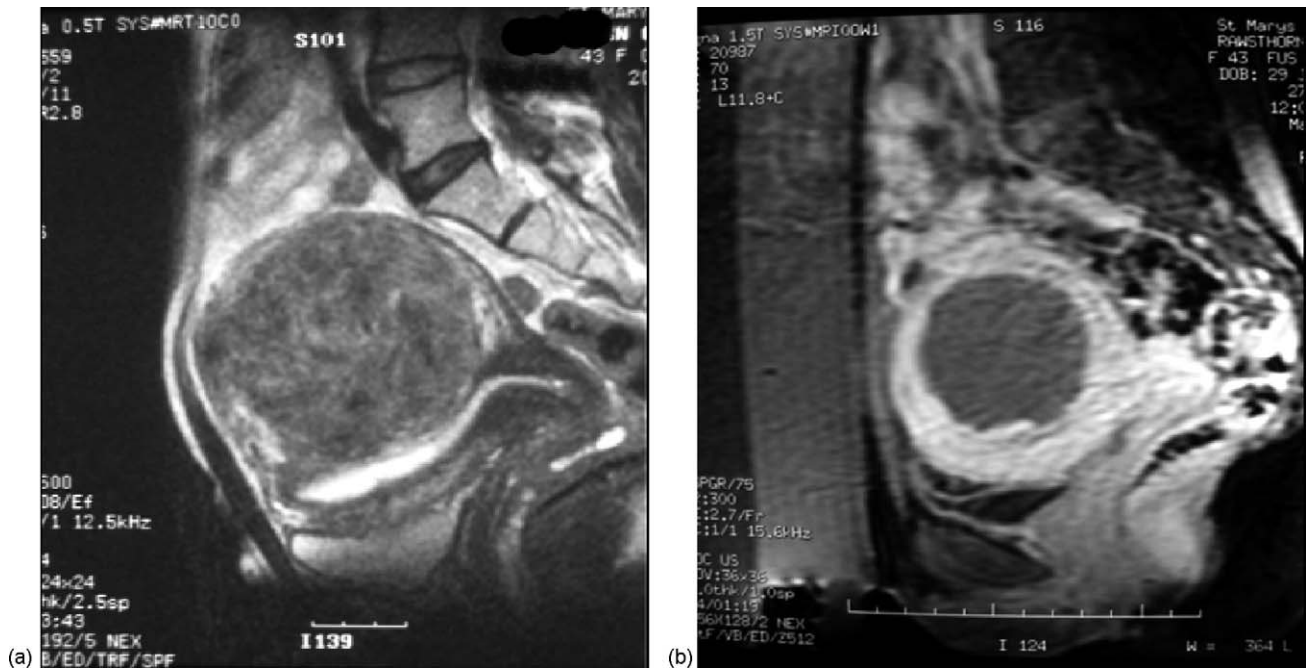


Fig. 2. Enlarged uterus measuring 717 cm³ due to a single intramural fibroid (a). Forty-one percent reduction in size was seen following GnRH treatment allowing a large area of non-perfusion to be created using FUS, as seen on the T1 contrast enhanced images post-treatment (b).

3. Results

In the study group, 27 women underwent a 3 months course of GnRH analogues before undergoing MRgFUS. The control group consisted of 23 subjects who underwent MRgFUS only.

3.1. Demographics

At the beginning of the study the two groups were similar ($P > 0.05$) regarding age, race, BMI and location of fibroids. Mean age was 42 years (S.D. ± 4.9 , range 35–53). The proportion of Black African or Afro-Caribbean patients was 33% and the average body mass index 24.5 (S.D. ± 3.5 , range 20–32).

Of the fibroids treated 52% ($n = 26$) were solitary tumours and 48% ($n = 24$) had more than one fibroid. Ninety-six percent of the subjects had fibroids that were intramural ($n = 48$) in addition 22% ($n = 11$) of subjects had at least one submucosal fibroid, 22% ($n = 11$) had one or more subserosal fibroids. One patient had an additional pedunculated fibroid, which was not treated in accordance with the study protocol.

3.2. Uterine volume

The mean uterine volume in the study group at enrolment was 1232 cm³ (S.D. ± 698) and the mean volume of the targeted fibroid was 579 cm³ (S.D. ± 353). Following 3 months treatment with GnRH agonist the average reduction in uterine size was 44.5% and reduction in the target fibroid was 36%. Resulting volumes at treatment were therefore; mean uterine volume 654.96 cm³ (S.D. ± 400) and mean target fibroid volume 385 cm³ (S.D. ± 270). Within the study group eight

women required two FUS treatments the remainder ($n = 19$) being treated in a single session.

3.3. Thermal dosimetry

The average number of sonications required to complete a treatment correlates directly with the size of the target fibroid. The overall mean number of individual sonications for patients receiving one treatment session was 39 (S.D. ± 9), with time in the MR scanner ranging from 165 to 240 min (mean = 211 min). For those women who required two sessions of FUS, mean number of sonications required was 81 (S.D. ± 17) and corresponding treatment duration of 390–430 min (mean = 401.25 min).

In the GnRH group, the average energy delivered to the target fibroid per patient was measured as 2434 J (S.D. ± 449). Following treatment the non-perfused portion of the target fibroid was measured. In this way it is possible to calculate the volume of leiomyoma that has undergone thermo-coagulation during the focused ultrasound procedure. This can be expressed as an absolute value in cubic centimetres and also as a ratio of the energy applied or the number of sonications delivered. Mean non-perfused volume (NPV) in the study group was measured as 136.51 cm³ (S.D. ± 118.7). Therefore, per sonication delivered to the target fibroid an average ablated volume of 3.13 cm³ was created. Per Joule of energy applied, this volume is equivalent to 0.06 cm³.

When we compare these values with the control group there are several important differences that can be observed. The thermal dosimetry data derived shows that, for women who have not had GnRH therapy the mean non-perfused volume following FUS treatment is 113.42 cm³ (S.D. ± 34.38) which is achieved

Table 1
Comparison of thermal dosimetry between study and control group

	Study group, GnRHa pre-treatment (n=27)	Control group (n=23)
Mean no. of sonication	39	33
Mean energy delivered (J)	2434	3385
Mean non-perfused volume created (cm ³)	136.5	113.4
NPV/sonication (cm ³)	3.5	3.4
NPV/J (cm ³)	0.06*	0.03*

NPV, non-perfused volume.

* $P < 0.05$.

following an average of 33 sonications (S.D. ± 13). However the average energy applied to produce this result was 3385 J. Although this gives a similar mean volume ablated per sonication of 3.44 cm³ when this result is expressed as a ratio of NPV per Joule the result is 50% lower than the equivalent value in our patient group treated with GnRH (0.03 cm³, $P < 0.05$) (Table 1).

3.4. Safety

All patients in both groups completed MR guided FUS as an outpatient procedure. Intravenous analgesia and sedation was given as required (maximum dose Pethidine 100 mg/Diazepam 10 mg). There were no device related adverse events reported in the course of this study.

4. Discussion

This study is the first to show that the size of the thermal lesion produced by MRgFUS can be enhanced by simple medical pre-treatment, in the form of GnRH agonists.

Despite the widespread prevalence of uterine fibroids, relatively little is known regarding their causation or the mechanisms involved in growth or regression. We therefore have to apply our current knowledge in order to explain this augmentation of the thermal effect. It has been widely observed that fibroids are responsive to changes in ovarian steroids and may grow rapidly during pregnancy. Equally in the hypo-oestrogenic environment of the menopause, or during the administration of GnRH agonists fibroids are seen to shrink. Several studies have examined the changes within fibroid tumours following suppression of circulating oestrogen and progesterone and, as yet, there is no precise and satisfactory explanation for the mechanism of shrinkage. Some histological studies have reported contradictory results concerning cellularity and collagen deposition, whereas others have failed to identify significant differences between treated and untreated leiomyomata [13]. One possible reason for this controversy may be the histological and cytogenetic variations among individual myoma nodules, even in the same uterus [14].

It is likely that the underlying pathogenesis represents an accelerated form of the process taking place after the onset of menopause, where smooth muscle tissue can undergo hydropic degeneration and be replaced by nodular hyaline tissue as a result of a diminished vascular supply [15]. This would be in keeping

with the clinical finding of reduced estimated blood loss during surgery [10] and borne out by more specific studies examining the size and number of vessels within both myometrium [16] and, more importantly, in myomas following administration of GnRH. One study demonstrated a 24% reduction in the diameters of intramyomatous arteries compared to subjects receiving placebo [17]. It has been suggested that this change in vascularisation is mediated via local peptide growth factors. The immuno-expression of several growth factors has been shown to be reduced in fibroids treated with GnRH agonist together with a decreased total number of vessels [18]. Those fibroids that respond to GnRH therapy tend to do so within the first 2 months in line with changes in vascularity. Examining the blood flow on Doppler ultrasound shows that reduction of blood flow to the myoma occurs within the first 4 weeks of therapy followed by a subsequent reduction in uterine size and uterine vascularity [19].

The enhanced tissue response to MRgFUS within the cohort receiving GnRH agonist pre-treatment is likely to be mediated via this effect of decreased vascularity. Diminished removal of heat by conduction will lead to an increase in local tissue temperatures and thus, even if the power applied is the same, a larger volume of coagulative necrosis will be created in the less vascular fibroid.

5. Conclusion

The results of this study suggest that there is a definite role for the use of GnRH agonists in combination with MRgFUS. Its use effects a significant reduction in uterine size such that successful therapy may be possible in women who would have otherwise been excluded on the basis of uterine size alone. More importantly the enhanced tissue response allows the creation of much larger areas of destruction to be created with each individual sonication. It is likely that as the reduction in vascularity, responsible for this effect, occurs within the first 4 weeks of treatment, there may be a role for short course therapy in women with smaller fibroids where size reduction is not necessary but decreased vascularity may improve the therapeutic outcome.

This is the first time that the potentiation of a thermal ablative therapy using simple adjuvant medical therapy has been shown and suggests other hormone sensitive tumours may also respond in this manner in conjunction with thermo-ablation.

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