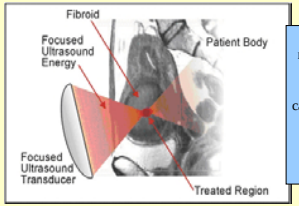
MAGNETIC RESONANCE GUIDED FOCUSED ULTRASOUND OF UTERINE FIBROIDS
The Effects of GNRH Analogue Pre-Treatment

OC SMART, JT HINDLEY, L REGAN, WMW GEDROYC.

DEPARTMENT OF OBSTETRICS & GYNAECOLOGY AND DEPARTMENT OF RADIOLOGY, ST MARY'S HOSPITAL,IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE, LONDON.

INTRODUCTION

Magnetic Resonance Guided Focused Ultrasound (MRgFUS) has emerged as a safe and effective non-invasive treatment for women with symptomatic uterine fibroids. This technique uses high intensity ultrasound waves which converge at a focal point to cause a rise in temperature. When tissues are heated above 56 ^{0}C, coagulation of cell proteins occurs. Intervening tissues in the beam pathway are subject to transient heating only, without cell damage.



Schematic representation of FUS pathway causing thermo-coagulation within the centre of the fibroid.

Fibroids are benign tumours of the uterus, also known as leiomyomas. They are extremely common and thought to occur in more than a quarter of women of childbearing age (Buttram & Reiter Fertil Steril. 1981). Symptoms produced such as heavy periods, pain and infertility, will cause a large proportion of women to seek treatment – often hysterectomy.

BACKGROUND

Initial studies using MR guided FUS to ablate uterine fibroids treated 55 symptomatic women. A proportion of this cohort underwent planned hysterectomy post treatment, providing pathological correlation of the thermal lesion produced (Stewart EA et al Am J Obstet Gynaecol 2003). It was demonstrated that, as an outpatient treatment MR guided FUS is extremely well tolerated with an excellent safety profile.

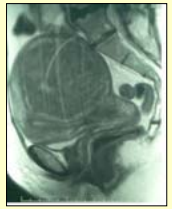
Phase III efficacy trials are now also complete and results from 109 women show a significant symptom improvement in 79% of those treated with this modality (Hindley J et al AJR Am J Roentgenol 2004). In this series a positive correlation was drawn between the volume of fibroid tissue ablated and the clinical outcome at six months.

Both of these studies were limited to women with a uterine diameter of less than 10 cm. The maximal volume of tissue which could be ablated was arbitrarily set at 150 cm^3 per patient.

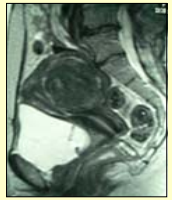
STUDY DESIGN

It is well established that the use of GnRH analogues will cause a marked decrease in fibroid volume if administered continuously for a period of between 3 and 6 months These drugs will not only cause cellular atrophy but also decrease in vascular flow to the tumour and hence GnRH analogues are, in many cases, administered prior to conventional surgical removal of fibroids. (Lethaby A, Cochrane Database Syst Rev. 2001).

It has been postulated that the use of sub-cutaneous goserelin for 3 months prior to MR guided Focused Ultrasound will enable this innovative treatment to be safely extended to women with larger fibroids without decreasing its effectiveness.



MRI pelvis. Sagittal T2 images showing reduction in uterine volume following 3/12 GnRH analogues.



MATERIALS AND METHODS

In this study we prospectively enrolled women with symptomatic fibroids in whom the maximal uterine diameter measured greater than 10 cm. All patients met the minimum symptom severity score of 21, as determined by the first eight questions of a Uterine Fibroid Symptoms and Quality of Life Questionnaire (Spies JB Obstet Gynecol 2002). This assesses both bleeding and pressure symptoms over the previous 3 months with responses being scored from 1 (not distressed) to 5 (distressed a great deal). A baseline raw score of between 8 and 40 points can thus be calculated.

A baseline MRI scan was performed to determine the number and configuration of fibroids present. In order for MRgFUS to be carried out safely there must be an adequate clear window for the sonication pathway. This must not cross abdominal wall scars or any loops of small bowel. Those patients found to be anatomically unsuitable were excluded from the study.

Women were requested to attend on the first or second day of their menstrual period. Pregnancy test was performed and, if negative, patients were administered 3.6mg of sub-cutaneous goserelin (Zoladex™, AstraZeneca). This was repeated at 28-day intervals for a total of 3 doses.

MR Guided Focused Ultrasound was carried out 14-21 days after the final injection of goserelin.

Patient lies prone within the MR scanner during FUS treatment. The acoustic transducer is positioned directly underneath the fibroid and a series of consecutive FUS pulses, each lasting approximately 20 seconds, is delivered to the target region to produce a larger area of thermal ablation. The system plots each individual sonication pathway to ensure accurate targeting.

Schematic representation of MRgFUS system

FOLLOW UP

Patients were asked to complete a 37 point fibroid specific questionnaire, UFS-QOL, to give an objective symptom severity score prior to commencing Zoladex injections. This was repeated on the day of treatment and at 3 and 6 month follow-up visits. Change in score from baseline value was the primary outcome measure of treatment.
Target fibroid volume was also measured at baseline, treatment and 6 months to determine change in size.

RESULTS

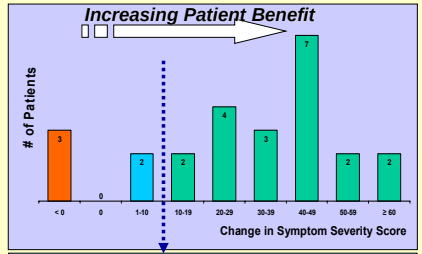
30 women were deemed suitable for the study and enrolled during a 12 month period. All women underwent a 3-month course of GnRH analogues. 3 women were excluded from the final analysis giving a study group of 27 women.

Demographics: Mean age was 42 years (SD +/- 4.9), range 35-53. The proportion of Black African or Afro-Caribbean patients was 33% and the average Body Mass Index 24.5 (SD +/- 3.5). 52% (n=14) of patients had a solitary tumour and 48% (n=13) had more than one fibroid. 96% of the subjects had fibroid that were intramural (n=26) in addition 22% (n=6) of subjects had a submucosal fibroid, 22% (n=6) had a subserosal fibroid and one patient had an additional pedunculated fibroid, which was not treated in accordance with the study protocol.

Symptom Scoring: At 6 months 81% of subjects reported some improvement in fibroid related symptom scores according to the UFS-QOL. 74% reported an improvement of 10 points or more. The mean change in score was a reduction of 31 points which is highly statistically significant (p<0.0001).

Uterine Volume: The mean uterine volume at enrolment was 1232 cm^3 (SD +/- 698) Following 3 months treatment with GnRH analogues the average reduction in uterine size was 44.5% giving a mean treatment volume of 654.96 cm^3 (SD +/- 400). The mean reduction in treated fibroid volume at 6 months was 29% (SD +/- 40), p = 0.0065.

Symptomatic outcome at 6 months following FUS



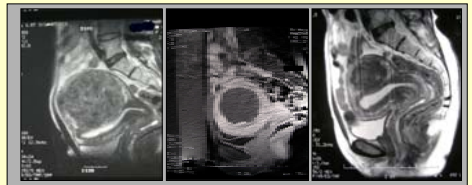


Figure 1 Figure 2 Figure 3

This 43 year old woman presented with symptoms of menorrhagia and pelvic pressure [QOL score 41] due to a 10 cm diameter fibroid (Figure 1). 40% reduction in uterine size was achieved with 3 months of GnRH therapy enabling a very large area of thermo-ablation to be produced in one treatment session (Figure 2). At 6 month follow-up she had complete relief from her symptoms [QOL score 9] and further decrease in the treated fibroid is noted (Figure 3)

DISCUSSION

GnRH analogue therapy has a well established role in the pre-treatment of patients undergoing conventional fibroid surgery. This study demonstrates that it can be used in combination with MR guided Focused Ultrasound to treat those patients whose fibroids would have previously been considered too large. Outcome, as judged by improvement in QOL score, is comparable to previous work (Hindley J et al AJR Am J Roentgenol 2004) and, at the 6-month stage, size reduction in the treated fibroid is 50% greater than early studies where GnRH was not used. It is likely that this is a manifestation of the reduced vascularity within the fibroid allowing higher temperatures and larger areas of thermo-coagulation to be produced, per Joule of energy applied.

Pre-treatment with GnRH analogues has increased the scope of patients whom this innovative therapy can be offered to. We believe that MR Guided Focused Ultrasound should no longer be restricted to women with smaller fibroids.

Acknowledgements:
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