

Prospective Study on the Effectiveness of Mrgfus in the Treatment of Uterine Fibroids.

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Abstract: Uterine fibroids are the most common solid benign tumours in women during the reproductive years. They are estimated to be present in 20-50% of women over the age of 30 years, they increase with age, and the prevalence is higher in Afro-Caribbean women.(1). Traditionally the mainstay of treatment for fibroids has been surgical, either myomectomy or hysterectomy but nowadays many women are interested in a less invasive therapy.

Magnetic resonance guided focused ultrasound is a new technique for treating a variety of solid tumours. MRgFUS is a noninvasive Walk-In And Walk-Out procedure and the patient can resume her normal activities the next day.

Aim: To Study The Effectiveness Of Magnetic Resonance Guided Focussed Ultrasound In The Treatment Of Uterine Leiomyomas In Terms Of Clinical Improvement.

Objective: Whether Mrgfus Can Be Considered As Primary Mode Of Noninvasive Treatment Of Uterine Fibroids.

Primary Outcome: The degree of symptom relief after 6 months, improvement of hematocrit, mean fibroid shrinkage and correlation with immediate nonperfused volume ratio., any adverse effects.

Secondary Outcome: Symptom relief at one year, any additional procedure required.

I. Introduction

Magnetic resonance guided high intensity focused ultrasound (MRgFUS) therapy of fibroids is a proven technique approved by US Food and Drug administration for treatment of fibroids by heat generated using high intensity ultrasound.⁴ Advantages of MRgFUS include: rapid resolution of uterine fibroids symptoms, short recovery times, fewer post-operative complications compared with UAE or hysterectomy, and a low incidence of complications.¹⁷

It can improve fibroid related symptoms and cause shrinkage of fibroids in due course of time. The purpose of this study is to prove the clinical efficacy of this procedure in patients with symptomatic fibroids using clinical symptom severity scoring (SSS) before the procedure and after 6 to 12 months follow up.

II. Materials And Methods

Place Of Study: The study was conducted in the Department of Radiology and Imaging, Bharat Scans, between January 2013 and December 2013 over a period of 12 months.

Type Of Study: Prospective Interventional study. The study was submitted to the scientific and ethical committee and was approved.

Inclusion Criteria: Patients who presented with symptomatic fibroids more than 18 years of age and who would otherwise have been offered conventional semi invasive or surgical therapy were considered for MRI guided focused ultrasound therapy.

Exclusion Criteria: Women with asymptomatic fibroids

1. Patients who were unsuitable for MRI. (Cardiac pacemakers, vascular clips etc.,)
2. Patients with serious systemic diseases.
3. Patients who weigh more than 150 kgs.
4. Fibroids more than 10 cm.
5. Patients with pedunculated fibroids with a slender stalk.
6. Patients who were pregnant during the procedure.
7. Patients with unmanageable bowel interposition and scars.
8. Deep seated fibroids. (> 13 cm from the anterior abdominal wall).
9. Fibroids with dense calcifications.

III. Methods Of Enrollment

All patients who met the eligibility criteria, were screened for MR compatibility like cardiac pacemaker, metallic implants and severe claustrophobia. The patient must be able to lie prone for about 3 hours and must be able to communicate sensations during the procedure. Importance was given to scars in the abdomen as they may disrupt the passage of US waves. In our study, all suitable subjects were given questionnaires for symptom severity scoring which were assigned a score on a 4 point scale. No symptoms-score 0, Mild symptoms-score 1, moderate symptoms-score 2, severe symptoms-score 3. These are subjective measurements for evaluation and monitoring.

Preprocedure Mri

The purpose of this screening MRI was:

- To confirm the diagnosis.
- To exclude associated adenomyosis, adnexal mass.
- To assess the exact number of fibroids, size, location and enhancement characters.
Small fibroids <3cm and large fibroids >10 cm were not included due to inability to target them or achieve necrosis.
- The path of Ultrasound beam: If fibroid was >12cm from the anterior abdominal wall, US waves may not penetrate the target. If it is very close to the sacrum, heating the sacral bone may lead to sciatic nerve injury. Sonications must be limited to at least 4cm from the sacral bone. All intervening or adjacent organs in the treatment path as well as scars must be avoided.

Ideal patient is one with

Anterior fibroid with uniform to low signal intensity, no intervening organ in pathway and with good perfusion.

Mrgfus Procedure:

The MRI-guided focused ultrasound therapy systems used in this study PHILIPS Sonalleve MR HIFU integrates with Achieva 1.5 T MR system to enable focused ultrasound therapy to be planned Directly With Mr Images And To Give Real-Time Mr Thermometry Imaging After Each Sonication.

Preprocedure Preparation:

- Patient were instructed to fast at least for 6 hours before the procedure. Ideal would be fasting for 12 hours.
- Abdomen was well cleaned and shaved from the umbilicus to one cm below the pubic bone to prevent any air bubbles trapped in hair which may increase the risk of burns.
- Conscious sedation with midazolam was given to alleviate anxiety and pain such that the patient was responsive throughout.
- Informed oral and written consent was obtained from all the participants after proper counseling about the procedure.
- Continuous bladder drainage was kept to keep the bladder empty because filling of the bladder during the procedure may displace the uterus and change the position of fibroids.
- Patient was given a PANIC BUTTON during treatment such that she can stop the treatment when she has severe pain or heat sensation.

Treatment Planning:

Patient was made to lie down in prone position such that her abdomen was in contact with acoustic gel pad in a waterbath of degassed and deionized water. Prior to initiating the procedure multiplanar T₂W images were taken and transferred for planning program. Region of treatment (ROT) was manually drawn and defined within the capsule of the fibroid.

Treatment areas were selected as small cells (Fig 2) of varying sizes ranging from 4mm to 32mm. Each cell was checked for safety in near field and far field. The cells were arranged in different clusters to cover the treatment area. (Fig 3)

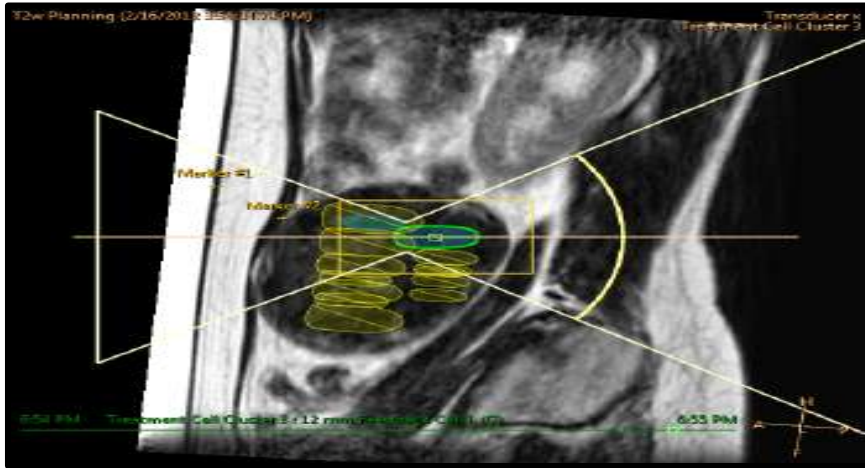


Fig 2 .Image Shows Sagittal Section In Planning Phase Where Cells Are Arranged In The Treatment Area And The Transducer Overlay Can Be Seen As Angled Beam.

Target volume was analysed with superimposed US beam paths in 3 planes. The beam path must be angled for optimal access of the fibroid such that scars, air bubbles and other intervening organs are avoided. If fibroid was close to the serosal surface, a 0.5cm margin of nontargeted tissue should be maintained to prevent thermal damage to tissues in close proximity.

Procedure:

After thermal imaging and marking the region of treatment, the procedure begins with delivery of subtherapeutic doses of low power sonication (50-100W) to the centre of fibroid. Real time thermometry was acquired through proton resonance frequency shift method.

Resultant images were provided for sonication location to reconfirm targeting accuracy.

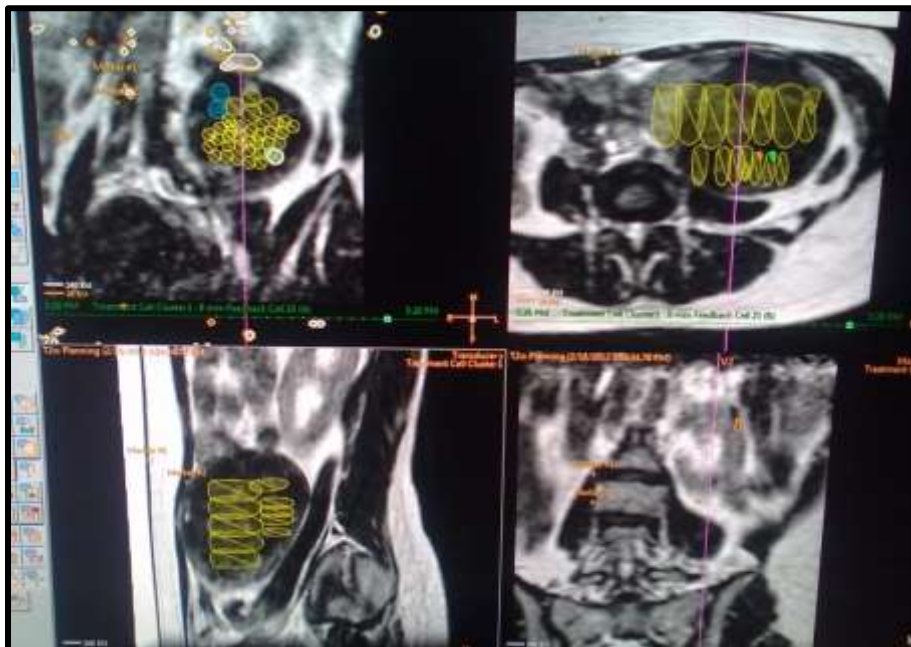


Image Shows The Planning Sequence In All Planes. The Treatment Cells Appear Circular Perpendicular To The Beam And They Are “Cigar Shaped” Parallel To The Beam.

A pre sonication image obtained was used as baseline and further images were added sequentially in a single sonication. Colourcodings (Blue to red scale) (Fig 4) representing the gradual increase in temperature were projected over the treatment area. Special graph showing the temperature rise was also made available on the screen. Next sonication was done after the lapse of reasonable cooling time. The sonication parameters were safely adjusted using the thermometry graphs for further safe sonications.

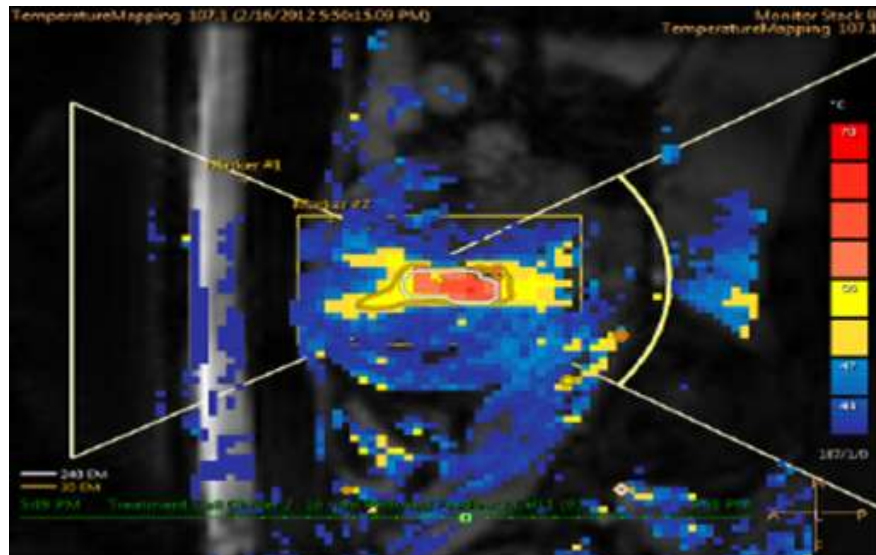


Fig 4. Temperature Mapping Seen As Color Codes from Blue To Red.

Subsequent sonications were given at therapeutic power level. Until therapeutic thermal dose, energy delivered was increased to coagulate the tissue at temperatures above 60°C. It is desirable to try and reach 70-80°C that ensures tissue necrosis. Each sonication lasts for 20-40 seconds. Between each sonication adequate cooling time should be given of upto 90 seconds to avoid thermal buildup which will damage the surrounding tissues.

For all planned sonications the same procedure was continued. To ensure no complications, continuous communication with the patient was important. The whole procedure would last for 3-4 hours. Criteria to terminate early were:

- Inability to visualize focal treatment spot.
- Patient complaints of unacceptable pain.
- Targeting difficulties due to patient motion.

After completing all the planned sonications, the last step was to assess the Nonperfused Volume by giving intravenous gadolinium as contrast.

Postprocedure

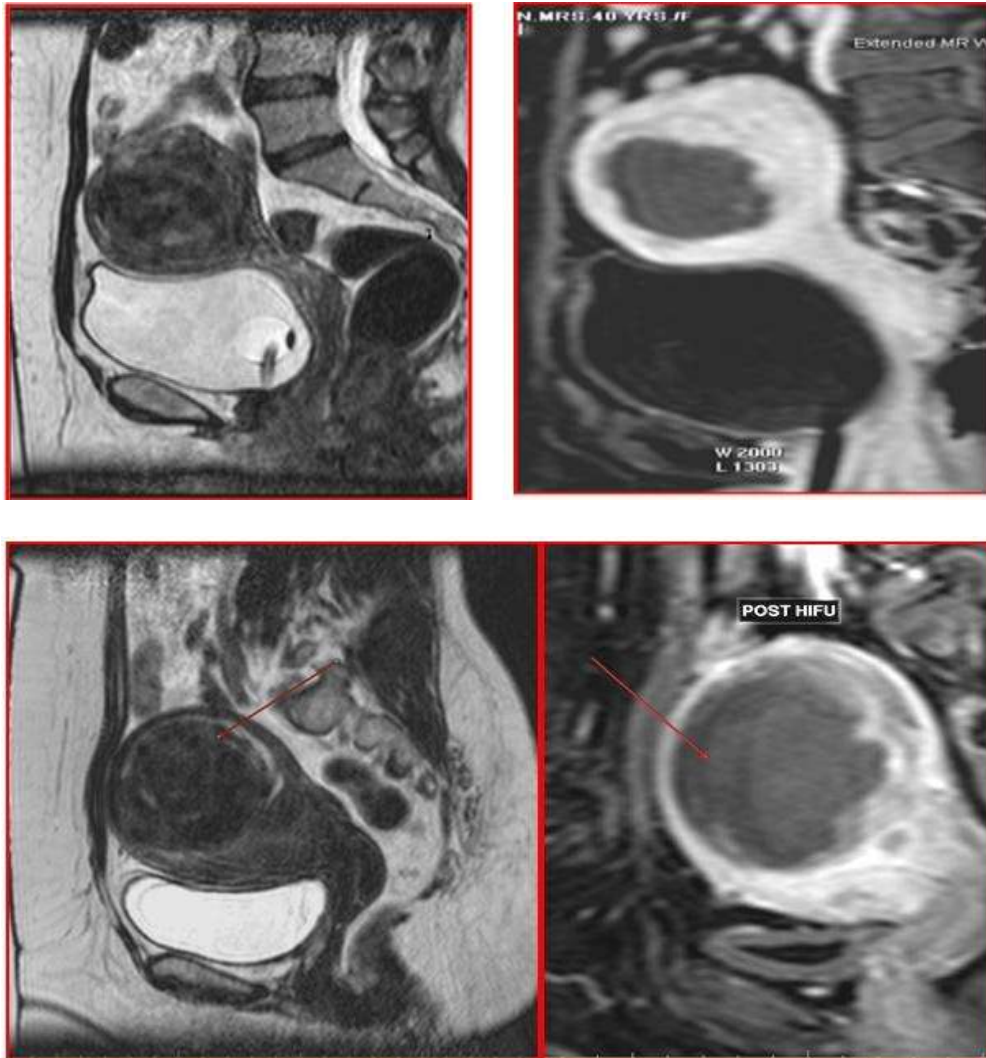
Following the procedure, the patient was taken to a holding area where the foley's catheter was removed. The skin surface would be examined for any heat induced changes. Body temperature would be recorded. Patient would be instructed not to drive and to take rest till she recovers from the sedation. She can resume activities the following day. The most common symptom was mild back pain, fever and general discomfort. Patient was discharged after one to two hours observation after the procedure.

Follow Up Of Patients

Patients were asked to come for follow up after 6 months and 12 months. They were given the same questionnaires regarding the improvement of symptoms. Their Hematocrit was measured and the values were noted. The fibroid shrinkage was assessed by clinical examination and Ultrasound pelvis.

Representative Cases

Case 1: Image (Left) - T2W preprocedure image showing a predominantly T2 hypointense anterior wall fibroid. Image (Right) - T1W post contrast image showing the non perfused area.



Case 2: Image (Left) - T2W preprocedure image showing a predominantly T2 hypointense anterior wall fibroid. Image (Right) – T1W post contrast image showing nearly 75% non perfused volume.

IV. Results

Demographic Data:

A total of 30 patients who underwent MR Guided focussed ultrasound therapy for fibroids at Bharat Scans between January 2014 and December 2014 over a period of 12 months, who fit the inclusion criteria were enrolled in this study. They underwent a preliminary screening MRI and those who were found to be eligible on screening were included in the study.

The parameters measured were:

- Hematocrit.
- Menorrhagia scoring.
- Dysmenorrhea scoring.
- Pressure symptoms scoring.
- Immediate Nonperfused volume
- Fibroid volume and fibroid shrinkage.

These parameters were measured at 6 months and at the end of 12 months. The efficacy of mrgfus was defined as improvement in the haematocrit, symptom scoring and attaining >50% Nonperfused volume. Continuous data were represented by mean and standard deviation and categorical data were represented by frequencies and percentages and were analyzed. A value of $p < 0.05$ was considered to be statistically significant. Data's were analyzed with SPSS 14.0 version.

Table – 1 Hematocrit Paired Sample Statistics

		Mean	N	Std. Deviation	Std. Error
Pair - I	HCT – Bef	28.40	30	2.207	0.403
	HCT – 6 mnths	31.30	30	2.231	0.407
Pair – II	HCT – Bef	28.40	30	2.207	0.403
	HCT – 12 mnths	33.07	30	1.964	0.359

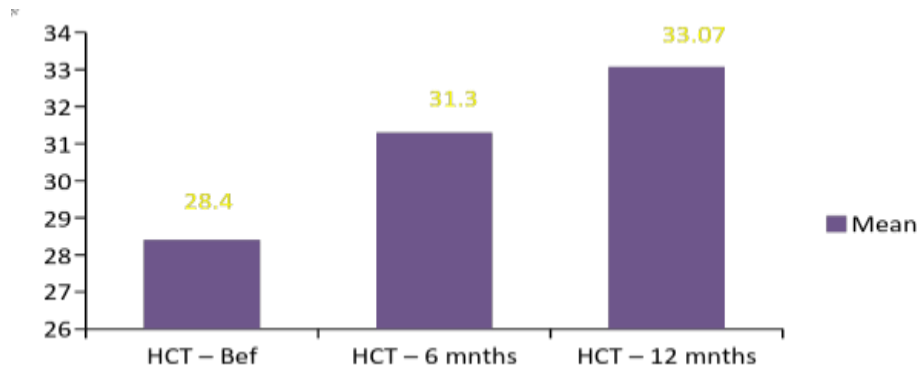


Table 1 shows the mean baseline hematocrit and the gradual increase in the mean hematocrit at 6months and at 12 months after treatment.It has increased from 28.4 to 33.07.

Paired Sample Test For Hematocrit

		Mean	Std. Deviation	Std. Error Mean	p value
Pair - I	HCT – Bef	-2.900	1.296	0.237	< 0.001
	HCT – 6 mnths				
Pair – II	HCT – Bef	-4.667	1.845	0.337	< 0.001
	HCT – 12 mnths				

The paired sample test between the hematocrit values before and after treatment at 6 months and 12 months showed a statistically significant increase with a p value of <0.001.

Table 2 Menorrhagia Scoring – Paired Sample Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair - I	Men Score – Bef	1.60	30	0.968	0.177
	Men score – 6 months.	0.40	30	0.563	0.103
Pair – II	Men score – Bef	1.60	30	0.968	0.177
	Men score – 12 months	0.17	30	0.379	0.069

Table shows the mean menorrhagia score before and after treatment at 6 months and 12 months. There was a significant decline in the scoring with symptom improvement.

Paired Samples Test

		Mean	N	Std. Deviation	Std. Error Mean	P value
Pair - I	Men score – Bef	1.2	30	0.664	0.121	<0.001
	Men score – 6 months.					
Pair – II	Men score – Bef	1.433	30	0.817	0.149	<0.001
	Men score – 12 months					

The paired sample test between the mean menorrhagia scoring before and after treatment at 6 months and 12 months was done and was found to be statistically significant with a p value <0.001.

Table 3 Dysmenorrheal Scoring

		Mean	N	Std. Deviation	Std. Error Mean
Pair - I	Dys Scoring – Bef	2.13	30	0.629	0.115
	Dys scoring– 6 months.	0.80	30	0.714	0.130
Pair – II	Dys scoring– Bef	2.13	30	0.629	0.115
	Dys scoring – 12 months	0.27	30	0.450	0.82

Table shows the mean dysmenorrhea score before and after treatment at 6 months and 12 months. There was a significant decline in the scoring with symptom improvement.

The mean baseline dysmenorrhea scoring decreased from 2.13 to 0.27. The paired sample test between the mean dysmenorrhea scoring before and after treatment at 6 months and 12 months was done and was found to be statistically significant with a p value <0.001.

Table 4 Pressure Symptoms Paired Sample Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair - I	Press symptoms scoring – Bef	1.10	30	0.960	0.175
	Press symptom scoring – 6 months.	0.53	30	0.776	0.142
Pair – II	Press symptom scoring – Bef	1.10	30	0.960	0.175
	Press symptom scoring – 12 months	0.50	30	0.731	0.133

Table shows the mean dysmenorrhea score before and after treatment at 6 months and 12 months. There was a significant decline in the scoring with symptom improvement.

The mean baseline pressure symptom scoring decreased from 1.10 to 0.5. The paired sample test between the mean pressure symptom scoring before and after treatment at 6 months and 12 months was done and was found to be statistically significant with a p value <0.001.

Table 5 Fibroid Shrinkage And Npv

FIBROID SHRINKAGE	NPV					
	<40%		41-60%		> 60%	
< 15%	1	100%	0		0	
16 – 30%	8	80%	2	20%	0	
> 30%	0		11	57.9%	8	42%
	9		13		8	

Chisquare Test

	Value	df	Value
Pearson chisquare	22.918	4	
Likelihood ratio	28.690	4	< 0.001
Linear by linear Association	17.122	1	

Table 5 shows that all fibroids that had a NPV ratio of >60% had a fibroid shrinkage of more than 30%. The values were analysed with chi square tests and were found to have a significant p value of <0.001.

Table 6. Acoustic Window And Npv

Age Group	Total	< 40%		40 – 60%		> 60%	
No Interference	18	4	(44.4)	7	(53.8)	7	(87.5)
Scar	6	4	(44.4)	2	(15.4)	0	(0)
Interference	6	1	(11.1)	4	(30.8)	1	(12.5)
Total	30	9		13		8	

Table shows that 87.5% of patients who belonged to >60% NPV ratio had no interference in the beam pathway.

Table 7 Number Of Fibroids And Npv

No. of Fibroids	Total	NPV		
		< 40%	40 – 60%	> 60%
Single	19	3	8	8
Multiple	11	6	5	0
Total	30	9	13	8
	Value	Df	P value	
Pearson Chisquare	8.139	2	0.017	

CHI-SQUARE TEST

Table shows the influence of the number of fibroids and NPV ratio. It shows that only single fibroids could attain a better NPV ratio. The analysis of the values gave a significant p value of <0.05.

Table 8 signal intensity and npv

Signal Intensity of fibroid	Total	NPV		
		< 40%	40 – 60%	> 60%
Low	22	3	11	8
High	8	6	2	0
Total	30	9	13	8

Chi-Square Test			
	Value	Df	P value
Pearson Chisquare	11.119	2	0.004

Table shows the influence of signal intensity of fibroids on T2 weighted MR Images. It is inferred from the table that low intensity fibroids attain a better NPV ratio. The values were analysed and was found to be significant with a p value of <0.05.

V. Discussion

This is a prospective study conducted at Coimbatore medical college Hospital in collaboration with BHARATH SCANS during the period 2013-2014.

The purpose of this study was to assess the effectiveness of MRgFUS in the treatment of uterine fibroids. In our study we had 30 eligible patients with symptomatic fibroids who met the inclusion criteria and were enrolled after a preliminary MRI screening.

Symptom severity scoring:

Symptoms like menorrhagia, dysmenorrhea, pressure symptoms and mass effect as reported by patients before, 6 months and 12 months after treatment were assessed on a 4 point scale with 0=none, 1=mild, 2=moderate and 3=severe.

The mean baseline for SSS OF MENORRHAGIA was

- At baseline: 1.6
- At 6 months follow up: 0.4
- At 12 months follow up: 0.17

The mean values for SSS of DYSMENORRHEA was

- At baseline: 2.13
- At 6 months follow up: 0.80
- At 12 months follow up: 0.27

The mean values for SSS of pressure symptoms and mass effect were as follows:

Pressure symptoms

1. At baseline: 1.10
2. At 6 months follow up: 0.53
3. At 12 months follow up: 0.50

All the above mentioned SSS showed improvement and had a statistical significance with p value < .001, hence proving the hypothesis that MRgFUS treatment brings about significant and sustained improvement in symptoms.

Stewart EA et al conducted a study in 2007 and concluded that the symptom severity scoring significantly reduced from the baseline as early as 3 months.²

Fenessey FM et al in 2007 showed that there was a significant 10 point improvement from baseline SSS score at the end of 12 months in those with NPV > 30%.²² Funaki K Sawadak et al in 2007 derived in his study of 63 patients that mean symptom scores were significantly reduced.³⁵ Rabinovici J Inbar Y Revel A et al in 2007 concluded that 69% of patients reported either significant or partial improvement in symptoms.³⁶

Hematocrit

In our study there was a mean increase in hematocrit from the baseline which was attributed to significant reduction in menorrhagia.

The mean values for hematocrit in our study:

- Before: 28.4
- At 6 months: 31.3
- At 12 months: 33.07

There was a statistically significant increase in hematocrit from a mean of 28.4 to 33.7 with a p value of <0.001.

Stewart EA et al, Rabinovici in 2007 showed higher symptom improvement and improvement in hematocrit with higher NPV ratio.

Factors Influencing Immediate Npv Signal Intensity Of Fibroid:

In our study of 30 patients, we had 22 fibroids of low intensity and 8 fibroids of high intensity, 100 percent of >60% NPV and 84.6 percent of 41-60% NPV were of low intensity fibroids. 75 percent of high intensity fibroids attained only <40% NPV. These values were coinciding well with a p value of <0.001. Ronit et

al in 2011 showed that hypointense fibroids had a better odd's ratio for a better NPV Ratio. FunakiK,FukunishiH.Funaki T et al in 2007 reported that the efficacy of MRgFUS correlates with the intensity of T₂ weighted images.Hypointense fibroids are suitable whereas hyperintense are not.

Acoustic Window

Among 30 patients in our study, 18 patients had no interference in the acoustic window. 6 patients had scars and 6 patients had some interference in the beam pathway lie bowel,other viscera.. 87.5% of >60% NPV ratio was attained only when there was no interference in the beam pathway.83% of NPV ratio <40% had some kind of interference in the form of scars,bowel or other viscera. Le Blang SD et al 2010 reported that factors limiting ablation were obstacles to passage of ultrasound beam like scars,bowel.

Nonperfused Volume Ratio.

The mean NPV ratio attained from a sample of 30 patients in our study is 48+ 14%.This is influenced by many factors like signal intensity of fibroid,number of fibroids,depth of fibroids and interference in the acoustic window.

The Immediate NPV ratio attained correlated well with the symptom improvement and fibroid shrinkage.

Okada A et al in 2009 reported a mean NPV ratio of 46.6%.

GornyKR et al in 2011 showed an immediate NPV Ratio of 45.4%.

LeBlang SD et al in 2010 reported in his sudy a mean NPV ratio of 55%.

Fibroid Shrinkage

In our study the mean shrinkage of fibroid by the end of 6 months was 32%.These value correlated well with the IMMEDIATE NPV RATIO.

The values were analysedwith chi square tests and were found to have a significant p value of <0.05.

Le Blang SD et al in 2010 reported in his study a mean fibroid shrinkage of 31%

LinYH,LeungTK,Wang HJ et al in 2009 showed that fibroid reduction by 6 months was 30.8%

RenXL Zhang J et al in 2007 reported a mean reduction in size of fibroid of about 49% by the end of 12 months.

Adverse Events Out of 30 patients who underwent MRgFUS in our study,five of them reported minor adverse effects like fever,back pain.

Two patients had fever which comprised of 6.6%. Three patients had back pain which comprised of 10% of patients.There was no incidence of skin burns,sciatic nerve palsy. Taran FA et al in 2009 reported in his study of incidence of 2.8% of fever.

Okada A et al in2009 reported postprocedure adverse events as follows:

Low back pain-8%,fever-6%,skin burns-1%,vaginal discharge-8%. Le Blang SD et al in 2010 showed that the incidence of minor sin burns was 2.5% and sciatica was 1.2%.

Any Additional Treatment

Among 30 patients in our study ,two of them opted out and went in for hysterectomy due to persistent symptoms especially the mass effect since the size of uterus was more than 16 weeks.This comprises of 6.6%.The hysterectomy specimen showed vast areas of necrosis. Taran FA et al in2009 reported a treatment failure rate of 3.7% Okada A et al showed that the rate of alternative treatment by the end of 12 months was 5%. Fenessey FM et al in 2007 showed that 28% sought alternative treatment . Gorny KR et al in 2011 reported that additional procedures for fibroid related symptoms within 1 year was 6.2%..

Summary:

- The sample studied was 30 women with symptomatic fibroids.
- Of these 19 had single fibroids and 11 had multiple fibroids.
- 22 were of low intensity and 8 were of high intensity fibroids on T₂ weighted MR images.
- There was a statistically significant decline in the symptom severity as per the symptom severity scoring for menorrhagia,dysmenorrhea,pressure symptoms and mass effect and discomfort.
- There was a stistically significant improvement in the mean hematocrit.Te mean hematocrit increased from 28.4 to 33.07 wih a significant p value of <0.001.
- The mean NPV ratio attained in our study was 48.63+14% .
- The mean fibroid shrinkage attained by 6 months was about 32% which correlated well with the immediate NPV Ratio with a significant p value <0.001.
- Factors influencing NPV ratio were found to be signal intensity of fibroids,number of fibroids and any interference in the pathway of the ultrasound

VI. Conclusion

Although hysterectomy has been the traditional treatment for uterine leiomyomas, there has been an upward trend towards the use of conservative ablative therapies with and without image guidance.

MRgFUS has been tested and approved by the FDA and is a very successful noninvasive therapy particularly in those who demand a minimum treatment recovery time.

From our study, there is evidence of improvements in the symptoms in patients treated with the MRgFUS, particularly for those presenting with symptoms of menorrhagia and dysmenorrhea. The symptom relief is sustained till one year.

In respect of safety, MRgFUS resulted in very minor adverse events like fever, abdominal discomfort, back pain. There were no serious complications.

The major benefits to the society are:

- Uterus sparing NonInvasive therapy for Fibroids
- Fast Outpatient Procedure
- High patient compliance
- Short recovery time
- Safe and effective procedure
- No Anaesthesia, No radiation, No scars, No hospital stay
- Walk-in & walk out procedure.

Thus MRgFUS therapy provides a potentially new noninvasive and effective treatment of fibroids. The total lack of ineffectiveness and the fact that it is performed as an outpatient procedure makes it very attractive for patients.

Limitations Of Our Study:

- Smaller sample size
- This sample population does not represent the true population.
- Follow up period is 12 months and hence durability of symptoms could not be proved beyond 12 months.
- Moreover there is no control group and whatever biases that may have existed in the patient selection is not known.

Nonetheless the results are encouraging and further evaluation with different protocols is definitely warranted.

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