SCALENE ASIA PACIFIC SDN BHD

ROTATIONAL FIELD QUANTUM NUCLEAR MAGNETIC RESONANCE (RFQMR) IN TREATMENT OF OSTEOARTHRITIS OF THE KNEE JOINT

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PROJECT SUMMARY

1. Title of the Project	:	Rotational Field Quantum Nuclear Magnetic Resonance (RFQMR) In Treatment of Osteoarthritis of the Knee Joint
2. Date of initiation	:	Jan 2004
3. Date of completion	:	Jul2006
4. Aim & Objective of the Project in brief	:	To evaluate the effects of RFQMR exposure to cartilage in the knee joint, stimulate chondrogenesis and treat osteoarthritis of knee joint.
5. Date of Submission of Report	:	11 Aug 2006
6. Conclusions & Recommendations	:	Contained in the text.

PHASE I
CLINICAL TRIAL

Phase I - clinical trial of RFQMR in treatment of OA of the knee joint

Materials and method for Phase I clinical trial

Thirty-five patients of osteoarthritis were treated with RPQMR focused on both knees for one hour every day for 21 days. They were evaluated before, immediately post treatment and one month after treatment with the Knee Society Scoring System. For the purpose of statistical analysis, each knee was taken as one case. Treatment effect measured as Pain Score (P), Range of Movement (ROM), Total Knee Score (TKS) and Functional Knee Score (FKS).The knee society score was analysed. According to the knee society scoring, pain has a maximum score of 50 for 'no pain'. The TKS and the TFS have a maximum score of 100 being 'the best'. The ROM has a maximum of 25 indicating 'normal or maximum' range of movement.

Knee society rating system

A new total knee rating system has been developed by The Knee Society, to provide an up-to date more stringent evaluation form. The system is subdivided into a knee score that rates only the knee joint itself and a functional score that rates the patient's ability to walk and climb stairs. The dual rating system eliminates the problem of declining knee scores associated with patient infirmity.

The Knee Society considered all the commonly used existing rating systems. By consensus it was agreed that the knee rating and the functional assessment should be separate. With regard to the knee assessment, it was decided that only the three main parameters of pain, stability and range of motion should be judged and that flexion contracture, extension lag and misalignment should be dealt with as deductions.

Thus, 100 points will be obtained by a well-aligned knee with no pain, 125 degrees of motion, and negligible anteroposterior and mediolateral instability. Patient function considers only walking distance and stair climbing, with deductions for walking aids. The maximum function score, which is also 100, is obtained by a patient who can walk an unlimited distance and go up and down stairs normally.

The form itself is largely self-explanatory: 50 points are allotted for pain, 25 for stability, and 25 for range of motion. Walking ability is expressed in blocks (approximately 100 meters). Stair climbing is considered normal if the patient can ascend and descend stairs without holding a railing.

Knee Society Clinical Rating System has adequate convergent construct validity. The other knee scoring systems such as The Western Ontario and McMaster University Osteoarthritis index (WOMAC) and the Medical Outcomes Study Short Form-36 (SF-36) are more responsive measures of outcome of total knee arthroplasty. The Knee Society Clinical Rating System is less labor-intensive for researchers to use and this instalment removes observer bias from the study design[95]

Results of Phase I clinical trial

There was highly significant improvement in Pain Score, Total Knee Score, Total Functional Score, ROM and force of extension as measured by Dynamometry immediately after the treatment vis-à-vis pre treatment values and this improvement persisted when evaluation was repeated after one month.

Pain

Every patient showed improvement after the course, of treatment. In all the cases there was a significant abatement of pain after the third or fourth day of treatment and the pain progressively reduced during the course of the exposure to RFQMR.

Range of Movement

The range of movement increased progressively in every patient.

Dynamometry

Dynamometry was done on all the patients to assess the load bearing capacity of the knee joint. After treatment with RFQMR, most patients could push 4 to 5 times the weight they could push before the treatment, indicating that the power of the leg from the thigh to the ankle as revealed by the extension pressure of the whole leg had improved considerably. In other words, they had greater control over their knee joint.

Total Knee Score and Total Functional Score

TKS and TFS improved spectacularly in all the patients who were able to walk comfortably for considerable distances at the end of the treatment.

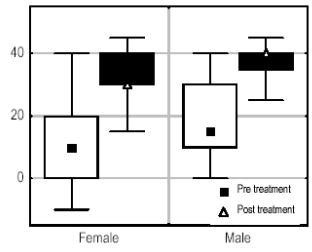


Fig 3 : Pain Score

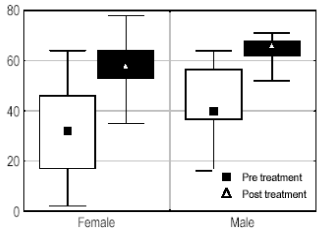
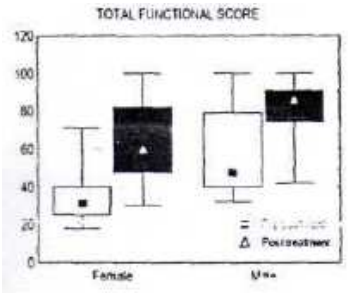


Fig 5: Total Knee Score



PHASE II

CLINICAL TRIAL

Phase-II clinical trial of RFQMR in treatment of OA of the knee joint

The quantitative assessment of osteoarthritis by cartilage thickness has now become possible, thanks to science of imaging. The potential of MRI approach for knee osteoarthritis evaluation is obvious, as image acquisitions are noninvasive and non-radiant, providing a clear advantage over arthroscopy and fluoroscopy. Moreover, the MRI quantification system makes possible highly reliable quantification of cartilage thickness. This technology enables the assessment of the intra-individual variability of cartilage thickness. This technology is critical for analysis of disease progression over time and reduces the number of patients required in clinical trial. It also improves retention of the patients and reduces the overall cost and the length of clinical trial. Recent studies performed on human specimens and data on cartilage thickness measurements using MRI compared with corresponding histological sections indicate a very good magnetic resonance/anatomic correlation[117-120]

The present phase II study has been designed with an objective to observe the effect of RFQMR therapy on various joint parameters and cartilage thickness

195 random subjects, with radiologically confirmed severe osteoarthritis were recruited for the study. Patients with pacemakers or surgical implants or any history of cancer were excluded: Assessment of the knee joint was done using both objective and subjective data. Objective data was obtained from X-rays, Ultrasonography and MRI. The condition of the knee joints was first assessed by X-Ray and ultrasound examination at the Department of Radiology, Institute of Aerospace Medicine (IAM), Indian Air Force (IAF), Bangalore. Ultrasonography was used to detect the presence of effusion in knee joint, to plan the dosage and map the region of interest to aid precise focusing of RFQMR beams.

Physical parameters such as height, weight, thigh girth, length of tibia, alignment and stability and goniometric measurements were carried out. Goniometric measurements included evaluation of flexion, range of movement, extension lag, medial lateral and anterior-posterior stability. Subjective factors such as pain and other disabilities were assessed by implementing the widely accepted Knee Society Clinical rating system. [120]Cartilage thickness was measured pre and post treatment by MRI. Magnetic resonance acquisitions were used for measuring cartilage thickness that is easily reproducible by any conventional magnetic resonance machine with 1.5 tesla capabilities. The method relies on a simple three-dimensional (3-D) co-ordinate transformation of tibial and femoral cartilage data to provide standardised and easy-to-use thickness maps. The MRI sequence used is Proton Density T-2 weighted with fat- suppressed gradient-echo sequences. [92, 93]The point selected for measurement of cartilage thickness is taken in the line of tibial spine on the medial tibial condyle. Clinical and subjective data was obtained from the internationally accepted Knee Society Scoring system. The assessment was done both pre and post exposure. The data was fed into the computer at the Center for Advanced Research and Development (CARD) and the scores were recorded as per the International Knee Society scoring system.

Written informed consent as approved by the Institute's Ethics Committee was obtained from all the subjects. The knees of the subjects were exposed to Multi-frequency Narrow Focused Quantum Magnetic Resonance using 'Cytotron' everyday for 30 minutes for 21 successive days. The affected joint (knee) was placed inside QMR machine and the desired exposure characteristics (like the cartilage to bone gap, skin to cartilage distance, Name, age, gender, height and weight etc) were fed into the computer, thereafter, the beams from 288 specially designed Mn-Pb-Cu guns were focused on the joint target tissue at an angle of 11.25 degrees, with the aid of subject's X-rays and MRI. After 21 exposures,

the patients were re-assessed using Total Knee Score (TKS), Total Functional Score (TFS) measurements on MRI. Cartilage thickness (CT) was measured pre and post treatment by MRI. To avoid any bias in the present trial, the cartilage thickness measurement has been done by various radiologists randomly using the technique vide supra and not by the principle investigator. The assessment was repeated after completion of the treatment at 90 days also.

The subjects did not feel any pain or discomfort during the treatment; the field strength on the body surface was periodically measured by the computer.

Statistical Analysis

For the purpose of statistical analysis, each knee was taken as one case and 404 cases were considered in total. Normality of the distribution was examined using Kolmogoroy-Smirnov test. The effect of RFQMR treatment was assessed and compared between right knee and left knee. The treatment effects were measured as Pain Score (P), Range of Movement (ROM), Total Knee Score (TKS), Total Functional Score (TFS) and Cartilage Thickness (CT) and compared for both the knees against the three treatment period (pretreatment, 21 days, and 90 days). Comparison of the these variables between the treatment periods: pretreatment & 21 days and pretreatment & 90 days for both right and left knees was done using paired student's T test. One Way ANOVA and Tukey Post hoc tests was used to compare the effect of treatment period for both right and left knee separately. Two way ANOVA and post hoc tests were used to compare the significance of the treatment against both the knees when considered together. All the values were given as mean ± SEM (unless stated otherwise) and the value of $p<0.005$ was considered as statistically significant.

RESULTS

RESULTS

The Knee Society Score consisting of P, TKS, TFS and ROM were analysed and CT was measured. According to the Knee Society Scoring, P has a maximum scale of 50 for 'no pain'-, the TKS has a maximum scale of 100 being 'the best', TFS also has a maximum scale of 100 and ROM has a maximum of 25 indicating 'normal or maximum' range of movement.

Demographic attributes

Amongst the study population, females comprised of 68% as compared 10 32/o of (Table 1). The mean age of the sample population was found out to be 64.23 ± 0.69 yrs (ranging from 29-85 years}.

Table 1. Distribution of the study patients

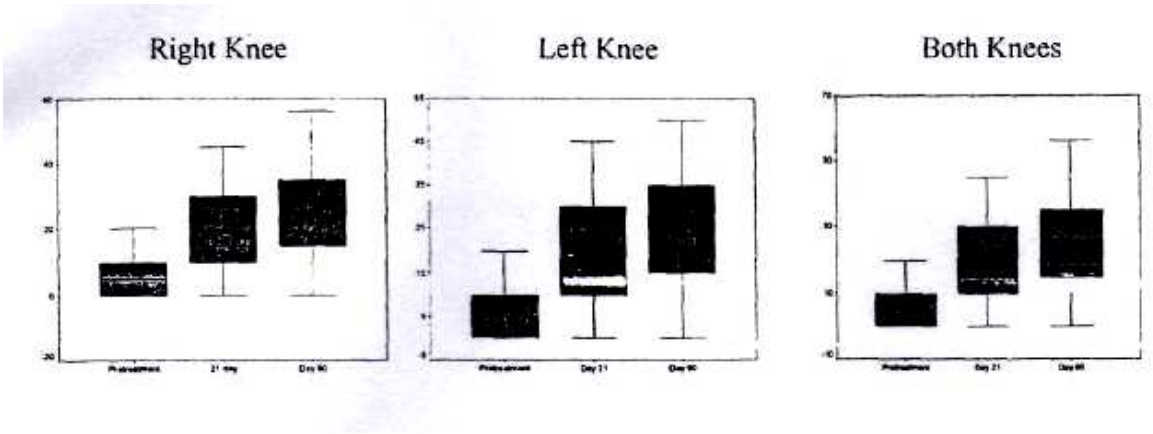
Sex	Number	Percentage
Males	65	32.2
Females	137	67.8
Total	202	100

Pain

The values indicated against 'Pain' are inversely proportional to the degree of pain. Zero representing severe pain, restricting mobility. Almost every patient showed improvement after the course of treatment. There was a significant abatement of pain after the fifth or sixth day of treatment and the pain in both of the right and left knees reduced progressively during the course of exposure to RFQMR. (Fig.l). Out of 202 (left knee), 50.53% had pain score of 0 at the start of treatment. After 21 days of treatment 29.25% had pain score of 10 and 26.59% had pain score of 20. After 90 days 50.53% had pain score of 40. Out of 202 (right knee), 51.59% had pain score of 0 at the start of treatment. After 21 days of treatment 29.25% had pain score of 10 and 26.59% had pain score of 20. After 90 days 50.53% had pain score of 40. The mean pairi values for both right and left knees when considered individually as well as together during the course of treatment are indicated in tables 2, 3 and 4 respectively. The mean pain score at the beginning of the treatment was 6.54 (±0.66) and 6.77 (±0.66) for left and right knee

respectively. The mean pain score significantly increased to 18.92 (±0.87) and 19.15 (±0.87) after 21 days and 28.77 (±0.95) and 28.83(±0.97) after 90 days for left and right knee respectively.

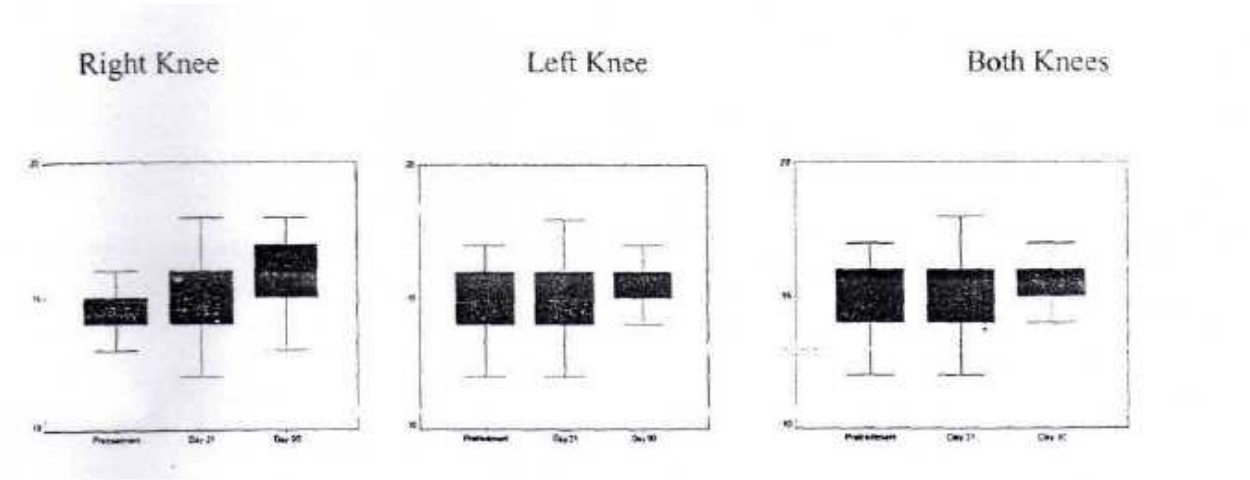
Figure.1 Pain Score



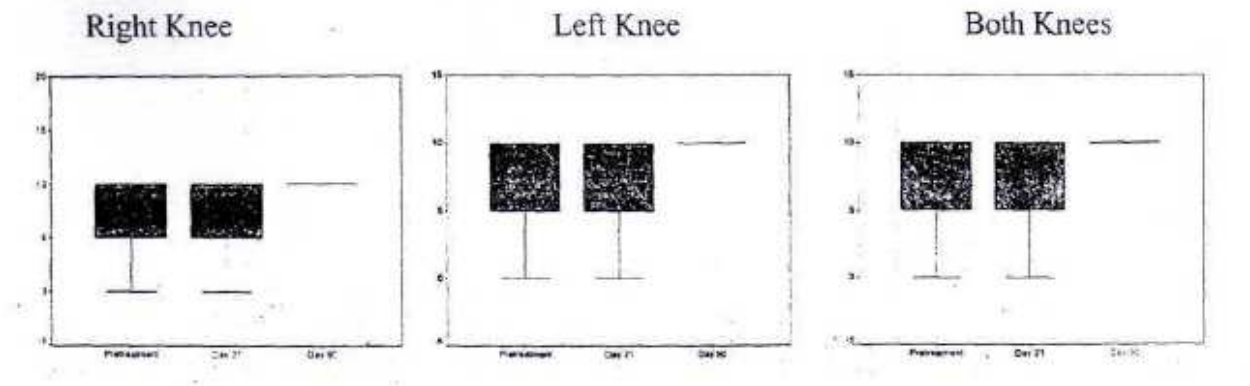
Range of Movement

ROM increased progressively in every patient. The figure shows the change in the ROM for both knees during the course of treatment (Fig. *2).* The range of movement score of knee joint increased significantly from 14.17 (±0.14) to 14.83 (±0.14) and 14.33. (±0.12) to 15.06 (±0.11) for left and right knee respectively after 21 days of treatment. After 90 days, the ROM scores for both knees further improved to 16.17 (±0.51) and 16.35 (±0.51) respectively. Out of 202 subjects (left knee), 74.46% had ROM score of 15 at the start of treatment. After 21 days of treatment 76.59% had ROM score of 15. After 90 days 58.51% had ROM score of 16. Out of 202 subjects (right knee), 34.57% had ROM score of 15 at the start of treatment. After 21 days of treatment 47.87% had ROM score of 16 and after 90 days 63.82%-had ROM score of 16. Further the effects of Medial Lateral (ML) and Anterior Posterior (AP) stability are also indicated. The mean ROM, ML and AP values for both right and left knees, when considered individually as well as together ^during the course of treatment, are indicated in tables 2, 3 and 4 respectively. There was no significant change in the AP values at all time intervals during the course of treatment. Medial lateral score of knee joint increased significantly from 6.28 (±0.18) to 7.08 (±0.20) and 6.15 (±0.18) to7.03 (±0.20) for left and right knee respectively after 21 days of treatment. After 90 days, the ROM scores for both knees further improved to 9.87 (±0.57) and 9.90 (±0.58) respectively.

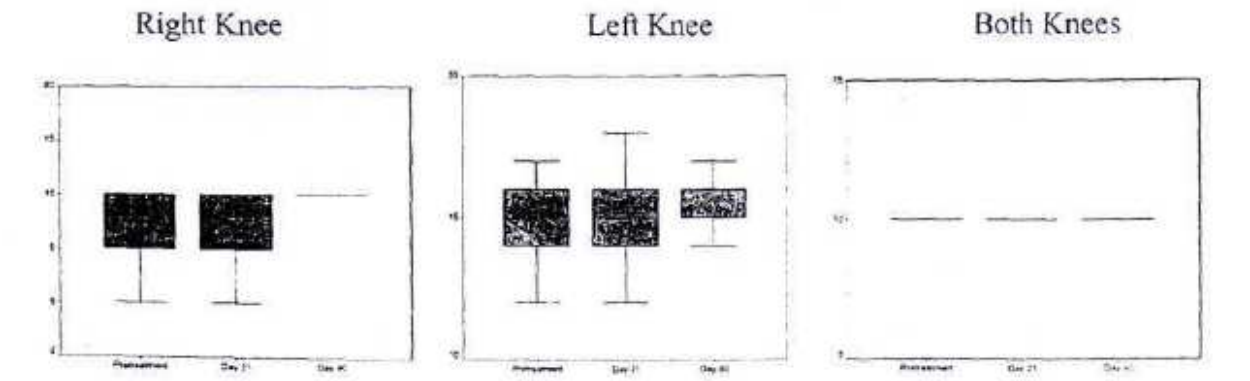
Figure.2 Range of Movement



Medial/Lateral Score



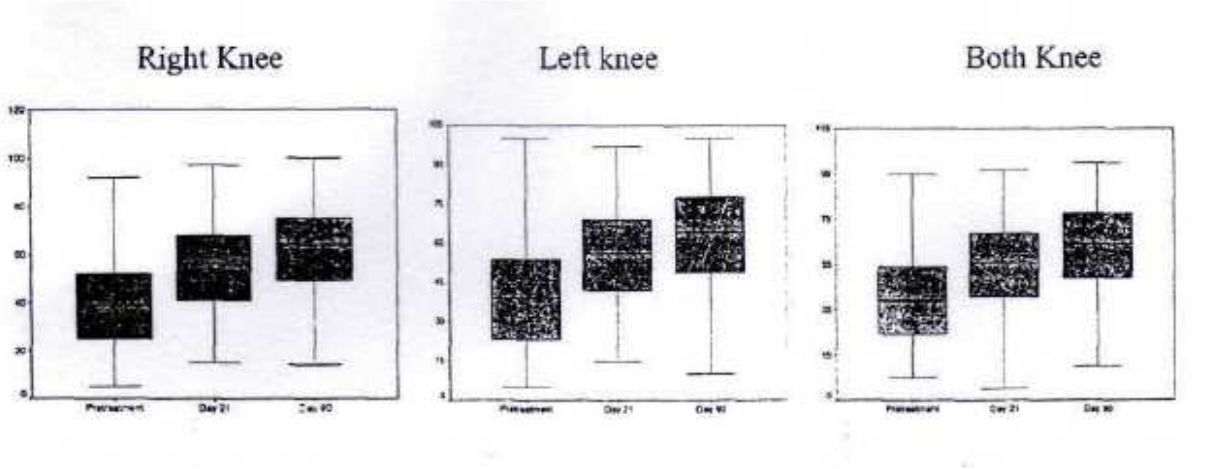
Anterior Posterior Score



Total Functional Score

TFS improved significantly in all the patients, who at the end of the treatment were able to walk comfortably for considerable distances (Fig.3). The mean TFS values for both right and left knees, when considered individually as well as together during the course of treatment, are indicated in tables 2, 3 and 4 respectively. Out of 202 subjects (left knee), 19.68% had functional score of 47.5 at the start of treatment. After 21 days of treatment 21.27% had functional score of 57.5 and 18.08% had functional score of 47.5. After 90 days 12.23% had functional score of 70. Out of 202 subjects (right knee), 34.57% had functional score of 32.5 at the start of treatment. After 21 days of treatment 19.68% had functional score of 47.5 and 17.55% had pain score of 47.5. After 90 days 12.76% had functional score of 60.

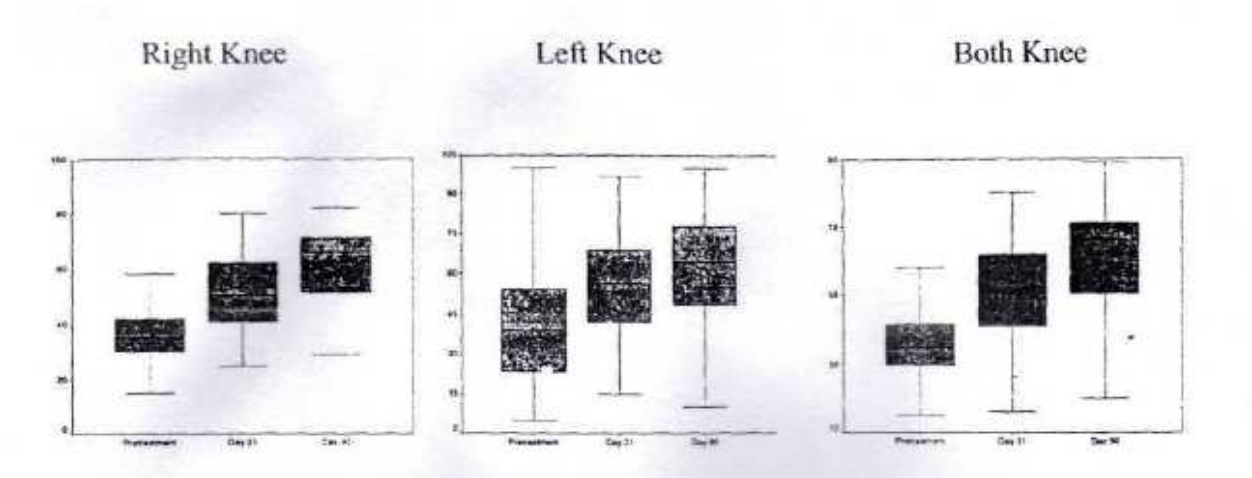
Figure 3. Total Functional Score



Total Knee Score

TKS improved significantly in all the patients, who were able to walk, comfortably for considerable distances at the end of the treatment (Fig. 4). The mean TKS values for both right and left knees when considered individually as well as together during the course of treatment are indicated in tables 2, 3 and 4 respectively. Out of 202 subjects (left knee), 57.44% had total knee score of 32.5 at the start of treatment. After 21 days of treatment 34.04% had total knee score of 47.5 and 23.40% had total knee score of 37.5. After 90 days 29.78% had total knee score of 70. Out of 202 subjects (right knee), 57.44% had total knee score of 32.5 at the start of treatment. After 21 days of treatment 34.04% had total knee score of 47.5. After 90 days 28.72% had total knee score of 70.

Figure 4 Total Knee Score



Cartilage thickness

There was a significant increase in cartilage thickness after RFQMR therapy (Fig. 5). The mean CT values for both right and left knees, when considered individually as well as together during the course of treatment, are indicated in tables 2, 3 and 4 respectively. The effect of the treatment can be seen objectively by Cartilage thickness measurement on MRI. There is significant improvement in the thickness of the cartilage. The mean thickness of cartilage increased from 0.67 (±0.02) to 0.66 (±0.02) and 3.25 (±0.74) to 2.71 (±0.58) in left and right knee joint respectively. Out of 202 subjects (left knee), 50.0% had cartilage thickness of 0.75mm at the start of treatment. After 90 days of treatment 51.06% had cartilage thickness of 1.00 mm. Out of 202 subjects (right knee), 74.46% had cartilage thickness of 0.5mm at the start of' treatment. After 90 days of treatment 51.06% had cartilage thickness of 1.00 mm. Six patients showed no change.

Figure 5 Cartilage Thickness

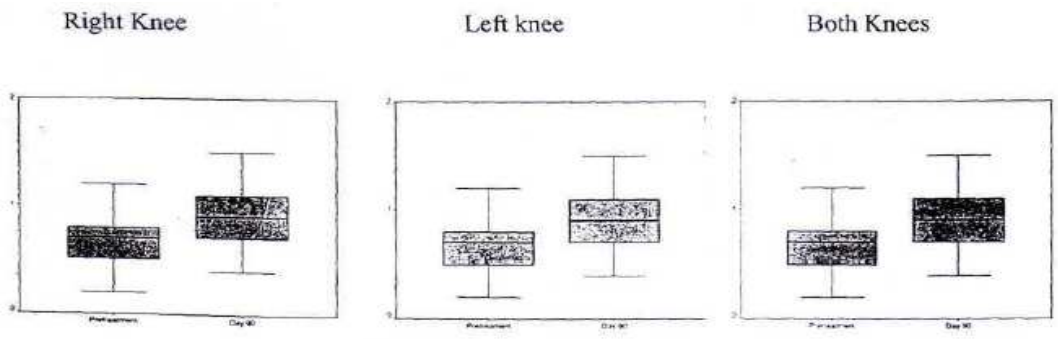


Table 2. Effect of RFQMR treatment on various parameters of right knee at different treatment periods

	Treatment period Pretreatment	21 days	90 days
Parameters	Mean ± SEM	Mean ± SEM	Mean ± SEM
Pain	6.77 ±0.66	19.15 ±0.87*	28.83 ±0.97[a]
ROM	14.33 ±0.12	15.06 ± 0.11*	16.35 ± 0.51 [a]
ML	6.15±0.18	7.03 ±0.20*	9.90 ± 0.58 [a]
AP	10.00 ±0.00	10.00 ± 0.00	11.10 ± 0.53
TFS	41.39 ± 1.47	55.14 ± 1.44*	60.74 ± 1.66[a]
TKS	37.37 ± 0.7	50.88 ±0.91*	59.85 ± 1.28[a]
CT	0.66 ± 0.02	-------	2.71 ± 0.58 [a]

Each value represents Mean± SEM of 195 observations. * represents p<0.001 between pretreatment and post treatment (21 days); a represents p<0.001 between pretreatment and post treatment (90 days).

Table 3. Effect of RFQMR treatment on various parameters of left knee at different treatment periods

	Treatment period Pretreatment	21 days	90 days
Parameters	Mean ± SEM	Mean ± SEM	Mean ± SEM
Pain	6.54 ± 0.66	18.92 ± 0.87*	28.77 ± 0.95[a]
ROM	14.17 ± 0.14	14.83 ±0.14*	16.17 ± 0.51[a]
ML	6.28 ±0.1 8	7.08 ± 0.20*	9.87 ± 0.57[a]
AP	10.00 ±0.00	9.95 ± 0.05	11. 24 ± 0.62
TFS	41.20 ±1.47	55.08 ±1.45*	61.19 ± 1.67[a]
TKS	37.11 ± 0.74	50.24 ±0.92*	59.93 ± 1.29[a]
CT	0.67 ± 0.02	-------	3.25 ± 0.74 [a]

Each value represents Mean± SEM of 195 observations. * represents p<0.001 between pretreatment and post treatment (21 days); [a] represents p<0.001 between pretreatment and post treatment (90 days).

Table 4. Effect of RFQMR treatment on various parameters at different treatment periods

	Treatment period		
	Pretreatment	21 days	90 days
Parameters	Mean ± SEM	Mean ± SEM	Mean ± SEM
Pain	6.65 ± 0.46	19.04 ± 0.61*	28.23 ± 0.65 [a]
ROM	14.25 ±0.09	14.94 ±0.09*	15.58 ± 0.07 [a]
ML	6.22 ± 0.13	7.05 ± 0.14*	8.67 ± 0.13 [a]
AP	10.00 ± 0.00	9.97 ± 0.03*	9.96 ± 0.29 [a]
TFS	41.29 ± 1.03	55.11 ± 1.02*	63.86 ± 0.97 [a]
TKS	37.24 ± 0.51	50.56 ± 0.65	62.53 ± 0.62 [a]
CT	0.67 ± 0.13	-------	1.03 ± 0.13 [a]

Each value represents Mean± SEM of 195 observations. * represents $p<0.001$ between pretreatment and post treatment (21 days); a represents $p<0.001$ between pretreatment and post treatment (90 days).

DISCUSSION

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CONCLUSION

Discussion

Hyaline cartilage, which forms a cap on the long bones and the inner surface of the patella in the knee joint, is constantly produced from the chondroblastic layer. This process is continuously activated by the constant use of the joint. Disuse atrophy, which is a well known biological phenomenon, applies specially to the knee joint since it is the most important load bearing joint in the human body. The disuse of the joint shows its effect in the form of degeneration of cartilage in the articular surfaces of the bones in the knee joint. Overuse, constant impact and injuries lead to early onset of degenerative change. The rate and extent of degeneration depend on the degree of disuse and the process of aging in the individual. Consequently, older persons exhibit a rapid progress of osteoarthritis because the regenerative capacity of the chondroblasts is progressively reduced with age and sedentary habits. Joint pain sets in, this in turn reduces mobility causing disuse atrophy of the supporting muscles leading to increased loading and the cartilage degenerates further and thus a negative cycle sets in. Hence, the earlier the disease is diagnosed and treated, the greater is the effectiveness in the activation and regeneration of the cartilage.

RFQMR stimulates the chondrocytes and initiates the regeneration process, reduces pain and increases mobility of the joint, thus reversing the negative cycle. This study demonstrates that use of RFQMR treatment for osteoarthritis decreases pain, increases mobility, stability and power of the knee joint and helps normalise the life of an osteoarthritic patient. The patients were followed up after 30 days of the treatment and showed no deterioration in their Knee Scores or pain status.

Conclusion

(a) Younger subjects had earlier subjective and objective relief, which was almost complete at 21 days.
(b) Subjects with lower pain scores (i.e. more pain) showed greater subjective improvements.
(c) No gender difference to treatment was seen.
(d) No significant difference in status at the end of treatment and at one month was noted.
(e) Exposure of the knee cartilage to RFQMR is an effective method of treatment and can be a new line of treatment for osteoarthritis.