CYTOTRON®

Tissue Regeneration Therapy®

...a QMRT® approach to Chondrogenesis

...the QMRT® approach

Like any other tissues, bone and cartilage are constantly being built up and broken down by various metabolic and physical influences. The major stimulus for the formation of bone and cartilage is a signal that is generated when these structures are subjected to tension or compression. This signal is also impaired following joint injury due to trauma or diseases such as Osteoarthritis.

CYTOTRON® produces the required signal to initiate regenerative activities by resetting the protein pathways that has ceased to restart, therefore regenerating the degenerated cartilage, this leads to growth of new cartilage tissue or chondrogenesis, thus relieving chronic pain and disability of the joint without surgical intervention.

Cell signalling

Trans Membrane Potential (TMP) is a well known cellular signaling pathway that regulates the synthesis of various proteins at the appropriate time in living cells. Many non-communicable illnesses like cancer, heart diseases and degenerative disorders like cartilage loss and different kinds of inflammation are also linked to disturbances in protein transcription process (Cone CD., Variation of trans-membrane potential as a basic mechanism of mitosis control: Oncology: 1970; 24:438-470). It was thought during the last few decades that if an appropriate method can be developed to alter TMP in a controlled manner, most of these disorders that are protein linked could be treated and cured.

CYTOTRON® based on an innovative technology that applies low spectrum (non ionising and non thermal), radio frequency (RF) carrier modulated with therapeutic signals in the presence of high instantaneous magnetic field to induce controlled therapeutic quantum magnetic resonance. This is applied in regenerative and degenerative medicine by altering cellular signalling pathways thus inducing apoptosis or controlled mitosis in tissue regeneration.

Generically referred to as Rotational Field Quantum Magnetic Resonance Therapy (or simply **QMRT®**), CYTOTRON® delivers complex modulated beams in the radio frequency band, with a near field multi - harmonic delivery system using specialized helical antennae. When appropriately controlled, it can alter the TMP to specific requirements like stimulation and synthesis of the HSP group of proteins in cartilage regeneration or the P53 group of proteins in case of malignant diseases. The delivered instantaneous mode wide or narrow spectrum magnetic and RF modulations are highly cell and site specific based on proton density, permittivity, permeability and depth of penetration of the target tissue.

Clinical efficacy of CYTOTRON® treatment

CYTOTRON® - **QMRT®** is the latest treatment option available for cartilage regeneration which when adopted may avoid or postpone surgery. This treatment requires no medication, is less expensive and a sustainable solution for cartilage loss with no known adverse effects. The treatment method involves exposure of the affected joint to the modulated radio beams that is generated by CYTOTRON®. Each exposure last about 30 to 60 minutes everyday for about 21 days. Special MRI - Proton Density sequence is required for dosimetry and diagnostic MRI are used to evaluate the patients before the treatment, and 90 days post treatment to examine efficacy and the extent of cartilage growth. This pre and post evaluation is carried out using 3D FLASH sequence with water excitation - a gold standard in cartilage delineation and assessment.

In a clinical trial conducted on 380 knee joints, as part of technology evaluation programme, as required by Medical Devices Directive (MDD), significant effects were observed. The study has proved that the increase in cartilage thickness is only due to CYTOTRON® therapy ($F=770.802$; $P=0.00E+00$).

Statistically, the data was examined for normality of distribution using Shapiro Wilk's 'W' statistic. To compare the physical attributes of subjects, an unpaired 't' test was used. Correlation coefficients were calculated between increase in the thickness of cartilage and physical attributes to examine if latter were influencing the former. For the rest of data (thickness of cartilage, pain, range of movement, Total Knee Score (TKS) and Total Functional Score (TFS)), a three way analysis of variance (ANOVA) was employed with gender and laterality as grouping variables. Correlation coefficients were computed, in the data pooled for two genders, to find out association between growth of cartilage and physical attributes. All data are presented as mean $\pm$ SD. Level of significance was set at $P<0.05$. However, exact significance is annotated in tables presenting the outcome of analysis.

Even though the data for pain, range of movement, TKS, TFS and stability exhibited departures from the assumption of normality, we persisted with the application of ANOVA due to the large sample size and relative insusceptibility of ANOVA to these violations.

Results and outcome*

A significant effect of the treatment was observed on all the variables studied (refer table 4). There were no gender based differences in the responsiveness to treatment as evident from an insignificant interaction effects between gender and laterality (refer 1x3; table 4). Similarly, there was no laterality effect in response to treatment as evident from an insignificant interaction of laterality with treatment (refer 2x3; table 4). Increase in thickness of cartilage (difference between the pre and post treatment values) had no worthwhile correlation with any physical attributes (refer table 5). Thus increase in cartilage thickness is due to the effect of **QMRT®** treatment only.

Table 1: Physical attributes of the subjects

	Age (yrs)	Height (cm)	Weight (kg)
Female (n=59)	63 ± 9	155 ± 7.1	70 ± 12
Male (n=131)	67 ± 10	167 ± 7.2	76 ± 12
Pooled (n=190)	64 ± 9	159 ± 9	72 ± 12

Table 2: Effect of treatment on cartilage thickness and functional knee status (right knee)

	Female		Male		Pooled	
	Before	After	Before	After	Before	After
Cartilage Thickness	0.675 ± 2.48	0.913 ± 0.242	0.628 ± 0.265	0.884 ± 0.235	0.660 ± 0.253	0.904 ± 0.239
Pain	8.7 ± 10.3	18.4 ± 13.4	10.6 ± 11.5	19 ± 11.8	9.3 ± 10.7	18.6 ± 12.9
Movement Range	13.9 ± 2.2	14.8 ± 2.1	15 ± 1	15.7 ± 1.1	14.2 ± 2	15.1 ± 19
TKS	33 ± 13	45 ± 16	36 ± 14	45 ± 13	34 ± 13	45 ± 15
TFS	41 ± 20	48 ± 21	50 ± 25	55 ± 25	44 ± 22	50 ± 22

TKS = Total Knee Score TFS = Total Functional Score For statical comparisons, refer table 4.
Pain assessed based on knee society clinical scoring system. (50=No pain, 0=severe pain)

Table 3: Effect of treatment on cartilage thickness and functional knee status (left knee)

	Female		Male		Pooled	
	Before	After	Before	After	Before	After
Cartilage Thickness	0.676 ± 0.239	0.928 ± 0.240	0.659 ± 0.290	0.912 ± 0.277	0.671 ± 0.255	0.923 ± 0.252
Pain	8.6 ± 10.3	18.4 ± 13.3	10.6 ± 11.2	19.3 ± 11.7	9.2 ± 10.6	18.7 ± 12.8
Movement Range	13.9 ± 2.1	14.7 ± 2.1	14.5 ± 1.9	15.1 ± 2.4	14.1 ± 2.1	14.8 ± 2.2
TKS	33 ± 13	45 ± 16	35 ± 14	45 ± 13	34 ± 13	45 ± 15
TFS	41 ± 21	48 ± 20	50 ± 25	55 ± 25	44 ± 22	50 ± 22

TKS = Total Knee Score, TFS = Total Functional Score

Table 4: Results from statistical analysis (ANOVA)

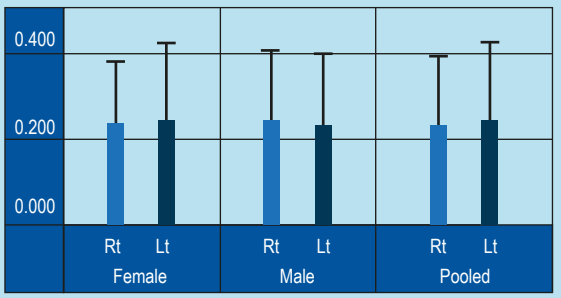
	Main Effect		
Variable	Gender [1]	Laterality [2]	Treatment [3]
Cartilage Thickness	F = 1.261, P = 0.262	F = 0.463, P = 0.497	F = 770.802, P = 0.0E+00
Pain	F = 0.74, P = 0.392	F = 0.06, P = 0.803	F = 99.64, P = 4.25E -19
Movement Range	F = 7.32, P = 0.007	F = 7.57, P = 0.007	F = 98.37, P = 6.49E -19
TKS	F = 0.51, P = 0.474	F = 0.18, P = 0.671	F = 120.34, P = 5.85E -22
TFS	F = 6.25, P = 0.013	F = 0.23, P = 0.630	F = 0.23, P = 0.630

Interaction Effect				
Variable	[1x2]	[1x3]	[2x3]	[1x2x3]
Cartilage Thickness	F = 0.079, P = 0.778	F = 0.318, P = 0.573	F = 0.217, P = 0.624	F = 0.375, P = 0.541
Pain	F = 0.44, P = 0.510	F = 0.41, P = 0.523	F = 0.33, P = 0.564	F = 0.13, P = 0.715
Movement Range	F = 4.46, P = 0.036	F = 2.33, P = 0.129	F = 1.17, P = 0.281	F = 0.51, P = 0.476
TKS	F = 0.91, P = 0.342	F = 1.01, P = 0.315	F = 1.87, P = 0.173	F = 0.12, P = 0.728
TFS	F = 0.00, P = 0.971	F = 0.92, P = 0.339	F = 0.09, P = 0.766	F = 0.03, P = 0.873

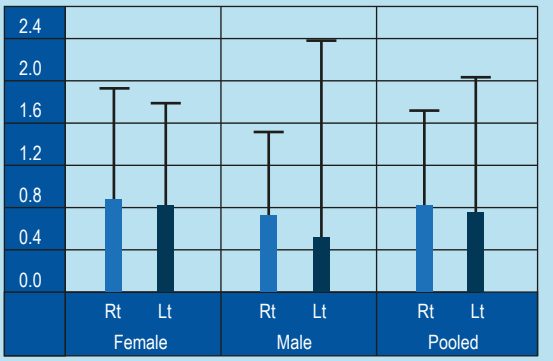
Table 5: Correlation of physical attributes with the increase in cartilage thickness.

Attributes	Increase in thickness of cartilage of knee joint	
Age (Yrs)	- 0.011	0.052
Height (Cm)	0.031	0.015
Weight (Kg)	- 0.021	0.008

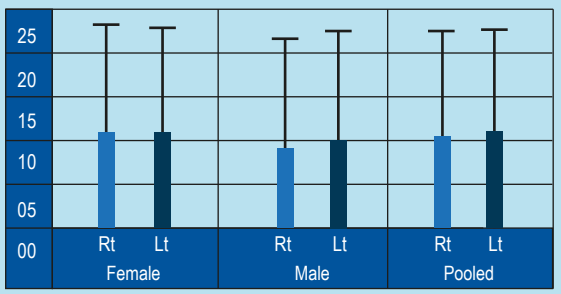
Change in thickness of cartilage with treatment (values on 'y' axis are in mm). Error bars represent +1 SD for outcome of statistical analysis. Refer Table 4 .



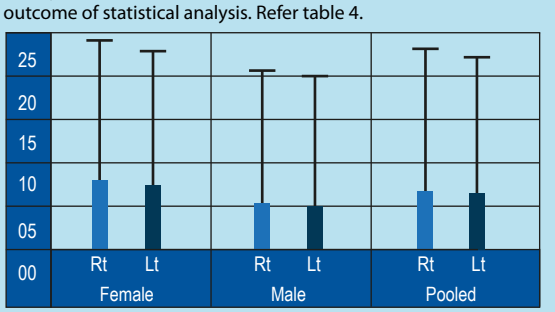
Change in range of movement with treatment (values on 'y' axis are in °). Error bars represent +1 SD for outcome of statistical analysis. Refer Table 4.



Change in total knee score with treatment. Error bars represent +1 SD forthe statistical analysis outcome. Refer table 4.



Change in total functional score. Error bars represent +1 SD for the outcome of statistical analysis. Refer table 4.

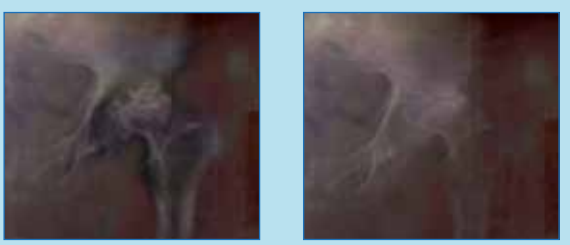


Physical attributes				
	Age (Yrs)	Height (Cm)	Weight (Kg)	N
Male	67 ± 10	167 ± 7.2	76 ± 12	59
Female	63 ± 9	155 ± 7.1	70 ± 12`	131
Pooled	64 ± 9	159 ± 9	72 ± 12	190

Increase in thickness of cartilage		
	Right	Left
Age (Yrs)	- 0.01	0.05
Height (Cm)	0.03	0.01
Weight (Kg)	- 0.02	0.01

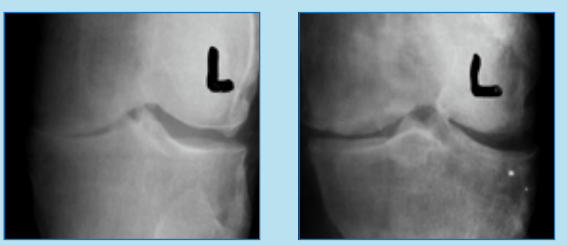
Note: Results stated above is on the specific device designated model; CYTOTRON® - RTE - 6040 - 864 GEN. This data is awaiting publication.

Chondrogenesis in Avascular necrosis



Hip - Pre | Hip - Post

Chondrogenesis in Osteoarthritis



Knee - Pre | Knee - Post

* Results stated above is on the specific device designated model; CYTOTRON® - RTE - 6040 - 864 GEN. This data is awaiting publication.

Conclusion

- Significant main effect, i.e. the increase in cartilage thickness, is due to the treatment only (F = 770.802; P = 0.00E + 00).
- There was no gender difference in the response to the treatment.
- There was no laterality effect in response to the treatment.
- Significant reduction in pain, increased range of movements, better joint stability.
- Significant improvement in general quality of life.
- "QMRT® is the only known modality that proves cartilage re-growth - and CYTOTRON® does it".

Technical Specification of CYTOTRON®

Classification: Class IIa Medical Device.

Indication of use: The Device is intended to be used for Regenerative and Degenerative Tissue Engineering i.e. it can be used for regenerating tissues in-situ and to cause degeneration of uncontrolled growth of tissues.

Regeneration of tissues the current indication is for use in protein linked degenerative disorders like Osteoarthritis enabling regrowth of tissue like articular cartilage.

Contraindications: Critically ill patients on life support system, pregnancy, patients unable to lie down for the duration of theraphy, Patients with electrically, Magnetically or mechanically activated implants. (e.g. cardiac pacemakers, Bio stimulators, Neuro stimulators, cochlear implants, hearing aids)

MRI Incompatible implants near the target region. E.g. intra medullary nail, intracranial aneurysm clips, stents, intra orbital metal fragments etc.

Patients with concomitant neoplastic disease especially chondrosarcoma.

Drug and other device interactions: The following group of drugs that use the same or similar cellular pathways as QMRT® may interact with the CYTOTRON® exposure; like Calcium Channel Blockers and Proton Pump Inhibitors, NSAIDs and Alkaloids (also food containing alkaloids) for all cellular regenerative protocol. Patients should be advised to take medication with different mode of action.

Ionizing radiations are known to damage multiplying (mitotic) cells. Hence exposure to X-ray or CT imaging of the affected joint should be avoided for atleast 12 weeks after therapy. However this will not impose any risk to the patient, in case imaging is inevitable, MRI may be advised.

Product Specifications

The power supply Cytotron must meet these specifications:

a. Voltage fluctuation+/- 10% or less
b. Voltage imbalance +/- 3% or less
c. Frequency variation +/- 4% or less
d. Voltage distortion THD = 10% or less

Recommended environmental specifications

Operating Temperature range 18°C to 30°C, Humidity range 10% to 75% RH, Atmospheric pressure 700 to 1060 hPa, Transport / Storage Temperature range 10°C to 80°C, Humidity range 10% to 90% RH, Atmospheric pressure 500 to 1060 hPa

Mode of usage: Continuous
Life of the equipment: Typically assessed at about ten years
Typical operating voltage: 230 V, 50 Hz, single phase
Maximum operating current: 12 Amps
Typical operating current: 6A
IEC classification: Type B, Class 1, IPX0
MDD classification: Class IIa
Target resolution: 11.25 degrees
Power supply type: Medical grade switch mode power supply complying with EN 60601-1, EN 60601-1-2
Frequency band: VLF, LF, HF and VHF radio bands

Instantaneous magnetic field strength: 1mT to 6T for the time duration 2.0µsec to10msec depends on the treatment and Dosimetry value.
E-Field: Broadband; average 100 dB V/m/MHz @ 4MHz
H-Field: Broadband; 20dB (below 1 kHz)
Broadband common mode current in control cables: 100dBmA/MHz @ 150 kHz
Fuses: Mains Fuse-12A, Isolation Transformer Fuse-2.5A

Laser Guiding System

Output: 625 to 680 nanometer wave length less than 5 mill watt, Complies with CFR Part 1040.10 and 1040.11 Class III A LASER application

QMRT Guns

Magnetic field

Type:	MF6040-L
Guns:	K- _ Ferrite type; Near Field; gain; 10dB
Typical voltage:	60 Volts
Typical current:	4 Amps

Radio frequency

Type of antenna:	Helical
Q factor of the antenna:	560
Antenna gain:	13 dB
Centre frequency:	68.4 MHz
3dB BW (Bandwidth):	±4 MHz
6dB BW (Bandwidth):	±10 MHz
Input impedance:	50 OHM
Input connector :	SMA

Physical Dimension

Cytotron device dimensions:	4500mm (L) x 1210mm (W) x 1600mm (H) Weight: approx. 1900 Kg
Central control unit dimensions:	1600mm (L) x 780mm (W) x 1455mm (H) Weight: approx. 200 Kg
Coating:	Powder coating/Paint and Lacquer coating body for scratch protection and prevent from corrosion
Patient weight:	Max. 157 Kg
Patient bed weight:	12.95 Kg (Part No: SCL-A-01-LB)
Earthing clip weight:	50 Gms (Part No: SCL-A-02-EP)
Patient transmission system: (Acrylic Sheet + Metal Frame)	22 Kg
Total bed safe working load:	170 Kg

Standard applied: BS EN 980:2008, BS EN 1041:2008, BS EN 62366:2008, IEC 60601-1, IEC 60601-1-1, IEC 60601-1-2, IEC 62304, ISO 9001:2008, ISO 13485:2003, ISO 14971:2007, ISO 14155-1:2003, ISO 14155-2:2003.

Approvals: ISO 9001:2008, ISO 13485:2003

Accreditations: ANAB, UKAS, CMDCAS

Product certification: Annex II of MDD 93/42/EEC as Amended by 2007/47/EC

* Owing to continuous development, specifications are subject to change without notice.

CYTOTRON®

A Breakthrough in Tissue Engineering

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