Study of rotating permanent magnetic field to treat steroid-induced osteonecrosis of femoral head

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Abstract Sixty New Zealand rabbit models with steroid-induced necrosis of femoral head were exposed to a rotating permanent magnetic field (RPMF) (group A1–2 h/d for one month and group A2–2 h/d for two months), and the changes of femoral head, blood viscosity, serum cholesterol, triglyceride, and pressure within the hip joint cavity were measured and statistically analysed compared to that of control group (B1 and B2) and sham group (C1 and C2). After RPMF treatment, the osteogenesis regeneration of the necrotic femoral head was markedly improved, as was shown by micro-CT. Blood viscosity, serum cholesterol, triglyceride, and pressure in the hip joint cavity were found significantly reduced. RPMF could affect various critical aspects in the course of femoral head necrosis, which will be a promising measure in the prevention and treatment of steroid-induced necrosis of femoral head, especially in the early stage.

Résumé 60 lapins de Nouvelle Zélande présentant une ostéonécrose de la tête fémorale induite par la cortisone ont été exposés à des champs magnétiques rotatoires (groupe A1–2h/d à un mois et groupe A2–2h/d à deux mois). Les

modifications de la tête fémorale de la viscosité sanguine du taux de cholestérol et des triglycérides ainsi que les pressions articulaires de la hanche ont été mesurées et analysées statistiquement. Ceci a permis de les comparer à un groupe contrôle (B1 et B2) et à un groupe leurre (C1 et C2). Après traitement par champs magnétiques, la régénération osseuse de la nécrose est améliorée avec une diminution de la viscosité sanguine, du taux de cholestérol et des pressions intra articulaires. Les champs magnétiques peuvent modifier de façon significative l'évolution de la nécrose de la tête fémorale et permettront peut être de prévenir et de traiter les nécroses de la tête fémorale secondaire à un traitement corticoïde surtout à un stade précoce.

Introduction

Osteonecrosis of the femoral head (ONFH) is a clinical entity characterised by the death of trabecular bone and bone marrow in the femoral head with resultant morbidity and disability of the hip joint. ONFH typically affects young patients in their mid-thirties and often leads to femoral head collapse with hip pain and loss of hip joint function if left untreated [16]. The prevalence of ONFH is assumed to be 10,000–20,000 annually in the United States and 2,500–3,000 in Japan [9]. ONFH always occurs in young and relatively active patients, for whom joint preservation surgery is often required in treatment, and this may include core decompression [3], vascularised and nonvascularised bone-grafting [12] and osteotomies [5] to hemiarthroplasty [13], total hip arthroplasty [16], percutaneous drilling and metal-on-metal total hip resurfacing [2].

Several theories have been developed to explain the causes of ONFH—artery disorder theory, venous return

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disorder theory [21], fat embolus theory [7, 10], injury to the wall of a vessel caused by vasculitis [22], and altered fibrinolysis [20]—but none have been proven yet.

Previous epidemiological studies revealed a close association between ONFH and the use of corticosteroids for the treatment of diseases that include autoimmune rheumatic disorders and inflammatory bowel conditions (steroid-induced ONFH), as well as alcohol abuse [8, 11, 23]. The steroid induced bone necrosis is presumed to arise from a circulatory impairment to the femoral head, although the exact pathogenesis is currently unclear.

Besides operation, physical therapeutics have been applied for treatment of ONFH and steroid-induced ONFH. These conservative therapies include high-energy shock wave [15], pulsed electromagnetic fields (PEMFs) [6, 18], and hyperbaric oxygen therapy [17]. The curative effect of these physical therapeutics alone or combined with operation treatment is still unsatisfactory. A new method is needed for the treatment of ONFH. Magnetic treatment has a history of approximately 1,000 years and is widely applied in China. In Chinese traditional medicine magnetic treatment is believed to have functions of tranquilising and allaying excitement, dephlogisticating, relieving pain, promoting blood flow, removing blood stasis, and strengthening bone architecture. In some Chinese hospitals, satisfactory therapeutic results in experimental treatment for sufferers of steroid-induced ONFH have been gained by applying a rotating permanent magnetic field (RPMF) designed by our research institution.

In this study, we applied RPMF for the treatment of steroid-induced ONFH in New Zealand rabbits. We hoped to explain the therapeutic mechanism of RPMF by observing the changes provoked by RPMF in different stages of steroid-induced ONFH.

Materials and methods

Animal model and grouping

Sixty healthy New Zealand rabbits (ripe, truebred, male, over 24 months old, weighing 2.5 ± 0.2 kg) were provided

by the Laboratory Animal Centre of Southern University, and raised in the SPF-grade Animal Centre of Shenzhen People's Hospital. The experimental animals were divided into two groups by random number table. Group C was the sham group and included eight rabbits. The rest of the rabbits were injected prednisolone acetate into their haunch muscles (dosage: 12.25 mg/kg weight, twice a week for eight weeks) and injected 4 mg/kg penicillin into their muscles once a week to prevent infection until the ninth week when nine of them died and four suffered from skin infection. The remaining 34 rabbits were examined by X-ray, which revealed that the bone trabeculae of femoral head were thinning with scattered fragmentation. When the bilateral avascular necrosis of rabbit femoral head was established, 32 of the rabbit models were further randomly divided into four subgroups (each with eight rabbits) according to whether they were exposed to RPMF or not and the time of exposure. The groups are group A1 (exposed to RPMF two hours per day for one month) and group A2 (exposed to RPMF two hours per day for two months), group B1 (positioned on RPMF device without magnetic field exposure for one month) and group B2 (positioned on RPMF device without magnetic field exposure for two months) (Table 1). During the study, four rabbits died because of shock induced by alimentary tract hemorrhage, three died due to heart failure from pulmonary infection, and two died due to liver and kidney failure.

Animals were kept individually in metal cages and fed with standard rabbit diet and water ad libitum. After the animals were euthanised with an overdose of sodium pentobarbital, both femoral heads of all rabbits were harvested at the assigned time and prepared for examination. This study was approved by the Animal Research Ethics Committee of the South Medical University of Guang Zhou (reference 2003A058), and the “principles of laboratory animal care” (NIH publication No. 85–23, revised 1985) were followed.

X-ray (KODAK CR-900)

X-ray was used to observe and record the change of the femoral head density and the bone trabeculae.

Table 1 Experimental animal groups defined by different manipulation

Group	1 month later	2 months later	Manipulation
RPMF (A)	8 (A1)	8 (A2)	Sacrificed after RPMF 2 h/d
Control (B)	8 (B1)	8 (B2)	Sacrificed without RPMF exposure
Sham (C)	4 (C1)	4 (C2)	Sacrificed without any manipulation

RPMF A1 New Zealand rabbit model of steroid-induced necrosis of femoral head sacrificed after exposed to RPMF 2 h/d for 1 month, *RPMF A2* model of necrosis of femoral head sacrificed after exposed to RPMF 2 h/d for 2 months, *Control B1* model of necrosis of femoral head sacrificed without exposed to RPMF 2 h/d for 1 month, *Control B2* model of necrosis of femoral head sacrificed without exposed to RPMF 2 h/d for 2 months, *Sham C1\ C2* normal New Zealand rabbit sacrificed without any manipulation 1 or 2 months later

Micro-computed tomography (Micro-CT)

A Micro-CT (vivaCT 40 scanner, 50–70 kVp/8W; SCANCO Medical, Switzerland) was used to detect the change of the excised femoral head sample and the bone trabeculae.

Determination of the blood rheology and blood fat

Blood was taken from the vein in the ear edge of the rabbits. The blood viscosity, triglyceride, and total cholesterol were accessed by a Peking Shi Emperor R80-A Blood Rheologic analyser and an Xunda XD-811 (Shanghai Xunda Medical Instrument Co., Ltd., China) semi-automatic multifunctional biochemical analyser.

Determination of pressure in the articular cavity

A #7 needle was inserted into the articular cavity of rabbits and connected directly to a brain pressure meter (HaKo MV20B) so that the pressure in the articular cavity could be determined. The average pressure of both articular cavities was recorded for later analysis.

Histological observation

The femoral head was removed through a antero-lateral incision, its profile was observed, and it was recorded whether the cartilage had collapsed. Then the femoral head was split along the coronal plane and treated for three days with decalcifying fluid (10%, standardised by methanoic acid), prepared with methanoic acid (10 ml), azotic acid (3 ml), hydrochloric acid (5 ml), glacial acetic acid (2 ml), formaldehyde (10 ml), distilled water (70 ml), and then washed with lotic water, imbedded with rout paraffin, stained with HE, and observed under light microscope ($\times 40$).

RPMF equipment

The low frequency transduction RPMF therapeutic system of the HMF-6000 type (developed by Department of Biotechnology, Shenzhen University, Chinese patent no. 2L93118017.1, American invention no. 5,667,469) has a bismuth-ferrum-boron permanent magnet revolving at 8–10 Hz (Fig. 1). In a 20 cm² area above the magnet the device provides a hemispherical RPMF with a diameter of 60 cm and a magnetic field intensity between 0.32T and 0.6T (determined by CT3 Gaussmeter). There is no ionizing radiation with the equipment.

Statistical analysis

The data were described as $\bar{x} \pm S$. GLM-UNIVARIATE by SPSS 11.5 (SPSS, Inc., Chicago, IL) was used to analyse the pressure in the articular cavity, the blood rheology, and blood fat. Statistical significance was considered when the *P* value was <0.05 .

Results

X-ray pictures

In the sham group (C1\C2), the bone trabeculae were intact and adequate in density. In the control group (group B), bone trabeculae in the femoral head were thinned, decreased in quantity, and were sparse, scattered and fragmented in the low density area, which was more conspicuous in group B2 than in group B1, revealing that the pathogenic condition was continuing to develop. Compared with group B1, group A1 (treated by RPMF) had more bone trabeculae, a little higher density and less low density areas; the improvement of group A2 was more obvious, with more bone trabeculae and higher density than group B2 as

Fig. 1 Low frequency transduction RPMF therapeutic system of the HMF-6000 type

Fig. 2 Images of X-ray examination of necrosis of femoral head in different groups. *C* The bone trabecula of sham group (C1\C2) was intact and well-distributed. *B1* The bone trabecula of control group (B1) begin to thin, with the amount diminishing and refracting, and scattering collapse in the low-density area. *A1* The bone trabeculae of RPMF group (A1) showed the amount increasing, with higher-density and reduction of low density areas compared with control group (B1).

well as group B1 and the low density areas disappear, but compared with sham group C2, the quantity of bone trabeculae is a little less and the distribution is sparser (Fig. 2).

Micro-CT pictures

In sham group C, the cartilage sending down fishbones connected by apo-bone trabeculae are compact and regular. In the positive control group B, the bone trabeculae in the femoral head were destroyed by absorption, decreased in quantity, collapsed and sparse, thus forming high density sclerotic areas and cavities in low density areas. Compared with group B1, in the disposed group A1, the increase of bone trabeculae is greater, the density is higher, and the cavitation in low density areas is less, while the improvement in group A2 is more obvious in that it has more bone trabeculae and higher density than groups B2 and B1. The confounding phenomenon of the high density sclerotic areas and cavitation in low density areas is obviously

B2 The collapse with the low density area of bone trabeculae of the control group (B2) was more obvious compared with the control group (B1). *A2* The amount and density of bone trabecula of the RPMF group (A2) were apparently increasing with the low density area vanishing compared with control group (B2), but the trabecula formation was poorer than the sham group (C2)

improved but compared with group C, it has less bone trabecula and a worse structure (Fig. 3).

Histological anatomy observation

In sham group C1\C2, the structure of the cartilage trabeculae in the femoral head and the adipose cell and haematopoietic cell rate were normal and the incidence of empty lacunae was low. In disposed group A and sham group B, there were typical osteonecrotic foci, bone lacunae vacuity or bone karyopyknosis, loose bone trabeculae, bone marrow stromatolysis in the cancellous bone areas of the femoral head and in the calcar, stromatolysis, adipose cell increase, part of the endothelial cells in the cartilage small vessel degeneration, and fibrin thrombus. In group B2, in the small vessels fat deposition and fibrin plugs were found forming relatively large mixed emboli, the bone trabeculae were sparse and had obvious micro-fractures, and the quantity of adipose cells and the anteroposterior diameter increased. In the disposed group A2, the bone trabecular

Fig. 3 Images of micro-CT examination of necrosis of femoral head in different groups. *C* The subchondral trabecula of femoral head of sham groups (C1\C2) were apparently intact and well-distributed. *B1* The subchondral trabeculae of control group (B1) were being destroyed, with the amount diminishing and thinning, forming complicated areas with high density sclerosis and low density cavitation. *A1* The subchondral trabeculae of the RPMF group (A1) showed the amount increasing, along with higher density and a

reduction of low density areas compared with control group (B1). *B2* The complicated area with high density sclerosis and low density cavitation of subchondral trabecula of control group (B2) were more obvious than that of control group (B1). *A2* The trabecula formation of RPMF group (A2) tended to be better distributed than that of control group (B2) and the RPMF group (A1), while the high density sclerotic area and low density cavitation area were reduced

Fig. 4 Images of pathological examination of necrosis of femoral head in different groups. *C* The subchondral trabecula of femoral head of sham group (C1\C2). *B1* The subchondral trabecula of control group (B1) with typical osteonecrosis with empty lacuna increasing and karyopyknosis, fat cell augmentation, forming lipo-thrombus and fibrin-thrombus in the small vessels, and some endothelial cell degeneration. *A1* The subchondral trabecula of the RPMF group (A1) showed osteonecrosis with empty lacunae and the appearance of

some punctiform revascularisation. *B2* The empty lacunae and fat cells of subchondral trabeculae of the control group (B2) were augmented and the amount increased more than in the control group (B1); also, mixed emboli appeared in the lumen of blood vessels. *A2* The empty lacunae and fat cells of subchondral trabeculae of the RPMF group (A2) tended to be thinner than those of the control group (B2) and the RPMF group (A1); new vascularisation and small marrow vessels were obviously regenerating

structure was almost normal. Bone trabeculae coarsened and increased in quantity with a decrease in bone lacuna vacuity, and the anteroposterior diameter of the adipose cells diminished. Compared with group A1, the punctiform neogenesis blood capillaries and small vessels inside the marrow in group A2 regenerate more profusely (Fig. 4).

The results of measuring the pressure of the articular cavity of the hip

Compared with sham group C, the disposed groups (A1, A2) had a $P > 0.05$, revealing that under treatment by RPMF, the pressure decreased to the normal range. This is more obvious in group A2 ($P < 0.01$), indicating that the longer time the group is exposed to RPMF, the better effect it has. Compared with the blank sham group C, the positive sham groups (B1, B2) have a $P < 0.01$, revealing that in the undisposed groups, the pressure in the articular cavity of

the hip is abnormal, which is more obvious in group B1 than in group B2 ($P < 0.01$), indicating that in the early stage of necrosis of femoral head, the increase of pressure in the articular cavity of the hip has a marked statistical significance. Compared with corresponding sham groups (B1, B2), the RPMF groups (A1, A2) had a $P < 0.01$, revealing that in the groups exposed to RPMF, the decrease of pressure has a marked statistical significance ($P < 0.01$) (Table 2).

Blood rheology and results of the detection of blood fat

Compared with the blank sham group C, the RPMF groups (A1, A2) have a $P > 0.05$, revealing that in the groups exposed to RPMF, all the indices decrease to the normal range, which is more obvious in group A2 ($P < 0.01$), indicating that the longer time the group is exposed, the better effect it has. Compared with the blank sham group C,

Table 2 The results of blood viscosity, serum cholesterol, triglyceride, and pressure in the coxa articular cavity in different groups ($\bar{x} \pm S$)

Group	<i>n</i>	Pressure in coxa articular cavity (kPa)	Blood viscosity (mPa·s)	Triglyceride (mmol/L)	Serum cholesterol (mmol/L)
Sham (C)	8	0.074±0.034	1.67±0.25	1.19±0.25	1.58±0.24
RPMF (A1)	8	0.081±0.037	1.58±0.37	1.04±0.51	1.50±0.28
Control (B1)	8	0.235±0.042	2.90±0.33	2.24±0.29	2.62±0.21
RPMF (A2)	8	0.072±0.029	1.41±0.25	1.06±0.28	1.53±0.21
Control (B2)	8	0.140±0.048	1.71±0.41	1.68±0.43	2.01±0.15
Multiple Comparisons (LSD)		$F=26.097, P=0.000$ $P=0.7151, P=0.9132$ $P=0.0003, P=0.0024$ $P=0.0005, P=0.0016$ $P=0.6367, P=0.0008$	$F=27.151, P=0.000$ $P=0.5831, P=0.1202$ $P=0.0003, P=0.8074$ $P=0.0005, P=0.0746$ $P=0.3067, P=0.0008$	$F=15.860, P=0.000$ $P=1.001, P=0.4822$ $P=0.0003, P=0.0114$ $P=0.0005, P=0.0026$ $P=0.9037, P=0.0048$	$F=36.94, P=0.000$ $P=0.4771, P=0.6562$ $P=0.0003, P=0.0004$ $P=0.0005, P=0.0006$ $P=0.7867, P=0.0008$

RPMF group (A1) compared with sham group (C), RPMF group (A2) compared with sham group (C), control group (B1) compared with sham group (C), control group (B2) compared with sham group (C), RPMF group (A1) compared with Control group (B1), RPMF group (A2) compared with control group (B2), RPMF group (A2) compared with RPMF group (A1), control group (B2) compared with control group (B1). The mean difference is significant at the 0.05 level

in the positive groups (B1, B2), most of the indices have $P < 0.01$ (except for the blood viscosity in sham group B2), revealing that the abnormality in the unexposed groups has a marked statistical significance. Compared with group C, in sham group B2, the value of P of the blood viscosity is > 0.05 , revealing that after the development of necrosis of the femoral head, the organism has a mechanism of self recovery. Compared with the corresponding positive sham groups (B1, B2), the value of P of the exposed groups (A1, A2) is < 0.01 , revealing that in the groups exposed to RPMF, blood rheology and the improvement of blood fat have a marked statistical significance ($P < 0.01$) (Table 2).

Discussion

In this study, we applied RPMF to treat steroid-induced ONFH in New Zealand rabbits. Changes of femoral head, blood viscosity, serum cholesterol, triglyceride and pressure in the hip joint cavity were measured and analysed in different rabbit groups. After RPMF treatment we found that the osteogenesis regeneration of the necrotic femoral head was improved. The RPMF decreased blood viscosity, serum cholesterol, triglyceride and pressure in the hip joint cavity and shows promise in the prevention and treatment of steroid-induced ONFH, especially at an early stage.

The unique energy transmission mode and noninvasive nature of the permanent magnetic field have a special biological effect on bone tissue. Kotani et al. found that a strong static magnetic field had the potential not only to stimulate bone formation, but also to regulate its orientation in both in vitro and in vivo models [14]. According to our magnetic theories in traditional Chinese medicine and satisfactory therapeutic results in experimental treatment for sufferers of steroid-induced ONFH in several Chinese hospitals, we believe that RPMF has potential for the treatment of bone fractures, vertebral fusion, bone defects, and bone rarefaction. We designed this study to confirm the therapeutic effects of RPMF on ONFH and further illustrate its mechanism. Chakeres et al. found that normal subjects exposed to varying magnetic field strengths of up to 8 T demonstrated no clinically significant changes in vital signs [4]. The intensity of magnetism of our RPMF device is 0.32–0.6T, which is relatively safe to be applied in treatment.

To ensure the success of animal models, we deploy relatively large dosage of hydrocortisone. The femoral head of homo sapiens carries the whole weight of the body, so collapse is found in the intermediate stage on X-ray plates, while for animal models, walking on four limbs, it is mainly bone rarefaction. Some researchers confirmed that extended steroid application, up to ten weeks, can cause collapse in the advanced stage of avascular necrosis of

femoral head of animals [1]. Because the duration of steroid administration was confined to eight weeks in our study, no collapse of the femoral head was found in the rabbits. In this way, a low death rate of the animals was ensured and a higher survival rate was a benefit for later grouping and observation. But we were limited to study the therapeutic effect of RPMF only on the early stage of avascular necrosis of the femoral head, without consideration of the collapsed femoral head.

In this study, hyperlipidaemia, the change of blood rheology, and the increase of the pressure in the articular capsule in positive sham groups (B1, B2) was clearly higher than in the blank sham group C ($P < 0.01$) and improved slightly over group B2. This demonstrates that steroids reduce the protein and mucopolysaccharide synthesis, induce the dyspoiesis of bone matrices, and interfere with the of blood rheology and hyperlipemia as described by Tang et al. [19]. Fat in lumen of blood vessels in bone marrow may finally induce avascular necrosis of femoral head. Compared with group B1, it was observed in group B2 that the development of necrosis of bones continues, indicating that self recovery of ONFH is fairly difficult.

Taken together, RPMF can reduce blood viscosity and pressure in the articular cavity, relieve hyper lipidaemia, and facilitate the recovery of osteonecrosis in the early stages; thus, RPMF is expected to become a new method to treat steroid-induced ONFH and is worthy of further clinical promotion.

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