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Dosage Effects of Extracorporeal Shockwave Therapy in Early Hip Necrosis

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Running title: ESWT enhances angiogenesis in early ONFH

Dosage Effects of Extracorporeal Shockwave Therapy in Early Hip Necrosis

Abstract:

Background: This study investigated the effects of different dosages of extracorporeal shockwave therapy (ESWT) in early osteonecrosis of the femoral head (ONFH).

Materials and Methods: Thirty-three patients (42 hips) were randomly divided into three groups. Group A (10 patients with 16 hips) received 2000 impulses of ESWT at 24 Kv to the affected hip. Group B (11 patients with 14 hips) and Group C (12 patients with 12 hips) received 4000 and 6000 impulses of ESWT respectively. The evaluations included clinical assessment, radiographs, dynamic contrast-enhanced MRI for microcirculation (K^{tran}) and plasma volume (Vp), and blood tests for biomarker analysis (NO3, VEGF, BMP-2, osteocalcin, TNF-α, IL-6. substance P, CGRP; DKK-1 and IGF).

Results: Significant differences of pain and Harris hip scores were noticed between Group A and C in 6 months after ESWT (all $P<0.05$). The pain score decreased, but not Harris hip score improved over the observation time period from 6 to 24 months. Total hip arthroplasty was performed in 3 patients (4 hips) in Group A, but none in Groups B and C. Group C showed significant changes in serum biomarkers for angiogenesis, osteogenesis, anti-inflammation, pain threshold and tissue regeneration between one week and one month after treatment (all $P<0.05$). However, no significant changes in the infarction volume in image studies were noted in all groups (all $P > 0.05$). The post-treatment K^{tran} and Vp in the peri-necrotic areas of Group B and C were significantly greater than pre-treatment data (both $P<0.05$).

Conclusions: High dosage ESWT is more effective in early stage ONFH. The systemic beneficial effects of ESWT may ultimately enhance angiogenesis with improvement of microcirculation of the peri-necrotic areas, that in turn, can improve

subchondral bone remodeling and prevent femoral head collapse.

Keywords: ESWT dosage, hip necrosis, angiogenesis, osteogenesis, anti-inflammation, pain threshold, tissue regeneration.

Introduction

The etiology of osteonecrosis of the femoral head (ONFH) is multi-factorial, and the treatment is disease stage dependent [1]. Core decompression with or without bone grafting for symptomatic early stage ONFH, and total hip replacement for late stage of the disease are considered the gold standards [2, 3]. However, the results of core decompression are inconsistent despite of good results reported in selective series, and many patients eventually undergo hip replacement surgery [4-11]. Therefore, an effective non-invasive method of treatment is imperative and attractive for patients with early ONFH.

Prior studies reported extracorporeal shockwave therapy (ESWT) had superior results over core decompression and non-vascularized bone graft in early stage of ONFH [12-20]. Other study demonstrated the regeneration effects of ONFH after ESWT [21]. Additional study reported the dosage-dependent effects of ESWT in bone healing [22]. However, the dosage selections of ESWT in ONFH are poorly understood. In prior study, the selections of ESWT dosages were empirical or manufacturer recommendations, and the optimal dosage had not been scientifically validated [23]. The incidence of ESWT device related morbidity such as ecchymosis was reported as high as 30% when the current protocol is used [24]. The new trend in the device design tends to reduce the voltage and increase the number of impulse that produces better efficacy and safety [24]. To our best knowledge, there has been no study reporting the optimal dosage of ESWT in early ONFH. The purpose of this study was to investigate the local and systemic effects of different ESWT dosages in early ONFH.

Materials and Methods:

The Institutional Review Board of our institution approved this prospective

clinical trial, and all patients signed the informed consent prior to participation in the study. The inclusion criteria included the age of patient greater than 18 years old and the ONFH in stage I, stage II or stage III-a according to ARCO classification at initial presentation [25]. The exclusion criteria included patients with late stages of the disease (stages III-b, III-c or stage IV), patients under 18 years of age, patients with cardiac arrhythmia or pacemaker, patients on immunosuppressant drugs, patients with infection or advanced arthritis, patients with coagulopathy, chronic renal failure, pregnancy and poor compliant patients.

Thirty-three patients with 42 hips were recruited in this study and were randomly divided into three groups. The randomization was performed using computer generated stickers with A, B or C. Group A consisted of 10 patients with 16 hips. Group B consisted of 11 patients with 14 hips and Group C 12 patients with 12 hips. There were no significant demographic differences in age, gender, duration and severity of the disease among the three groups. The demographic characteristics of the patients are summarized in Table 1.

Shockwave application:

ESWT was performed under either general or spinal anesthesia. Both legs were properly positioned on fracture table. Under C-arm and MRI guidance, the junctional zone between normal bone and necrotic bone within the femoral head was delineated. Within the junctional zone, four points approximately 1.0 cm apart were chosen under C-arm imaging control and the corresponding locations were marked on the skin in the groin area. Patients in Group A were designated as low dosage group and received 2000 impulses of ESWT at 24 Kv (equivalent to 0.510 mJ/mm^2 energy flux density) to the affected hip. Patients in Group B were designated as medium dosage group and received 4000 impulses of ESWT at 24 Kv to the affected hip. Patients in Group C were designated as high dosage group and received 6000 impulses of ESWT at 24 Kv

to the affected hip. ESWT was applied in one single session.

The evaluation parameters included clinical assessments, radiographs, MR images and blood tests. The primary end-point is the number of hip that required replacement surgery during the course of treatment. The secondary end-point is the improvement in hip pain and function after treatment, and the third end point includes the changes on image studies and blood test results.

Clinical assessment:

After ESWT, patients walked on crutches with partial weight bearing on the affected limb for 4 to 6 weeks or until hip pain subsided. Patients were allowed to do range of motion and muscle strengthening exercises as tolerated. Pain score and Harris hip score of each patient were documented before treatment and at 6, 12 and 24 months after ESWT.

Blood tests:

Ten milliliters of peripheral venous blood were obtained for the measurements of serum nitrate (NO3) and vascular endothelial growth factor (VEGF) for angiogenesis, bone morphogenetic protein 2 (BMP-2) and osteocalcin for osteogenesis, tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) for anti-inflammatory cytokines, substance P and calcitonin-gene related peptide (CGRP) for pain threshold, and dickkopf-related protein 1 (DKK-1) and insulin-like growth factor (IGF) for tissue regeneration before treatment, and at 1 week, 1, 3, and 6 months after treatment.

Imaging study:

Before ESWT treatment, radiographs and MR imaging (MRI) of the affected hips were preformed in each patient and the staging of ONFH was recorded according to ARCO classification [25]. The necrotic areas of femoral heads on MRI were estimated on a high-resolution monitor (Barco view, MGD 521MK II, Kortrijk, Belgium) via the PACS system (Centricity Workstation, version 3.0, General Electric

Medical Systems, Milwaukee, Wis.). The percentage of the infarcted femoral head volume (IFHV) was measured by the infarcted femoral head volume divided by total femoral head volume. The radiographs and MRI were repeated at 6 months after ESWT. Bone marrow edema around the necrotic regions were graded on MRI as follows: grade 0: no bone marrow edema; grade 1: peri-necrotic; grade 2: edema extending to femoral head; grade 3: edema extending to femoral neck and grade 4: edema extending to intertrochanteric region.

Dynamic contrast enhancement MR image (DCE-MRI) is a noninvasive quantitative technique that can be used to measure characteristics of tissue microvasculation and is a promising biomarker candidate for assessing antiangiogenic treatment [26]. DCE-MR uses two-dimensional T1-wieghted fast low-angle shot sequence to assess the microcirculation of the respective tissue [27]. DCE-MRI is the acquisition of serial MR images before, during and after the administration of an intravenous contrast agent to measure perfusion, vessel permeability, and the volume of the extravascular-extracellular space (EES) that reveal kinetics of contrast wash-in and wash-out to characterize the tissues or tumors [28]. Using this technique, microcirculatory quantitative parameters including the volume transfer constant (K^{trans}) of contrast agent across the capillary wall and the plasma volume per unit volume of tissue (Vp), can be measured. The K^{trans} represents the endothelial permeability and surface area of the tissue microcirculation. Some authors have proved good correlation of the K^{trans} with microvessel density and level of vascular endothelial growth factor [27]. However, the Vp can represent the percentage of plasma volume in the tissue. DCE-MRI may be feasible to evaluate the microcirculation of necrotic and peri-necrotic tissues in patients with ONFH. DCE-MRI was carried out for each affected femoral head before and 6 months after treatment respectively. Axial sections were performed to evaluate the necrotic and

perinecrotic areas of ONFH in the DCE-MRI study. Post processing of all DCE-MRI data was analyzed by using a commercial software tool (MIStars; Apollo Medical Imaging, Melbourne, Australia). All interested necrotic and peri-necrotic regions of the femoral heads at each section were selected manually for calculation. The available areas 1cm away from the necrotic border in the femoral heads or necks were selected as peri-necrotic areas of interest. The K^{trans} and Vp were automatically calculated from the fitted curve pixel by pixel. Finally, the means of the two parameters of pixels within drawn regions of interest were recorded.

Statistical analysis:

A power analysis revealed that for a power of 95% and α= 0.05, a sample size of 12 hips in each group was required to achieve significance with a mean difference 1.5, standard deviation difference 0.6 on pain score at 6 months after treatment. The paired samples of serum biomarker levels, and K^{tran} and Vp in DCE-MRI in each group before treatment and after ESWT were analyzed by Wilcoxon Signed Ranks tests. All paired samples of K^{tran} and Vp in the peri-necrotic areas of the femoral heads were compared to the corresponding necrotic areas of the femoral heads by Wilcoxon Signed Ranks tests. The Kruskal-Wallis tests were adopted to test the differences of pain score, Harris scores, serum biomarkers levels, K^{tran} and Vp between the three groups at each time point. If the Kruskal-Wallis tests showed significant differences, and then the Mann-Whitney tests with Bonferroni correction were employed for further analysis. The McNemar's tests were adopted to analyze the differences in grades of bone marrow edema of affected femur on MRI in each group. The P value <0.05 was considered statistically significant.

Results:

Pain score and Harris hip score are summarized in Fig. 1-a. Pain score was

significant decrease in Group C compared with Group A in 6, 12 and 24 months after treatment (P=0.037, 0.013 and < 0.001 respectively). Nonetheless, Harris hip score showed significant improvement in Group C relative to Group A only in 6 months after treatment (P=0.017) but not in 12 and 24 months. Three patients with 4 hips in Group A underwent total hip arthroplasty (THA) during the course of treatment because of increasing pain. MRI of the hip was not performed in these 4 hips at 6 months after treatment. No THA was performed in Group B and Group C.

Two patients in Group B and one patient in Group C developed local redness and mild ecchymosis at the treatment sites that resolved spontaneously. There was no neurovascular or systemic complication. There was no device related problem.

The serum NO3 and VEGF levels are summarized in Fig. 1-b. Significant increases of NO3 were observed at 1 month after ESWT in Group B (P=0.011) and Group C (P=0.012) relative to Group A. The VEGF expressions in Group C also showed significant increase in one week after ESWT (P=0.008). The VEGF level in Group C was significantly elevated relative to Group A in one week after ESWT (P=0.013).

The serum BMP-2 and osteocalcin levels are summarized in Fig. 2-a. Significant increases of BMP-2 and osteocalcin were observed in Group B and Group C in one week to one month after ESWT (all P<0.05). The osteocalcin levels in Group B and Group C were significantly elevated relative to Group A in one month after ESWT (P=0.004 and 0.012).

The serum TNF-α and IL-6 levels are summarized in Fig. 2-b. Group C showed significant reductions in serum TNF-α and IL-6 inflammatory biomarkers cytokine in one week after ESWT (both P=0.030). Significantly lower IL-6 level in Group C than Group A was also noted in one week after ESWT (P=0.016).

The serum substance P and CGRP levels are summarized in Fig. 3-a. Group C

showed significant reduction of substance P and CGRP levels in one week after ESWT as compared with before treatment (P=0.003 and 0.028).

The serum DKK-1 and IGF levels are summarized in Fig. 3-b. Significant decreases of DKK-1 were noted in one week after ESWT in Group B (P=0.019) and Group C (P=0.035). Group C also showed significant decrease of DKK1 (P=0.01) compared to Group A in one week after ESWT. Significant increase IGF level in Group C was noted in one month after ESWT (P=0.011). Group C also showed significant increase of IGF (P=0.012) relative to Group A in one month after ESWT.

The size, IFHV and stage of the avascular lesion on radiographs and MRI are summarized in Table 2. The size, IFHV and stage of the lesions on radiographs and MRI showed no significant differences before and after treatment in all groups (all P>0.05). However, bone marrow edema on MRI was significantly reduced 6 months after ESWT in Group C (P=0.039).

The results of microcirculatory DCE-MRI before treatment and 6 months after ESWT are summarized in Fig. 4. All K^{tran} and Vp in the peri-necrotic areas of the femoral heads in all three groups were significantly greater than those in the necrotic areas of the femoral heads before treatment and 6 months after ESWT (all P <0.05). There were no significant differences of K^{tran} and Vp in the necrotic areas between pre-treatment and 6 months after ESWT among the three groups (all P> 0.05). The K^{tran} and Vp in the peri-necrotic areas in Group B and Group C at 6 months after ESWT were significantly greater than those before treatment (both P<0.05), but no significant difference was noted in Group A. Group B and Group C revealed significantly greater K^{tran} and Vp in the peri-necrotic areas than Group A 6 months after ESWT (both P<0.05).

Discussions

The study was tailored to compare the effects of different ESWT dosages in ONFH and no control group was included in this study. However, our previous study compared ESWT with core decompression for early stage ONFH showed ESWT group had significantly better results than the core decompression group [16]. Other prior studies also showed ESWT effectively improved pain and function of the hip with early ONFH [13, 16, 18-20]. The reduction of hip pain correlated with the improvement of hip function for activities of daily living including work capacity. The results of the current study are compatible to or better than other reports [16,20,21]. High dosage ESWT was more effective than low dosage and the beneficial effects of ESWT in early stage ONFH appears to be dosage-dependent.

The effects of ESWT on ONFH can be mechanical or biological or both. The interaction between biological and mechanical mechanism of ESWT remains controversial. Prior studies showed ESWT promotes the ingrowth of neovascularization associated with ~~and~~ up-regulation of angiogenetic growth factors and tissue regeneration [29-31]. It appears that ESWT may imply both biological and mechanical mechanisms that produce the therapeutic effects with neo-angiogenesis and tissue regeneration in hips with early ONFH.

Under normal circumstance, a decrease in pain score is usually associated with an increase in Harris hip score. In this study, significant decrease of pain score was noted in Group C compared with Group A from 6 to 24 months after treatment but Harris hip score only revealed significant improvement in 6 months after treatment. The explanations are attributed to the complexity of Harris hip scores including pain, function (limp, support, distance walked), activities (stairs, shoes and socks, sitting and public transportation), deformity, and range of motion which may affect the hip function during the observational period.

Our study revealed significant increases of serum biomarkers including angiogenesis (NO3 and VEGF), osteogenesis (BMP-2 and osteocalcin) and regeneration (IGF) within one week to one month after the application of high dosage ESWT. At the same time, significant decreases in inflammatory cytokines (TNF-α and IL-6), pain threshold (substance P and CGRP) and tissue regeneration inhibitor (DKK-1) were also noted within one week to one month after ESWT especially in high dosage Group C. Therefore, it appears that high dosage ESWT is associated with systemic changes in serum biomarkers for angiogenesis, osteogenesis, anti-inflammation, pain threshold, and tissue regeneration in one week to one month after shockwave treatment. It appears that ESWT showed both local and systemic effects in early hip necrosis.

In our study, medium ESWT dosage (Group B) did not demonstrate significant differences with high ESWT dosage (Group C) in all serum biomarker levels and dynamic contrast-enhanced MRI study in microcirculation (K^{tran}) and plasma volume (Vp). Nonetheless, Group B delineated significantly better effects only in some serum biomarkers (osteocalcin, BMP2 and DKK-1), K^{tran} and Vp. It seemed that Group C showed best therapeutic effects in the study.

Despite clinical success of ESWT in early ONFH, the changes on the lesion size and the stage of the disease on radiographs or MRI after ESWT are ambiguous. The ischemic lesions in avascular necrotic femoral head appear to be indolent in nature on radiographs and MRI examinations. Our study demonstrated the K^{tran} and Vp in the peri-necrotic areas were significantly greater than those in the necrotic areas before treatment and 6 months after ESWT. Post-infarction reactive changes with increased vascularity in the peri-necrotic areas might lead to elevation of K^{tran} and Vp. The higher dosage groups also revealed significantly elevated K^{tran} and Vp in the peri-necrotic areas of femoral heads 6 months after ESWT. Nonetheless, no

significant change of K^{tran} and Vp were noted in the necrotic areas 6 months after ESWT. Therefore, high dosage ESWT could significantly enhance the permeability and microcirculation in the peri-necrotic areas. These findings correlated with the angiogenesis promoting therapeutic effect of ESWT in the peri-necrotic areas. The ischemic lesion of ONFH is similar to a well-healed scar tissue, which may preclude the revascularization inside the necrotic area, and such lesions revealed no changes after ESWT. However, the positive effects of ESWT are supported by clinical assessments and the positive expressions of angiogenesis, osteogenesis, anti-inflammation, pain threshold and tissue regeneration in blood tests. At present, the key of success appears to rely on the improvement of angiogenesis and tissue proliferation in the peri-necrotic bones that improves subchondral bone remodeling and prevents femoral head collapse.

There are limitations in this study. The main findings of this study revealed high dosage ESWT was more effective than low dosage ESWT in early ONFH. These findings are supported by clinical assessment, peripheral blood tests and microcirculatory assessment of DCE-MRI. However, there is no device that can correlate the outcome of treatment with direct measurement of intra-osseous pressure before and after treatment. In this study, ESWT was given in one single session only. The difference between single session versus multiple sessions treatments is unknown when ESWT is utilized in hips with early ONFH.

Conclusion:

High dosage ESWT is more effective than low dosage in early stage ONFH. Application of ESWT was associated with systemic changes in angiogenesis, osteogenesis, anti-inflammation, pain threshold and tissue regeneration. High dosage ESWT enhances the angiogenesis with the improvement of permeability and

microcirculation of the peri-necrotic areas of the femoral head that may improve subchondral bone remodeling and prevent femoral head collapse.

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Legends

Fig. 1-a shows pain score and Harris hip score before treatment (PRE) and in 6, 12 and 24 months after treatment. Fig. 1-b shows serum nitrate (NO3) and VEGF levels before treatment (PRE) and in 1 week, 1, 3 and 6 months after treatment. Group A: 10 patients with 16 hips, Group B: 11 patients with 14 hips and Group C: 12 patients with 12 hips. The P value <0.05 is considered statistically significant. *Significant difference as assessed by Wilcoxon Signed Ranks test. #Significant difference as analyzed using the Mann-Whitney tests with Bonferroni correction.

Fig. 2-a shows serum BMP-2 and osteocalcin levels, and Fig. 2-b shows serum TNF-α and IL-6 levels before treatment (PRE) and in 1 week, 1, 3 and 6 months after treatment. Group A: 10 patients with 16 hips, Group B: 11 patients with 14 hips and Group C: 12 patients with 12 hips. The P value <0.05 is considered statistically significant. *Significant difference as assessed by Wilcoxon Signed Ranks test. #Significant difference as analyzed using the Mann-Whitney tests with Bonferroni correction.

Fig. 3-a shows serum substance P and CGRP levels, and Fig. 3-b shows serum DKK-1 and IGF levels before treatment (PRE) and at 1 week, 1, 3 and 6 months after treatment. Group A: 10 patients with 16 hips, Group B: 11 patients with 14 hips and Group C: 12 patients with 12 hips. The P value <0.05 is considered statistically significant. *Significant difference as assessed by Wilcoxon Signed Ranks test. #Significant difference as analyzed using the Mann-Whitney tests with Bonferroni correction.

Fig. 4 shows microcirculatory dynamic contrast-enhanced MR imagine before treatment (PRE) and 6 months after treatment. All paired samples of K^{tran} and Vp in the peri-necrotic areas were significantly greater than the corresponding necrotic areas of the femoral heads in all three groups (all P <0.05). Group A: 10 patients with 16 hips,

Group B: 11 patients with 14 hips and Group C: 12 patients with 12 hips. The P value <0.05 is considered statistically significant. K^{tran}: volume transfer constant. Vp: plasma volume per unit volume of tissue. *Significant difference as assessed by Wilcoxon Signed Ranks test. #Significant difference as analyzed using the Mann-Whitney tests with Bonferroni correction.

Table 1. Patient Demographic Characteristics.

	Group A	Group B	Group C	Total
Number of patients / hips	10 / 16	11 / 14	12 / 12	33 / 42
Ave. age (years)				
Mean±SD	46.1±6.2	40.5±9.3	39.4±10.2	41.8±9.1
(Range)	(35-55)	(29-60)	(18-52)	(18-60)
Gender (M / F)	4 / 2	10 / 4	8 / 4	32 / 10
Side of lesion				
Right / Left	9 / 7	7 / 7	5/ 7	21 / 21
Bilateral hips	6	3	0	9
Patients with opposite THA	2	2	5	9
Duration of symptoms (months)				
Mean±SD	10.8±9.9	8.1±8.8	8.7±5.8	9.3±8.4
(Range)	(1-36)	(1-36)	(2-24)	(1-36)
Patients/Hips with stage I lesion	1 / 1	3 / 3	2 / 2	5/ 6
Patients/Hips with stage II lesion	6 / 10	6 / 8	8 / 8	20 / 26
Patients/Hips with stage III lesion	3/ 5	2 / 3	2 / 2	7 / 10
Medical history				
Steroid intake	2	3	4	9
Alcoholic abuse	6	5	6	17
Negative	2	3	2	7
Length of follow-up (months)				
Mean ± SD	33.8±7.6	30.0±7.1	30.7±8.0	31.4±7.5
(Range)	(18-45)	(18-44)	(18-45)	(18-45)

THA: total hip arthroplasty.

Table 2. The radiographs and MR imaging in patients with early osteonecrosis of femoral head.

	Group A (N =14)	Group B (N =14)	Group C (N =11)	P-value[1]
Radiographs				
Size of lesion (%)				
Before treatment	35.1±9.4	36.2±8.6	30.5±13.1	0.153
6 months After treatment	34.2±5.9	36.6±7.7	30.2±7.3	0.057
P-value[2]	0.972	0.861	0.965	
MRI				
IFHV of lesion (%)				
Before treatment	20.8±18.7	23.0±14.1	22.3±15.7	0.775
6 months After treatment	19.3±19.0	22.5±16.4	18.9±12.5	0.612
P-value[2]	0.480	0.834	0.028	
Stage of Lesion	I II III IV	I II III IV	I II III IV	
Before treatment	1 10 5 0	3 8 3 0	2 8 2 0	0.753
6 months After treatment*	1 8 3 2	3 7 4 0	2 7 2 0	0.736
Grade of bone marrow edema	0 I II III IV	0 I II III IV	0 I II III IV	
Before treatment	3 2 7 2 2	4 2 3 1 4	3 1 6 0 2	0.841
6 months After treatment	3 3 6 0 2	4 7 2 1 0	8 2 1 0 0	0.039
P-value[3]	0.854	0.137	0.032	

IFHV: infracted femoral head volume. *: Three patients with 4 hips in group A underwent hip arthroplasty in 3 months and one patient with 1 hip in group C withdrew in 3 months.

P-value[1]: Compared by Kruskal-Wallis tests. If the Kruskal-Wallis test showed significant difference, and then the Mann-Whitney test with Bonferroni correction is employed for further analysis.

P-value[2] : Compared by Wilcoxon Signed Ranks test.

P-value[3]: analyzed by McNemar's test.

Fig. 1-a

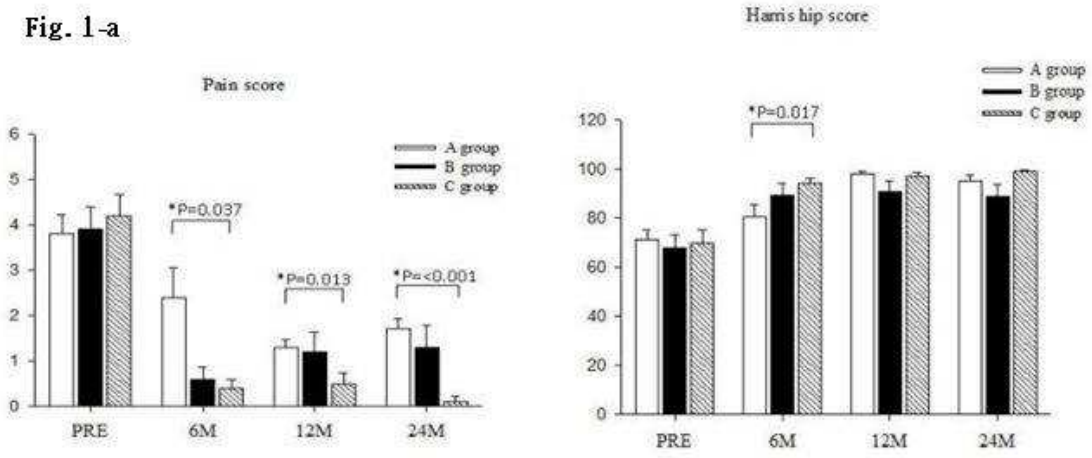


Fig.1-b

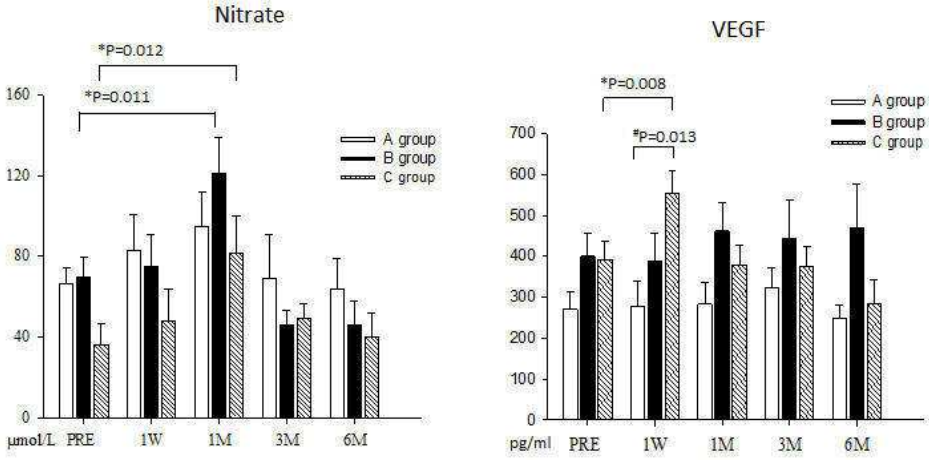


Fig.2-a

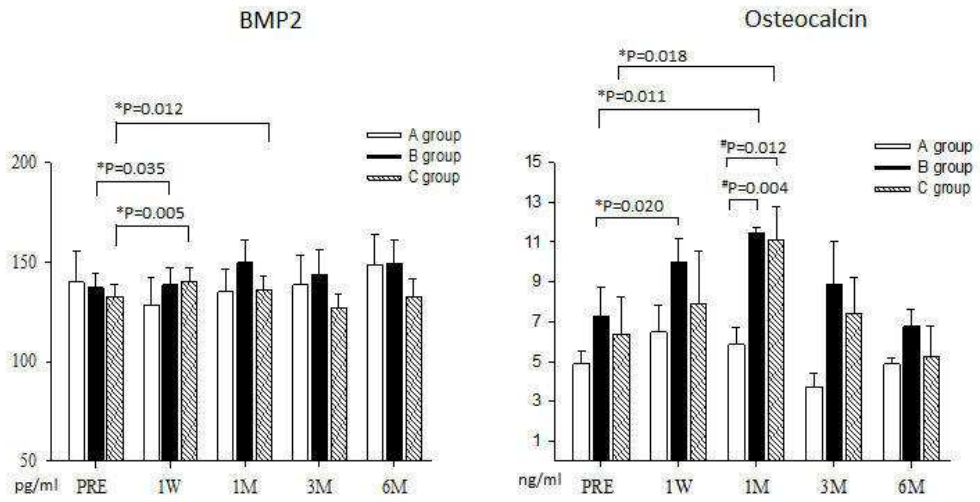


Fig.2-b

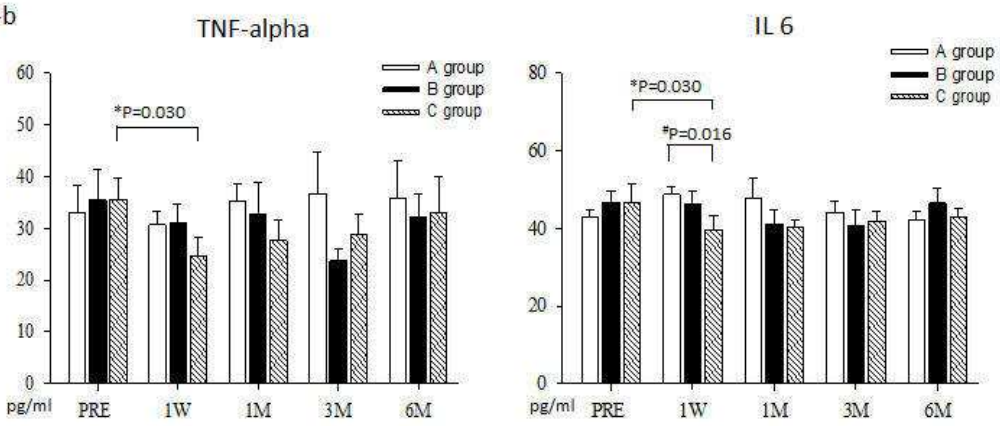


Fig.3-a

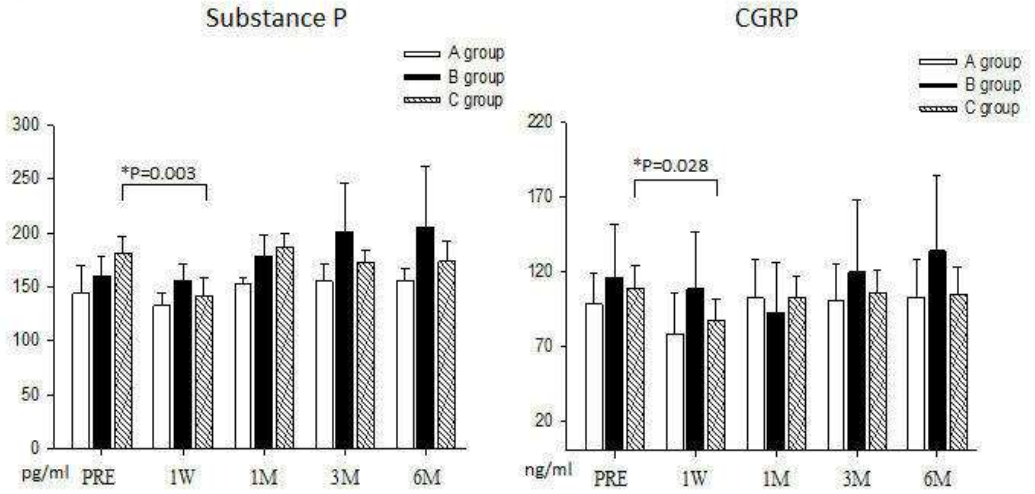


Fig. 3-b

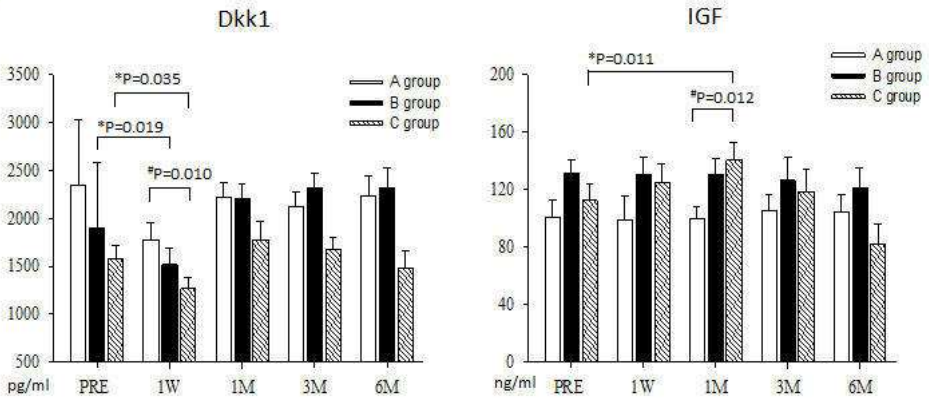
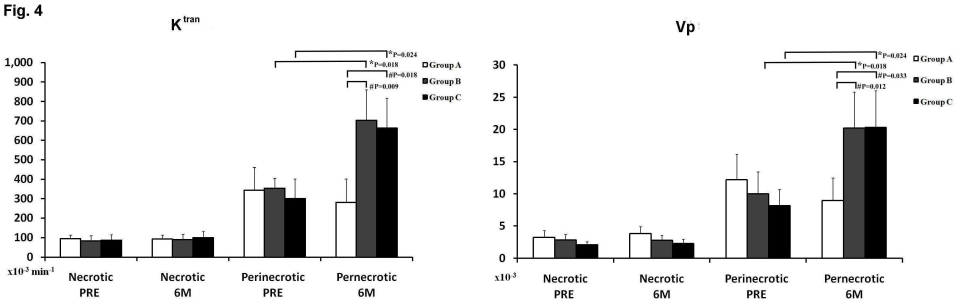


Fig. 4



Highlights

High dosage of extracorporeal shockwave therapy is more effective in early osteonecrosis of the femoral head. The systemic beneficial effects may significantly improve serum angiogenesis, osteogenesis, anti-inflammation, pain threshold and tissue regeneration biomarkers within one month after treatment. Ultimately, the therapy can enhance microcirculation of perinecrotic areas and prevent femoral head collapse.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

The authors declared that they did not receive any honoraria or consultancy fee in the writing of this article. No fund was received or will be received from a commercial party related to the subject in this article. One author (CJW) serves as a member of the advisory committee of Sanuwave. Alpharetta GA, and such relationship is irrelevant to the current study. The remaining authors declared no conflict of interest.

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Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

The Institutional Review Board of our institution approved this prospective clinical trial, and all patients signed the informed consent prior to participation in the study.
98-2554A3

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ISRCTN74606904

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Ching-Jen Wang participated in the study with primary duties in conception and design of the study, patient's examination, data analysis and interpretation, reference search, drafting the article and read proof the submitted manuscript.

Chung-Cheng Huang participated in the study with the primary duties in the analysis of image studies including radiographs and MRI, reference search, data analysis and read proof the submitted version of the manuscript.

Hon-Kan Yip participated in the study with primary duties in conception and design of the study, supervision of laboratory studies, data collection and analysis, and final approval of the submitted manuscript.

Ya-Ju Yang performed patient registration, scheduled and technically performed ESWT application, arranged MRI, radiographs and coordinated the follow-up study at outpatient department, and final approval of the submitted manuscript.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

CC Huang & CJ Wang

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