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ORIGINAL ARTICLE

The effects of shockwave on systemic concentrations of nitric oxide level, angiogenesis and osteogenesis factors in hip necrosis

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Abstract This study investigated the effects of shockwave on systemic concentrations of nitric oxide (NO) level, angiogenic and osteogenic and anti-inflammatory factors in hips with osteonecrosis of the femoral head (ONFH). Thirty-five patients (47 hips) with ONFH were enrolled in this study. Each hip was treated with 6,000 impulses of shockwave at 28 kV in a single session. Ten milliliters of peripheral blood was obtained for the measurements of serum NO level, angiogenic factors (VEGF, vWF, FGF basic and TGF-β1); osteogenic factors (BMP-2, osteocalcin, alkaline phosphatase, DKK-1 and IGF); and anti-inflammation markers (sICAM and sVCAM) before treatment and at 1, 3, 6 and 12 months after treatment. The hips were evaluated with clinical assessment, serial radiograph and MRI. At 12 months, the overall results showed 83% improved and 17% un-improved. Total hip was performed in 4 cases (8.5%). Serum NO3 level showed significant elevation at 1 month after treatment, but the changes at 3, 6 and 12 months were not significant. For angiogenesis, significant elevations of VEGF, vWF and FGF basic and a decrease in TGF-β1 were observed at 1 month, but the changes at 3, 6 and 12 months were non-significant. For osteogenesis, BMP-2, osteocalcin, alkaline phosphatase and IGF were significantly elevated, while DKK-1 was decreased at 1 month, but the changes at 3, 6 and 12 months were not significant. For anti-inflammation markers, significant decreases in sICAM and sVCAM were noted at 1 month after treatment, but the changes at 3, 6 and 12 months were non-significant. Local ESWT application results in significant elevations of serum NO level, angiogenic and osteogenic and anti-inflammatory factors in ONFH.

Keywords Shockwave · Osteonecrosis · Nitric oxide (NO) · Angiogenesis and osteogenesis · Anti-inflammation

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Introduction

The etiology of osteonecrosis of the femoral head (ONFH) is multi-factorial, including steroid administration, alcohol abuse, traumatic event, vascular injury and idiopathic origin, and among others [1–5]. Treatment of ONFH is stage-dependent with the type of treatment varying according to the stage of the disease [6, 7]. While conservative treatments such as NSAID, physical therapy and protected weight bearing are recommended for early stages, the results are generally unsatisfactory [8]. Surgical interventions such as core decompression, vascularized or non-vascularized bone graft, muscle pedicle graft and derotational osteotomy are often indicated in symptomatic hips, but the results are inconsistent and unpredictable [9, 10]. Many patients eventually require total hip replacement (THA),

but this approach is prone to complications, particularly in young patients [11].

Prior studies have demonstrated the effectiveness of ESWT in the treatment of hip necrosis [12]. Recently, other studies reported that ESWT shows regeneration effects including angiogenesis and bone remodeling in hips with osteonecrosis of the femoral head [13]. However, the mechanism of ESWT in hip necrosis is poorly understood. What target tissue does ESWT actually work on remains unknown. Whether shockwave treatment in hip necrosis is a local event or a systemic treatment remains unclear. Some studies demonstrated shockwave treatment rapidly released substance P and prostaglandin E2 (PGE2), and subsequent increases in systemic osteogenic factors in rabbit femur [14]. Others reported NO as the mediator in callus formation in fracture healing after mechanical stimulation [15–17]. A growing number of studies demonstrated that the increases in systemic osteogenic factors reflecting a local stimulation of bone formation during bone healing [18, 19]. We hypothesized that local stimulation with ESWT may result in systemic elevations of serum NO level, angiogenic, osteogenic and anti-inflammatory factors in hips with ONFH. The specific aim of this study was to investigate the effects of shockwave treatment in hips with ONFH and the systemic concentrations of serum NO level, the angiogenesis factors including VEGF, vWF, FGF basic and TGF-β1; the osteogenesis factors including BMP-2, osteocalcin, alkaline phosphatase, DKK-1 and IGF; and the anti-inflammation markers including sICAM and sVCAM.

Patients and methods

Institutional Review Board approved this study, and written informed consents were obtained from the study subjects. The studies were in compliance with the Declaration of Helsinki ethical principles for medical research involving human subjects.

The inclusion criteria included patients with stage I, II or III ONFH according to ARCO classification [20]. The exclusion criteria included patients with stage IV lesions, history of infection, patients with coagulopathy, patients with cardiac pacemaker and/or cardiac arrhythmia, patients receiving immunosuppressive drugs or anti-coagulation therapy and pregnancy. From July 2006 to May 2008, 35 patients with 47 hips were enrolled in this study. The patient demographic characteristics are summarized in Table 1.

Pre-treatment evaluations included a complete history and physical including the prior treatments, the type of surgery, if any, complete blood count including platelet count, coagulation profiles, electrocardiogram and chest X-ray. Ten milliliters of peripheral blood was obtained for measurements of serum NO level, VEGF, vWF, FGF basic and TGF-β1; BMP-2, osteocalcin, alkaline phosphatase, DKK-1 and IGF; sICAM and sVCAM before treatment, and at 1, 3, 6 and 12 months after treatment.

Table 1 Patient demographic characteristics

Number of patients/hips	35/47
Average age (years)	
Mean ± SD	38.8 ± 11.9
(Range)	(17 ~ 64)
Gender (Males/Females)	27/8
Side of lesion	
Right/Left	29/18
Bilateral hips	12
Duration of symptoms (months)	
Mean ± SD	7.4 ± 3.0
(Range)	(6 ~ 18)
Patients/hips with stage I & II lesions	21/30
Patients/hips with stage III lesions	14/17
Medical history	
Steroid intake	6
Alcoholic abuse	23
Negative	6
Length of follow-up (months)	
Mean ± SD	12.5 ± 0.96
(Range)	(12 ~ 16)

Shockwave application

The source of shockwave was from an OssaTron (Sanuwave, Alpharetta, GA). The treatment was performed on the operation table under general anesthesia. The hip joint was properly positioned by adduction and internal or external rotation of the leg. The femoral artery was identified with digital palpitation and confirmed with ultrasound Doppler and was protected from direct shockwave contact. The junctional zone between avascular and normal bones of the femoral head was delineated with C-arm imaging. Four points with 1.0 cm apart within the zone were chosen with a metallic pin under C-arm imaging, and the corresponding locations were marked on the skin in the groin area. The depth of treatment was determined by raising the table until the two ring markers synchronized under C-arm imaging. Surgical lubricate was applied to the skin of contact with the shockwave tube. Each of the four locations was treated with 1,500 impulses of shockwave at 28 kV (equivalent to 0.62 mJ/mm^2 energy flux density), and a total of 6,000 shocks were applied to the femoral head. After treatment, patients walked with crutches with partial weight bearing on the affected leg for 4–6 weeks.

Measurements of serum NO level, VEGF, vWF, FGF basic and TGF-β1; BMP-2, osteocalcin, alkaline phosphatase, DKK-1 and IGF; sICAm and sVCAM

The measurements of serum NO level including nitrite and nitrate were performed using a nitric oxide analyzer (NOA280; Sievers Inc., Denver, USA). The measurements of serum levels of the angiogenesis factors including VEGF, vWF, FGF basic and TGF-β1; the osteogenesis factors including BMP-2, osteocalcin, alkaline phosphatase, DKK-1 and IGF; and the anti-inflammation markers including sICAM and sVCAM were performed using ELISA kits (R&D Systems, Inc. Minneapolis, USA) with the specific reagents according to the manufacturer instructions.

Follow-up examinations were scheduled at 1, 3, 6 and 12 months. Clinical assessments included the intensity of pain based on VAS (visual analogue scale) from 0 to 10 with 0 for no pain and 10 for severe hip and thigh pain, the capacity of walking and the ability to work. Serial radiographs of the affected hip in A–P and lateral views were obtained at each visit to assess the size of the lesion, the crescent sign due to collapse of the femoral head, joint congruency and degenerative changes of the hip. MRI was performed before treatment and at 6 and 12 months after treatment, and the MRI was used to evaluate the size of the lesion, the collapse of femoral head, bone marrow edema and degenerative changes of the affected hip.

Statistical analysis

The data at different time intervals at 1, 3, 6 and 12 months after treatment were compared with the baseline data before treatment using a paired *t* test. The data between patients with stages I and II lesions and patients with stage III lesions were compared statistically using Mann–Whitney *U* test. The statistical significance is set at P value < 0.05.

Results

The overall clinical results are summarized in Table 2. At 12 months after ESWT, the results showed improvement in 83% and non-improvement in 17%. Total hip was performed in 4 cases (8.5%) due to progressive deterioration of the lesion with increasing hip pain and functional disability.

The results of radiographic and MRI studies are summarized in Table 3. Significant improvement in bone marrow edema was noted after ESWT ($P = 0.040$). The lesions showed regression in 19% (9 of 47 hips), progression in 13% (6 of 47 hips) and unchanged in 68% (32 of 47 hips). There was a trend of decrease in the size of the lesion after treatment; however, the changes in the size of the lesion and the stage of the disease were statistically not significant.

Table 2 The overall clinical results

	Total ($N = 47$ hips)	Stage I & II ($N = 30$ hips)	Stage III ($N = 17$ hips)	P value
Improved	83% (39/47)	93% (28/30)	65% (11/17)	0.012
Un-improved	17% (8/47)	7% (2/30)	35% (6/17)	0.012
THA	8.5% (4/47)	7% (2/30)	12% (2/17)	0.583

P value Comparison of patients with stage I & II and patients with stage III lesions; *THA* total hip arthroplasty

The results of serum NO level, the angiogenesis factors (VEGF, vWF, FGF basic and TGF-β1), the osteogenesis factors (BMP-2, osteocalcin and alkaline phosphatase, DKK-1 and IGF); and the anti-inflammation markers (sICAM-1 and sVCAM-1) are summarized in Table 4. Serum NO3 level showed significant elevation at 1 month after treatment, but the changes at 3, 6 and 12 months were non-significant when compared to the baseline data before treatment. For angiogenesis factors, significant elevations of VEGF, vWF and FGF basic and a decrease in TGF–β1 were observed at 1 month after treatment, but the changes at 3, 6 and 12 months were not significant. For osteogenesis factors, BMP-2, osteocalcin, alkaline phosphatase and IGF were significantly elevated, while DKK-1 was decreased at 1 month after treatment, but the changes at 3, 6 and 12 months were non-significant. For anti-inflammation markers, significant decreases in sICAM and sVCAM were noted at 1 month after treatment, but the changes at 3, 6 and 12 months were not significant.

The serum NO level, the angiogenic and osteogenic factors and the anti-inflammation markers were analyzed between patients with stages I and II lesions and patients with stage III lesions, and the results are summarized in Table 5. The changes in serum NO level, the angiogenic and osteogenic factors and the anti-inflammatory markers showed no significant differences between patients with stages I and II lesions and patients with stage III lesions. It appears that effects of shockwave are independent of the stage of the disease.

Discussions

The results of the current study demonstrated that ESWT is effective in early ONFH with 83% improvement in hip pain and function. Application of ESWT in hip with ONFH was associated with significant elevations of serum NO level, the angiogenic, osteogenic and anti-inflammatory factors. Nitric oxide is a potent regulator for bone healing in mechanically stimulated bone formation [15–17]. An increase in vWF (von Willebrand factor) is indicative of

Table 3 The changes on radiographs and MR images before and after treatment

	Size of lesion (%)[a]	Stage of lesion[b]				Bone marrow edema[c]					Changes of lesion (%)	
		1	2	3	4	0	1	2	3	4		
Before treatment	27.23 ± 18.9	2	28	17	0	17	9	6	4	11	Progression	13 (6 of 47)
After treatment	27.04 ± 19.17	2	22	20	3	31	5	5	3	3	Regression	19 (9 of 47)
P value	0.400	0.265				0.040					Unchanged	68 (32 of 47)

[a] The percentage (%) of the lesion size over the total surface of the femoral head

[b] Stage I: lesion shown on MRI, but not on X-ray; stage 2: lesion shown on X-ray and MRI, but no collapse of the femoral head (crescent sign); stage 3: lesion with collapse of the femoral head (crescent sign); and stage 4: lesion with collapse of the femoral head and degenerative changes of the hip joint

[c] Grade 0: no bone marrow edema on MRI; grade 1: peri-necrotic bone marrow edema; grade 2: bone marrow edema extended to the femoral head; grade 3: bone marrow edema extended to the femoral head and neck; and grade 4: bone marrow edema extended to intertrochanteric region

new vessel formation. An increase in VEGF (vessel endothelial factor) is an indication of increased vascular permeability and microvascular activity including angiogenic growth of new blood vessels. FGF basic (fibroblast growth factor basic) stimulates the proliferation of endothelial cells and osteoblasts. The activated FGF basic mediates the formation of new vessels (angiogenesis). TGF-β1 (transforming growth factor-beta 1) modulates cell proliferation and enhances the deposition of extracellular matrix. BMP-2 (bone morphogenic protein 2) is a protein regulator of cartilage and bone, and potently induces osteoblast differentiation and bone formation. Osteocalcin is the major non-collagenous protein of the bone matrix. The circulating levels of osteocalcin reflect the rate of bone formation. DKK-1 (dickkopf-1) is a negative regulator of normal bone homeostasis. A decrease in DKK-1 results in an increase in Wnt activity and high bone mass phenotype; and gradual DKK-1 reduction results in increased trabecular and cortical bone mass. IGF-1 (insulin-like growth factor 1) mediates the action of growth hormone and affects physiological and pathological processes including normal growth and development. Up-regulation of sICAM (soluble intercellular adhesion molecule-1) generally is by inflammatory cytokines (TNF-α, and IL-1 and 6), and down-regulation is by anti-inflammatory agents (e.g. glucocorticoids). The sVCAM-1 (soluble vascular cell adhesion molecule-1) ligand interactions regulate the rate and timing of leukocyte extravasation. It appears that ESWT induces NO production and promotes angiogenesis and osteogenesis, and anti-inflammatory responses that are complimentary in the treatment of hip necrosis. The severity of hip pain in ONFH often is associated with the degree of bone marrow edema, and many cases showed decreased hip pain with reduced bone marrow edema after ESWT [12, 21]. Bone marrow edema may represent an inflammatory process during the natural course in the development of ONFH. Increased angiogenesis and osteogenesis after ESWT will enhance bone quality and bone strength of the femoral head. This may explain in part why ESWT is effective in pain relief and prevention of femoral head collapse in hip necrosis.

The exact mechanism of ESWT remains unknown. Some studies showed that ESWT promoted osteogenesis in tissue, bone marrow and osteoblast-like cells [22–25]. Other studies demonstrated that ESWT induced the ingrowth of neovascularization and up-regulations of osteogenesis related growth factors including induction of eNOS, VEGF, PCNA and BMP-2 [26–28]. However, no study we are aware of addressed the effects of shockwave on the changes in the systemic concentrations of nitric oxide and the angiogenic and osteogenic growth factors and the anti-inflammatory indicators in ONFH. The results of recent study demonstrated that ESWT-promoted osteogenesis of bone marrow stromal cells from patients with hip necrosis through induction of osteogenic factors mediated by NO synthase pathway [29, 30]. It appears that osteogenesis of bone marrow stromal cells may play an important role when ESWT is utilized to treat hips with ONFH. The formation of new bone may replace the lesion within the femoral head in total or in part depending on the effect of osteogenesis after ESWT. This is reflected on clinical observation that some of the lesions regressed, while others progressed after treatment [12].

Some studies suggested that ESWT induced the shear force on the cell membrane, which could result in induction of gene expression [31]. Our previous study showed that shockwave stimulates oxygen radical-mediated osteogenesis of the mesenchymal cells from human umbilical cord blood [32]. Some studies investigated the biological mechanism of ESWT in bone healing at tissue level and demonstrated that ESWT accelerated bone healing with the ingrowth of neovascularization and up-regulation of angiogenesis and osteogenesis growth factors including eNOS, VEGF, PCNA and BMP-2 [30]. Other studies showed that ESWT triggers the cascade of angiogenic and osteogenic transcription factors (Cbfal/Runx2, HIF-1α and VEGF) in osteoblast cells [33, 34]. Many studies showed that acoustic

Table 4 Serum concentrations of NO level, angiogenic and osteogenic factors

Time courses	Before treatment	1 month treatment	3 months treatment	6 months treatment	12 months treatment
(I) NO3 ($N = 35$)	43 ± 48	86 ± 73	47 ± 41	55 ± 49	58 ± 43
P value		0.001	0.063	0.084	0.711
(II) Angiogenesis factors					
(1) VEGF	267 ± 124	368 ± 172	281 ± 184	259 ± 145	246 ± 172
P value		0.011	0.390	0.184	0.063
(2) vWF	1,583 ± 686	2,130 ± 627	1,708 ± 689	1,823 ± 708	1,951 ± 598
P value		<0.011	0.192	0.661	0.084
(3) FGF basic	8.74 ± 4.81	10.84 ± 6.47	8.11 ± 5.31	8.74 ± 6.12	7.64 ± 4.66
P value		0.001	0.089	0.507	0.316
(4) TGF-β1	46,333 ± 19,699	32,249 ± 14,100	53,081 ± 18,261	48,983 ± 19,022	51,128 ± 12,509
P value		<0.001	0.067	0.639	0.492
(III) Osteogenesis factors					
(1) BMP2	108 ± 16	143 ± 42	113 ± 18	116 ± 29	111 ± 24
P value		0.001	0.283	0.212	0.108
(2) Osteocalcin	1.94 ± 1.93	4.76 ± 4.69	2.48 ± 2.96	1.69 ± 0.76	2.10 ± 2.19
P value		0.036	0.314	0.177	0.381
(3) Alk-p-tase	0.84 ± 0.26	1.17 ± 0.4	0.83 ± 0.15	1.02 ± 0.41	1.00 ± 0.29
P value		0.002	0.074	0.056	0.076
(4) DKK-1	1,866 ± 290	1,338 ± 205	2,401 ± 280	2,071 ± 337	1,880 ± 233
P value		0.039	0.053	0.055	0.709
(5) IGF	64 ± 54	176 ± 109	73 ± 60	64 ± 46	45 ± 24
P value		0.001	0.059	0.619	0.542
(IV) Anti-inflammation markers					
(1) sICAM	222 ± 77	189 ± 84	248 ± 66	272 ± 71	215 ± 67
P value		0.044	0.396	0.053	0.176
(2) sVCAM	242 ± 146	167 ± 71	234 ± 98	262 ± 115	279 ± 103
P value		<0.001	0.054	0.53	0.122

P values Comparison of data at different time courses with the baseline data before treatment

shockwave energy induces nitric oxide (NO) elevation that promotes proliferation and differentiation of human osteoblasts [22]. It appears that shockwave-promoted healing in ONFH was linked to NO modulation and activation of angiogenic, osteogenic and anti-inflammatory growth factors. The systemic releases of serum NO level, angiogenic, osteogenic anti-inflammatory growth factors after local application of ESWT to the hip appear to be time-dependent with peak levels at 1 month after treatment. Therefore, the systemic changes in NO level and the angiogenic, osteogenic and anti-inflammatory growth factors may represent a systemic reflection of local stimulation with ESWT in ONFH. It is reasonable to believe that shockwave treatment may provoke NO production, which in turn may activate the mitogenic, osteogenic and angiogenic responses within the bone microenvironment in time fashion [35].

There are limitations in this study. The optimal dosage of ESWT in hip necrosis is undetermined. The ESWT dosage used in this study was based on our previous clinical experiments [12, 13] and animal experiment [36] as well as the recommendations from the manufacturer company. We have been satisfied with the efficacy and safety of the shockwave dosage. Additional weakness of this study was lack of a control or sham group. We were aware that one of the weak points is lack of the control or sham treatment group in this study; therefore, we interpreted the results with more reservation. The serum NO level, angiogenic, osteogenic and anti-inflammatory factors were obtained from the cohort of patients before treatment and at 1, 3, 6 and 12 months after treatment. Despite lack of the control or sham treatment, the data clearly demonstrated that local application of ESWT caused systemic elevations of serum NO level, angiogenic, osteogenic and anti-inflammatory factors. It appears that NO mediates the ESWT-promoted angiogenesis, osteogenesis and anti-inflammation in hip with ONFH. Similar findings were reported in patients with non-union of long bone fracture [29]. The results appear to be clinically relevant and evidence based. Therefore, we

Table 5 Serum concentrations of NO level, angiogenic and osteogenic factors between patients with stages I and II lesions and patients with stage III lesions at 1 month

	NO3	VEGF	vWF	FGF basic	TGFβ1	BMP2	OCN	ALK-P	Dkk-1	IGF	sICAM	sVCAM
Total ($N = 35$)	86 ± 73	368 ± 172	2,130 ± 627	10.84 ± 6.47	32,249 ± 14,100	143 ± 42	4.76 ± 4.69	1.17 ± 0.4	1,338 ± 205	176 ± 109	194 ± 85	167 ± 71
Stage I & II ($N = 21$)	104 ± 83	351 ± 128	2,323 ± 646	11.85 ± 8.37	36,075 ± 11,280	141 ± 46	6.31 ± 5.72	1.27 ± 0.43	1,422 ± 966	176 ± 134	163 ± 78	177 ± 80
Stage III ($N = 14$)	55 ± 37	381 ± 207	1,880 ± 528	9.53 ± 2.38	25,820 ± 11,243	145 ± 25	4.08 ± 3.45	1.16 ± 0.55	1,080 ± 714	157 ± 73	198 ± 69	158 ± 64
P value	0.674	0.600	0.131	0.784	0.263	0.345	0.735	0.575	0.144	0.345	0.237	0.799

P values Comparison of patients with stage I & II lesions and patients with stage III lesion

speculate that measurements of serum NO level, angiogenic, osteogenic and anti-inflammatory biomarkers may be used as the clinical predictor of therapeutic success in ONFH.

In conclusion, application of shockwave in hips with ONFH is associated with systemic elevations of serum NO level, the angiogenic, osteogenic and anti-inflammatory growth factors. Local mechanical stimulation with shockwave may reflect the systemic effects of angiogenesis and osteogenesis and anti-inflammation in hips with ONFH. It appears that measurements of serum NO level, the angiogenic, osteogenic and anti-inflammatory biomarkers may be used as the clinical predictors when ESWT is utilized in the treatment of hips with ONFH.

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References

1. Aldridge JM 3rd, Urbaniak JR (2004) Avascualr necrosis of the femoral head: etiology, pathophysiology, classification, and current treatment guidelines. Am J Orthop 33(7):327–332
2. Wang GJ, Cui Q, Balian G (2000) The pathogenesis and prevention of steroid-induced osteonecrosis. Clin Orthop 370:295–310
3. Wang GJ, Gui Q (1997) The pathogenesis of steroid-induced osteonecrosis and the effect of lipid-clearing agents on this mechanism. In: Urbaniak JR, Jones JP (eds) Osteonecrosis: etiology, diagnosis, and treatment. American Academy of Orthopedic Surgeons, Rosemont, IL, pp 159–166
4. Zhou Q, Li Q, Yang L, Liu F (2000) Changes of blood vessels in glucocorticoid-induced avascular necrosis of the femoral head in rabbits. Chung-Hua Wai Ko Tsa Chih (Chin J Surg) 38:212–215
5. Koo KH, Kim R, Kim YS et al (2002) Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. Clin Rheumatol 21:299–303
6. Ficat RF (1985) Idiopathic bone necrosis of the femoral head: early diagnosis and treatment. Bone Joint Surg 67B:3–9
7. Steinberg ME, Hayken GD, Steinberg DR (1995) A quantitative system for staging avascular necrosis. J Bone Joint Surg 77B:34–41
8. Mont MA, Jones LC, Hungerford DS (2006) Nontraumatic osteonecrosis of the femoral head: 10 years later. J Bone Joint Surg 88A:1117–1132
9. Mont MA, Carbone JJ, Fairbank AC (1996) Core decompression versus non-operative management for osteonecrosis of the hip. Clin Orthop 324:169–178
10. Scully SP, Aaron RK, Urbaniak JR (1998) Survival analysis of hips treated with core decompression or vascularized fibular

grafting because of avascular necrosis. J Bone Joint Surg 80A:1270–1275
11. Dudkiewicz I, Covo A, Salai M, Israeli A, Amit Y, Chechik A (2004) Total hip arthroplasty after avascular necrosis of the femoral head: does etiology affect the results? Arch Orthop Trauma Surg 124:82–85
12. Wang CJ, Wang FS, Huang CC, Yang KD, Weng LH, Huang HY (2005) Treatment of osteonecrosis of the femoral head—comparison of extracorporeal shockwave and core decompression and bone grafting. J Bone Joint Surg 87A:2380–2387
13. Wang CJ, Wang FS, Ko JY et al (2008) Extracorporeal shockwave shows regeneration in hip necrosis. Rheumatology 47:542–546
14. Maier M, Averbeck B, Milz S, Refior HJ, Schmitz C (2003) Substance P prostaglandin E2 released after shock wave application to the rabbit femur. Clin Orthop 406:237–245
15. Diwan AD, Wang MX, Jang D, Zhu W, Murrell GAC (2003) Nitric oxide modulates fracture healing. J Bone Miner Res 15:342–351
16. Fox SW, Chambers TJ, Chow JW (1995) Nitric oxide is an early mediator of the increase in bone formation by mechanical stimulation. Am J Physiol 270:955–960
17. Salter DM, Wallace WHB, Robb JE, Caldwell H, Wright MO (2001) Human bone cell hyperpolarization response to cyclic mechanical strain is mediated by an interleukin-1 autocrine/paracrine loop. J Bone Miner Res 15:1746–1755
18. Park JK, Cui Y, Kim MK et al (2002) Effect of extracorporeal shock wave lithotripsy on plasma levels of nitric oxide and cyclic nucleotides in human subjects. J Urol 168:38–42
19. Sarci K, Balat A, Erbagi A, Cekmen M, Yurekli M, Yagci F (2003) Effect of shock wave lithotripsy on plasma and urinary levels of nitrite and adrenomedullin. Urol Res 31:347–351
20. Gardeniers JWM (1993) ARCO (Association Research Circulation Osseous) international classification of osteonecrosis. ARCO Committee on Terminology and Staging. Report on the committee meeting at Santiago de Compostella. ARCO Newsl 5:79–82
21. Kim VM, Oh HC, Kim HJ (2000) The pattern of bone marrow edema on MRI in osteonecrosis of the femoral head. J Bone Joint Surg (Br) 82B:837–841
22. Martini L, Giavaresi G, Fini M et al (2003) Effect of extracorporeal shock wave therapy on osteoblast-like cells. Clin Orthop 413:269–280
23. Wang FS, Yang KD, Kuo YR et al (2003) Temporal and spatial expression of bone morphogenetic proteins in extracorporeal shock wave-promoted healing of segmental defect. Bone 32:387–396
24. McCormack D, Lane H, McElwain J (1996) The osteogenic potential of extracorporeal shock wave therapy: an in vivo study. Ir J Med Sci 165:20–22
25. Wang FS, Yang KD, Chen RF, Wang CJ, Sheen-Chen SM (2002) Extracorporeal shock wave promotes bone marrow stromal cell growth and differentiation toward osteoprogenitors associated with TGF-β1 induction. J Bone Joint Surg 84B:457–461
26. Wang CJ (2003) An overview of shock wave therapy in musculoskeletal disorders. Chang Gung Med J 26:220–232
27. Wang CJ, Hung HY, Pai CH (2002) Shock wave-enhanced neovascularization at the tendon-bone junction: an experiment in dogs. J Foot Ankle Surg 41:16–22
28. Wang CJ, Wang FS, Yang KD, Huang CS, Hsu CC (2003) Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 21:984–989
29. Wang CJ, Yang KD, Ko JY, Huang CC, Huang SY, Wang FS (2009) The effects of shockwave on bone healing and systemic concentrations of nitric oxide (NO), TGF-β1, VEGF and BMP-2 in long bone non-unions. Nitric Oxide 20:298–303
30. Wang CJ, Wang FS, Yang KD (2008) Biological effects of extracorporeal shockwave in bone healing: a study in rabbits. Achiv Orthop Trauma Surg 128:879–884
31. Mainsonhaute E, Prado C, White PC, Compton RG (2004) Surface acoustic cavitation understood via nanosecond electrochemistry, part III: shear stress in ultrasonic cleaning. Ultrasound Sonochem 9:297–303
32. Wang FS, Yang KD, Wang CJ et al (2004) Shockwave stimulates oxygen radical-mediated osteogenesis of the mesenchymal cells from human umbilical cord blood. J Bone Miner Res 19(6):973–982
33. Wang FS, Wang CJ, Sheen-Chen SM, Kuo YR, Chen RF, Yang KD (2002) Superoxide mediates shock wave induction of RRK-dependent osteogenic transcription factor (CBFA 1) and mesenchymal cells differentiation toward osteoprogenitors. J Biol Chem 277(3):10931–10937
34. Wang FS, Wang CJ, Chen YJ et al (2004) Ras Induction of superoxide activates ERK-dependent angiogenic transcription (HIF-1α) and VEGF-An expression in shock wave-stimulated osteoblasts. J Biol Chem 279:10331–10337
35. Kaspar D, Neidlinger-Wilke C, Holbein O, Claes L, Ignatius A (2003) Mitogens are increased in the systemic circulation during bone callus healing. J Orthop Res 21:320–325
36. Wang CJ, Yang KD, Wang FS, Chen HS, Chen HH, Hsu CC (2004) Shock wave therapy enhances bone mass and bone strength after fracture of the femur. A study in rabbits. BONE 34:225–230