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Original Research Article

Effect of a combination of alendronate sodium and radial shock wave on hemorheology and degree of pain in patients with femoral head necrosis

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Abstract

Purpose: *To determine the effect of alendronate sodium combined with radial shock wave on hemorheology and degree of pain in patients with femoral head necrosis.*
Methods: *The study comprised 188 patients with femoral head necrosis treated in Taizhou People's Hospital, China from June 2020 to June 2022. They were divided into control group (CG, n = 96) and study group (SG, n = 92). Control group was given radial shock wave therapy once in 30 days, while the study group was given alendronate sodium orally (10 mg/daily) for 3 months, as well as radial shock wave therapy. Hemorheology indices (plasma viscosity (PV), low-cut reduced viscosity (LRV), high-cut reduced viscosity (HRV)); degree of pain (McGill Pain Questionnaire (MPQ)), joint muscle strength, and clinical efficacy in both groups were compared.*
Results: *The SG had significantly lower levels of PV, LRV and HRV, and lesser MPQ scores at 1 month (T1) and 2 months post-treatment (T2) than CG ($p < 0.05$). The post-treatment levels of PV, LRV, HRV, and MPQ scores at T1 stage in the two groups were significantly lower than the pre-treatment (T0) scores ($p < 0.001$). The scores of PV, LRV, HRV, and MPQ at T2 in both groups were significantly lower than the corresponding T1 scores ($p < 0.05$). Higher numbers of cases with grade 4 and grade 5 joint muscle strength were seen in SG than in CG at T2. Treatment efficacy/effectiveness in SG was significantly higher than in CG ($p < 0.05$).*
Conclusion: *Alendronate sodium combination with radial shock wave, produces significant improvement in femoral head necrosis, mitigates symptoms and enhances joint muscle strength of patients. Future studies with larger sample sizes will be necessary to validate the outcome of this study.*

Keywords: *Radial shock wave, Alendronate sodium, Femoral head necrosis, Hemorheology, Joint muscle strength*

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INTRODUCTION

Femoral head necrosis is a disabling disease of bone and joints seen often in orthopedics [1]. Different etiologies lead to poor blood supply of the femoral head, resulting in necrosis of bone marrow stromal cells, osteocytes and adipocytes which cause the collapse and deformation of the femoral head structure [2,3]. Femoral head necrosis is characterized by concealed onset and

inconspicuous clinical features at the early stage. Thus, most patients receive clinical treatment only in the middle and late stages, resulting in a high mutilation rate [4].

Radial shock wave therapy is the main clinical treatment method for this disease, and it is widely used in orthopedics and the field of sports medicine owing to its strong effectiveness in enhancing tissue healing [5]. Shock wave accumulates energy at the interface between human bones and soft tissues, *causing energy reflection and absorption*, promoting neovascularization, and improving tissue blood circulation, thereby producing therapeutic effect. However, shock wave therapy alone does not effectively relieve pain and reduce the clinical symptoms in patients. Hence, currently, its combination with other treatment methods has become a subject of great interest in the medical field.

Alendronate sodium belongs to the third generation of diphosphates, and it is mainly used for the prevention and treatment of osteoporosis in clinical settings, with definite curative effects [6]. Recent studies have revealed that alendronate sodium inhibits the maturation of immature osteoclasts, reduces the number of mature osteoclasts, accelerates apoptosis of osteoclasts, restores the dynamic balance between osteoclasts and osteoblasts, and inhibits the collapse of femoral head necrosis. The combined application of alendronate sodium and radial shock wave in clinical treatment is expected to improve the clinical treatment efficacy of femoral head necrosis.

Based on the above theory, this study investigated the effect of the combined treatment scheme on hemorheology and degree of pain in patients with femoral head necrosis, with a view to generating a novel method for therapy of the illness.

METHODS

Clinical data

In this study, 188 patients with femoral head necrosis in Taizhou People's Hospital, Taizhou, China were selected. The subjects were assigned to control group (CG, n = 96) and study group (SG, n = 92). A flow chart for the study is presented in Figure 1. The study received approval from the ethical authority of Taizhou People's Hospital (approval no. 20200411) and was carried out in line with Helsinki Guidelines [7].

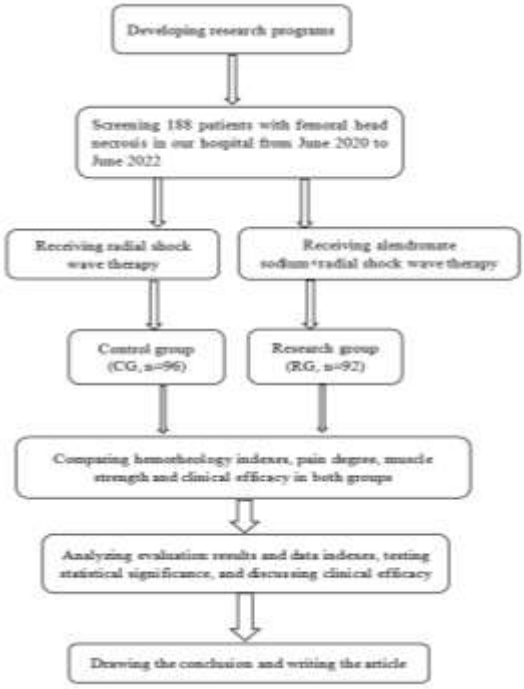

Figure 1: Flow chart for this study

Inclusion criteria

The included patients were those who met the diagnostic criteria of *Practical Diagnosis and Treatment of Femoral Head Necrosis* [8]; patients who were clinically confirmed to have femoral head necrosis through X-ray and MRI medical imaging, with hip joint pain; patients who met the staging criteria for stage I or stage II of femoral head necrosis (Association Research Circulation Osseous, ARCO) [9], and patients who, with their families, were aware of the purpose of study and signed informed consent.

Exclusion criteria

The following categories of patients were excluded from the study: patients who had ankylosing spondylitis, rheumatoid arthritis, and bone tuberculosis; patients who had received hormonal treatment within one month prior to the study; those who had blood diseases, immune system abnormalities, digestive system abnormalities, and malignant tumors, and patients who had dysfunctions in heart, lung and liver.

Protocol

Gymna-ShockMaster 500 extracorporeal shock wave therapy apparatus manufactured by Guangzhou Vedo Health & Science Co. Ltd., was used in CG for radial shock wave therapy. The coupling agent was uniformly smeared on the patient's skin, with a treatment frequency of 10 -

17 Hz and pulse of 0.15 - 0.35 mJ/mm^2/wave number. The treatment time was 5 - 10 min once daily, with a treatment interval of 3 days. One course of treatment lasted 30 days, and 3 consecutive courses of treatment were used [10].

In addition to the above treatment, SG was treated with alendronate sodium (specification: 70 mg; NMPA approval no. J20130085; manufacturer: Merck Sharp & Dohme Pty. Limited). In the morning, the patients were given 10 mg of alendronate sodium orally with warm water, in fasting state, once a day. Calcium beverage was contraindicated within 30 min of taking alendronate sodium, and patients were maintained in an upright sitting position for 30 min, with treatment lasting for 3 months [11].

Evaluation of parameters/indices

Pre-treatment (T0) 1-month (T1) and 2-month (T2) post-treatment values of hemorheology indices, degree of pain and joint muscle strength were compared between the two cohorts. Then, treatment effectiveness was evaluated and analyzed in line with the clinical manifestations of patients after treatment.

Hemorheology indices

In the morning, 5 mL of blood was taken from the vein of each patient in the fasted state and kept in a heparinized tube. Plasma viscosity (PV), low-cut reduced viscosity (LRV) and high-cut reduced viscosity (HRV) were measured using MVIS-2040A automatic hemorheology analyzer (manufacturer: Chongqing Tianhai Medical Equipment Co. Ltd).

Severity of pain

Dynamic pain assessment was performed on patients using the McGill Pain Questionnaire Short-Form (MPQ) [12]. The MPQ was composed of 20 groups of pain descriptors in sense, emotion, evaluation and other related categories. The pain intensity was divided into 4 categories: painless, low, moderate and severe, with 0 - 3 points, and a maximum score of 60 points. The score was directly proportional to the intensity of pain in patients.

Joint muscle strength

The attending physician conducted a barehanded muscle strength test on the patient's muscle strength of the hip flexor and extensor. This was divided into 6 grades, based on the patient's muscle strength status [13], as shown in Table 1.

Table 1: Evaluation of joint muscle strength

Grade	Evaluation criterion
0	There was no contractile response in the muscle.
1	There was a contractile response in the muscle, but the limb was unable to move.
2	Limbs could move horizontally, but could not complete lifting action.
3	Limbs could leave the bed, but could not resist resistance.
4	Limbs could resist some weaker resistance
5	Muscle strength was not different from that of normal people.

Clinical treatment efficacy

Efficacy was categorized as indicated in Table 2. Treatment effectiveness (TE) was calculated using Eq 1.

$$TE\ (\%) = \{(ME+E)/N\}100 \quad \ldots\ldots\ldots\ldots\ldots\ (1)$$

where N is total number of patients.

Statistical analysis

Data were statistically analyzed with SPSS 26.0 software package, while graphs were drawn using GraphPad Prism 7. Student's *t*-test and Chi-squared test were used for comparison of counted and measured data which are shown as (n (%)) and mean ± standard deviation (SD), respectively. Statistical significance of difference was assumed at $p < 0.05$.

Table 2: Efficacy criteria

Degree of improvement	Evaluation criterion [14]
Markedly effective (ME)	The symptoms were significantly improved; the joint muscle strength reached grade 4 and above, and was in a stable state under X-ray imaging.
Effective (E)	The symptoms were obviously improved, and the joint muscle strength reached grade 3 or above, and was basically in a stable state under X-ray imaging.
Ineffective (I)	The symptoms were not improved, or the condition was aggravated, and the joint muscle strength was at grade 2 or below.

RESULTS

Patients' background data

Both groups showed no statistical difference in general clinical data ($p > 0.05$), as shown in Table 3.

Hemorheological indices

The SG had significantly lower levels of PV, LRV and HRV than CG at T1 and T2 stages (T1 stage: $t = 4.358$, $p < 0.001$; $t = 8.593$, $p < 0.001$, and $t = 3.369$, $p = 0.001$, respectively; T2 stage: $t = 3.998$, $p < 0.001$; $t = 5.727$, $p < 0.001$, and $t = 8.860$, $p < 0.001$, respectively), but PV, LRV and HRV were comparable in the 2 groups at T0 stage ($t = 0.059$, $p = 0.269$; $t = 1.227$, $p = 0.223$; $t = 0.530$, $p = 0.598$). In both cohorts, there were marked reductions in levels of PV, LRV and HRV at T1 stage, relative to T0 stage ($p < 0.001$). However, at T2 stage, both cohorts had lower levels of PV, LRV and HRV than at T1 stage ($p < 0.05$; Table 4).

Degree of pain

After treatment, the SG subjects had lower MPQ scores than those in CG at T1 and T2 stages, and the differences were statistically significant ($p < 0.05$), but there was no marked difference in MPQ score between both groups at T0 stage. At T1 stage, there were significantly lower MPQ scores in the two groups than at T0 stage, but MPQ scores in the two groups at T2 were markedly reduced, relative to those at T1 ($p < 0.001$), as shown in Table 5.

Table 3: Background data on each cohort

Parameter	CG (n = 96)	SG (n = 92)	χ^2/t	*P*-value
Sex			0.010	0.920
Male	56 (58.33)	53 (54.61)		
Female	40 (41.67)	39 (42.39)		
Age (mean ± SD, years)	47.49±4.34	47.1f±4.85	0.535	0.077
Duration (mean ± SD, months)	2.98±0.84	2.95±0.93	0.218	0.196
ARCO* stages			0.003	0.955
Stage Ⅰ	57 (59.38)	55 (59.78)		
Stage Ⅱ	39 (40.63)	37 (40.22)		
Positions of affected limb				
Left side	27 (28.13)	25 (27.17)	0.022	0.989
Right side	39 (40.63)	38 (41.30)		
Both sides	30 (31.25)	29 (21.52)		
Basic disease			0.008	0.996
Diabetes	29 (30.21)	28 (30.43)		
Hypertension	34 (35.42)	32 (34.78)		
Hyperlipidemia	33 (34.38)	32 (34.78)		
Family income (CNY/month)			0.039	0.981
Above 12000	22 (22.92)	20 (21.74)		
6000-12000	45 (46.88)	44 (47.83)		
Below 6000	29 (30.21)	28 (30.43)		

*ARCO = Association Research Circulation Osseous; CNY, Chinese Yuan

Table 4: Comparison of hemorheology indices (PV, LRV, and HRV at T0, T1 and T2) in both groups (n = 96)

Group	Time-point	PV (mPa)	LRV (mPa)	HRV (mPa)
	T0	2.96±0.43	51.36±4.24	5.88±0.45
CG	T1	2.70±0.37**	42.61±3.45**	5.47±0.41**
	T2	2.52±0.32$^{\#}$	38.58±2.75$^{\#\#}$	4.99±0.38$^{\#\#}$
	T0	2.95±0.40	50.40±4.56	5.85±0.51
SG	T1	2.49±0.38**	38.27±3.38**	5.26±3.40**
	T2	2.30±0.36$^{\#}$	36.09±3.06$^{\#\#}$	4.46±0.37$^{\#\#}$

**$P < 0.001$, T0 vs. T1; $^{\#}p < 0.05$, T1 vs. T2; $^{\#\#}p < 0.001$, T1 vs. T2

Table 5: MPQ scores in both groups

Time point	**CG** (n=96)	**SG** (n=92)	*t*	*P*-value
T0	51.54±3.38	51.30±3.40	0.491	0.624
T1	45.67±3.53**	42.57±4.09**	5.220	<0.001
T2	35.22±3.50$^{\#\#}$	30.47±5.17$^{\#\#}$	7.485	<0.001

**$P < 0.001$, T0 vs. T1; $^{\#\#}p < 0.001$, T1 vs. T2

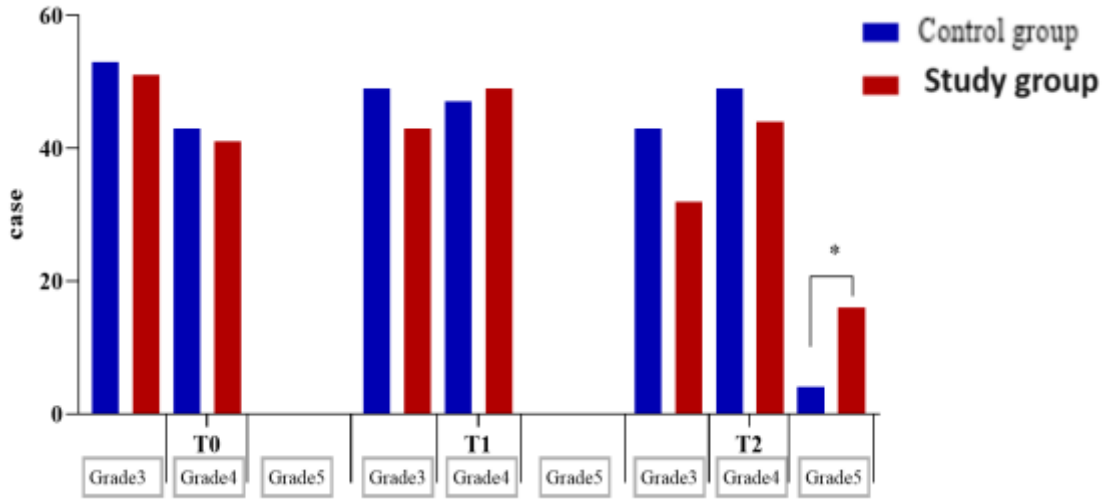

Figure 2: Joint muscle strength in both cohorts

Joint muscle strength

There were no statistically significant differences in grades of joint muscle strength between both groups at T0 stage (χ^2 = 0.001, p = 0.975). After treatment, there was still no significant difference in muscle strength grade between the 2 cohorts at T1 stage (χ^2 = 0.348, p = 0.555), but the SG had significantly smaller number of patients with grade 4 of joint muscle strength and significantly more patients with grade 5 than CG at T2 stage (χ^2 = 9.001, p = 0.011; Figure 2).

Efficacy

At the end of follow-up, treatment effectiveness in ERG was 95.65 %, which was significantly higher than 79.17 % in CG (χ^2 = 11.635, p = 0.003), as shown in Figure 3.

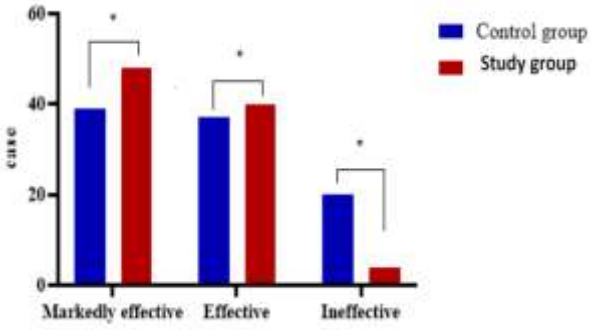

Figure 3: Comparison of clinical efficacy between both groups

DISCUSSION

Femoral head necrosis is a difficult orthopedic disease, and its pathogenesis has not yet been clarified. At present, the academic theory of hemodynamic disorder in femoral head is widely accepted in clinical practice. This theory posits that various factors inside and outside the bone and joint cause decrease in the supply of nutrient-rich blood to bone tissue and ischemia necrotic bone tissue, thereby leading to the collapse of femoral head [15]. In the late stage, this disease is accompanied by serious complications such as muscle atrophy and claudication which cause some degree of disability, with serious impact on the daily life of patients [16]. Therefore, the objective of current clinical treatments is to improve blood supply, relieve clinical symptoms, and control the disease early in patients.

Shock wave was originally a physical concept that was first applied for the treatment of urinary calculus. It accelerates the wave by creating a high pressure within a few nanoseconds: this changes the waveform, releases huge energy, and causes changes in human tissues and cells, resulting in therapeutic effects [17]. Radial shock wave has a significant therapeutic effect in the clinical treatment of femoral head necrosis [18]. The data obtained in this study showed that radial shock waves effectively improved the hemorheology of patients. The reason for this effect is that radial shock wave stimulates the expressions of growth factors in bone, tendon and early neovascularization, thereby effectively promoting neovascularization and tissue blood circulation which improves blood supply to the lesion sites, and induces the formation of new bone [19].

Osteonecrosis caused by chronic alcoholism or glucocorticoid is a common type of femoral head necrosis. A medical study has found that hormones have negative impacts on osteoblasts, thereby delaying osteogenesis, mediating

apoptosis and causing bone loss [20]. Therefore, some studies have found that osteonecrosis is the result of the interactions of apoptosis and necrosis of hormone-induced osteocytes with osteoblasts. Alendronate sodium, an amino bisphosphonate, has a strong affinity for hydroxyapatite in bone [22]. It is often used as a bone metabolism regulator in clinical practice. In the clinical treatment of femoral head necrosis, Alendronate reduces bone turnover, increases bone mass and graft bone destruction, and delays bone collapse. Data obtained in the present investigation revealed that SG had lower values of PV, LRV, HRV and MPQ scores at T1 and T2 stages, and higher joint muscle strength in patients with grade 4 and grade 5 at T2 stages than those in CG. This indicates that the combination of alendronate sodium and radial shock wave significantly improved clinical efficacy, promoted re-vascularization, and improved the joint muscle strength of patients. On studying the underlying mechanism, it was found that alendronate sodium entered the hydroxyapatite crystals in bone matrix and was released when osteoclasts dissolved hydroxyapatite crystals, thereby inhibiting bone resorption by inhibiting osteoclast activity [23]. Alendronate sodium reduced bone transformation (i.e., the number of bone reconstruction sites), and corrected the bone repair process that led to loss of dynamic balance at these reconstruction sites [24]. Thus, it ensured that bone formation was greater than bone resorption, with attendant bone mass increase, thereby effectively inhibiting bone destruction, delaying femoral head collapse, and improving joint muscle strength.

At the last follow-up, SG had significantly higher clinical treatment effectiveness than CG. This indicates that radial shock wave in combination with alendronate sodium, produced good synergistic effect. The combined treatment not only promoted bone reconstruction and mitigated blood supply disorder, but also inhibited apoptosis of femoral head cells, delayed femoral head collapse, and improved clinical treatment efficiency.

Limitations of the study

Due to study limitations and time constraints, no long-term efficacy observation was conducted. Given the economic burden on patients, the imaging diagnosis and examination of femoral head necrosis before treatment were not unified, and thus, there may be some errors in grading and staging.

CONCLUSION

Radial shock waves in combination with alendronate sodium produce significant effect on femoral head necrosis. It improves hemorheological indices, relieves pain, and improves joint muscle strength of patients. The combination is of great importance in enhancing the quality of life of subjects. Future studies will be necessary to expand the sample range and improve the test design scheme, to obtain more objective results.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Lei Jiang, Xiafen Zhang and Fan Zhang conceived and designed the study, and drafted the manuscript. Yichao Ji, Xu Shen and Fan Zhang collected, analyzed and interpreted the experimental data. All authors revised the manuscript for important intellectual content as well as read and approved the final manuscript for publication.

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