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Application of extracorporeal shockwave to regulate subchondral bone homeostasis through tumor necrosis factor-α/hypoxia-inducible factor-1α/vascular endothelial growth factor signaling pathway in treatment of talus bone marrow edema

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Abstract

To investigate the effect of extracorporeal shock wave on the treatment of talus bone marrow edema by regulating subchondral bone homeostasis through tumor necrosis factor-α (TNF-α)/hypoxia-inducible factor-1α (HIF-1α)/vascular endothelial growth factor (VEGF) signaling pathway. A total of 81 patients with talus bone marrow edema admitted to our hospital from May 2019 to May 2021 were studied and divided into control group (n = 40) and extracorporeal shock group (n = 41) according to random number table method. The control group was given conventional treatment, and the extracorporeal shock group was combined with extracorporeal shock wave therapy on the basis of the control group. The expression of TNF-α, HIF-1α, and VEGF in the 2 groups were compared, pain degree, and the area of talus bone marrow edema was evaluated by magnetic resonance imaging. The visual analogue scale scores of 1 month, 2 months and 5 months after treatment were decreased in both groups, and the extracorporeal shock group was lower than the control group ($P < .05$). After 5 months of treatment, the expressions of TNF-α and HIF-1α were decreased in both groups, and the extracorporeal shock group was lower than the control group, VEGF was increased, and the extracorporeal shock group was higher than the control group ($P < .05$), and the western blot expression levels of TNF-α, HIF-1α and VEGF in the extracorporeal shock group were higher than the control group ($P < .05$). The dorsiflexion motion and plantar flexion motion of both groups were increased, and the extracorporeal shock group was higher than the control group ($P < .05$). Extracorporeal shock wave therapy can regulate subchondral bone homeostasis through TNF-α/HIF-1α/VEGF signaling pathway to treat talus bone marrow edema, reduce the pain degree of talus bone marrow edema, and improve ankle joint function.

Abbreviations: BMI = body mass index, HIF-1α = hypoxia-inducible factor-1α, TNF-α = tumor necrosis factor-α, VAS = visual analogue scale, VEGF = vascular endothelial growth factor.

Keywords: extracorporeal shock wave, HIF-1α, subchondral bone homeostasis, talus bone marrow edema, TNF-α, VEGF

1. Introduction

Talar bone marrow edema is a rare condition characterized by foot and ankle pain, the cause of which is unknown.[1] There are 2 causes of bone marrow edema, 1 is primary, the other is secondary, and the pathogenesis is still unclear.[2,3] Studies have shown that ischemia can cause talus bone marrow edema.[4] As a pathological condition, mild bone marrow edema of talus, that is, abnormal fluid accumulation in the bone marrow tissue, may be caused by excessive exercise, anemia, synovitis, osteoarthritis, lumbar disc herniation and other reasons, and needs to be treated by daily care and drugs.[5] Patients are advised to use ferrous fumarate granules, compound ammonium ferric citrate syrup and other iron agents for treatment under the guidance of doctors.[6] The synovial membrane is stimulated

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

The ethic approval was reviewed and approved from The Putuo People's Hospital, School of Medicine, Tongji University and written informed consent was obtained from all patients.

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to produce inflammation, resulting in secretion imbalance and accumulation, which may cause the disease, manifested as talus pain, cold limbs, etc, and accompanied by the above symptoms. The etiology of this disease is unknown, which can lead to pain, stiffness, swelling, bone marrow edema, etc of talar joint in patients.[7,8] Lumbar intervertebral disc herniation may be caused by factors such as disc degeneration and chronic strain, and the above symptoms may be caused during the onset of the disease, accompanied by sciatica, numbness, and fatigue.[9,10]

Hemorrhagic necrosis of talus is the earliest reversible stage. Extracorporeal shock wave cavitation and pressure wave action can repair tissue cells and reduce nerve sensitivity, thus relieving pain.[11] Extracorporeal shock wave therapy is a new therapeutic method for the treatment of osteogenic knee joint. It is used to treat soft tissue fascia tendinitis, including knee arthritis, shoulder calcifying tendinitis, tennis elbow, plantar fasciitis and other orthopedic diseases,[12] with a cure rate of 80% to 90% and a recurrence rate of only 5% to 10%.[13] In the process of electro-hydraulic energy conversion and transmission, shock wave can cause energy gradient difference and torsional tension between tissues with different densities, thus releasing adhesion.[14,15] Meanwhile, microcirculation of tissues at the impacted site accelerates, improves blood circulation in local tissues, activates bone cells, promotes bone tissue regeneration, adapts to pain, gradually improves the pain area, and thus alleviates pain. To achieve the therapeutic purpose.[16–18] However, since extracorporeal shock wave therapy for osteoarthritis of the knee is the result of comprehensive effects, its therapeutic mechanism and efficacy evaluation methods are still unclear. The purpose of this study was to investigate the effect of extracorporeal shock wave on the treatment of talus bone marrow edema by regulating subchondral bone homeostasis through TNF-α/HIF-1α/VEGF signaling pathway.

2. Data and methods

2.1. General information

A total of 81 patients with talus bone marrow edema admitted to our hospital from May 2019 to May 2021 were selected as the study objects. Inclusion criteria: all patients were diagnosed with talus myeloid edema; the patient complained of ankle joint pain. Exclusion criteria: combined hemorrhagic disease; a history of old fracture; there are contraindications of shock wave therapy. The ethic approval was reviewed and approved from The Putuo People's Hospital, School of Medicine, Tongji University, and all patients and their families have informed consent and signed informed consent.

2.2. Methods

2.2.1. Treatment. The control group received conventional treatment. The nonsteroid anti-inflammatory drug diclofenac sodium sustained-release tablets (Shandong Dezhou Pharmaceutical Co., Ltd, H10970008, Dezhou, Shandong) were given orally once a day, 1 tablet (100 mg), or 1 tablet (75 mg), 1 to 2 times a day, + bisphosphonate sodium alendronate (Shandong Dezhou Pharmaceutical Co., Ltd, Dezhou, Shandong) National Drug Approval number H10970008) Orally take 1 tablet (100 mg) once a day, or 1 tablet (75 mg) once or twice a day. Both groups were instructed to avoid high-intensity exercise, walking and sitting for long periods of time during treatment. All patients were observed for 5 months.

The extracorporeal shock group was combined with extracorporeal shock wave therapy on the basis of the control group, and was treated with DOLORCLAST extracorporeal shock wave therapy instrument of Swiss EMS company. Patients were supine or seated, exposed to the affected limb, and couplers were applied locally, centered on the pain point of the knee joint, and administered horizontally and vertically at a pressure of 2 to 3 bar with a frequency of 8 to 10 Hz. During the treatment, pressure, pressure and frequency were adjusted according to the patient's pain and tolerance, every 20 minutes, once a week, every 5 times as a course of treatment, and the interval of the 2 courses was 2 months. All patients were observed for 5 months.

2.2.2. Western blotting. An equal amount of denatured protein samples were taken for western blot. Prepare SDS-PAGE gel (electrophoresis after gel preparation is completed: after installing the electrophoresis tank, add marker (2–4 μL; #SM1811, Biyuntian) in the first hole of loading sample, add sample next to it (the loading amount is generally 200 μg, and the loading volume can be converted by concentration), and add waste sample in the last hole. After electrophoresis, remove the gel and cut the required strip with reference to Marker. The protein on the adhesive strip was transferred to the NC film by electric transfer instrument. Sealing: Remove the NC film and place the Washing buffer (1X) upside-down in the petri dish with Washing buffer (1X), wash away the Washing buffer (1X) in the shaking bed for 5 minutes × 3 times, directly add the Washing buffer (1X) into the sealing solution, and seal it for 2 hours. Incubation of primary antibody: Discard or recycle the sealing solution, wash the film once with Washing buffer (1X), add primary antibody, and leave at 4°C overnight (diluted with a primary antibody diluent, with the dilution ratio of 1:1000 except actin, which were all 1:500). Recycle the primary antibody and add it into the Washing buffer (1X), wash it in the washing table for 5 minutes × 3 times, and then put the membrane into a small tank with the secondary antibody added. Fluorescent secondary antibodies (all diluted with secondary antibody diluent, dilution ratio of 1:10,000) were kept away from light at room temperature for 2 hours. Take it out of the refrigerator at 4°C and reheat it for 30 minutes. washing film in washing buffer: Recycle secondary antibodies and add them into washing buffer (1X), 5 minutes × 3 times. Odyssey 2-color infrared imaging system scans NC film.

2.3. Observation indicators

2.3.1. Pain degree the visual analogue scale (VAS). Pain degree the visual analogue scale (VAS) was used to evaluate the pain degree of patients in the 2 groups before treatment, 1 month, 2 months and 5 months after treatment.[7] The scale has a total score of 0 to 10, and the higher the score, the more severe the pain.

2.3.2. Serum indicators. Five mL of abdominal venous blood was collected before treatment and 5 months after treatment, and TNF-α, HIF-1α, and VEGF were detected by enzyme-linked immunosorbent assay. The immunoblot expression levels of the 2 groups were compared 5 months after treatment.

2.3.3. The ankle flexion and plantar flexion angles. The ankle flexion and plantar flexion angles of the 2 groups were measured with a joint protractor.

2.4. Statistical methods

SSPS 25.0 software was used to process and analyze the rows of report data. The pain score level was represented in the form of "mean ± standard deviation", *t* test was performed, gender was represented in the form of "%", and Chi-square test was performed. If $P < .05$, the difference was considered statistically significant. OD values of protein expression were measured using Image J software, and OD values shown in the results were relative OD values obtained after comparing the measured values with those of the corresponding normal control group.

3. Results

3.1. Basic characteristics of the 2 groups

They were divided into control group (n = 40) and extracorporeal shock group (n = 41) according to random number table method. Control group: 21 males and 19 females; The average age was (54.39 ± 5.12) years. The course of disease was 4 to 10 months, with an average of (5.93 ± 1.72) months. Body mass index (BMI) 19~21 kg/m^2, average BMI (20.14 ± 1.54) kg/m^2; There were 15 cases of hypertension, 15 cases of diabetes and 15 cases of cardiovascular disease. In the extracorporeal shock group, there were 25 males and 16 females. The average age was (54.74 ± 4.57) years. The course of disease was 4 to 10 months, with an average of (5.42 ± 1.03) months. BMI 19~21 kg/m^2, average BMI (19.98 ± 1.62) kg/m^2; There were 12 cases of hypertension, 15 cases of diabetes and 18 cases of cardiovascular disease. There was no significant difference in the general data between the 2 groups ($P > .05$), which was comparable.

3.2. Comparison of pain degree between the 2 groups

Before treatment, there was no statistical significance in VAS scores between the 2 groups ($P > .05$), and VAS scores of the 2 groups decreased at 1 month, 2 months and 5 months after treatment, and the extracorporeal shock group was lower than the control group ($P < .05$; Table 1).

3.3. Comparison of serum levels between the 2 groups

Before treatment, there was no statistical significance in the expression levels of TNF-α, HIF-1α, and VEGF in 2 groups ($P > .05$). After 5 months of treatment, the expressions of TNF-α and HIF-1α in 2 groups were decreased, and the extracorporeal shock group was lower than the control group, and VEGF was increased, and the extracorporeal shock group was higher than the control group ($P < .05$). The immunoblot expression levels of TNF-α, HIF-1α and VEGF in extracorporeal shock group were higher than those in control group ($P < .05$; Tables 2, 3 and Fig. 1).

3.4. Comparison of activity levels of dorsiflexion and plantar flexion between the 2 groups

Before treatment, there was no statistical significance in the expression levels of dorsiflexion activity and plantar flexion activity in 2 groups ($P > .05$). After 5 months of treatment, both dorsiflexion activity and plantar flexion activity in 2 groups were increased, and the extracorporeal shock group was higher than the control group ($P < .05$; Table 4).

4. Discussion

Extracorporeal shock wave has high safety. The study conducted by Huang et al showed that the total effective rate of the extracorporeal shock group and the VAS score, WOMAC index score, Lequesne index score, interleukin-6 level and interleukin −8 level ratio after treatment were significantly different from the control group ($P < .05$), indicating that the effect of extracorporeal shock wave was quite good. The incidence of adverse reactions between the 2 groups was significantly different ($P < .05$).[19]

In this study, VAS scores of both groups decreased at 1 month, 2 months and 5 months after treatment, and the extracorporeal shock group was lower than the control group ($P < .05$), indicating that the treatment of talus bone marrow edema can be treated by ECKVD through TNF-α/HIF-1α/VEGF signaling pathway to regulate subchondral bone homeostasis and reduce the pain degree of talus bone marrow edema. The impact of shock wave therapy on the interface of various tissues. During the treatment of shock wave therapy, the tiny cavitation of gas nuclei in the interstitial-fluid of tissues oscillates under the excitation of shock waves, and when the shock wave intensity is greater than a certain value, there will be phenomena such as growth and collapse.[20,21] In the body, due to the propagation of sound waves, its vibration can be continuously absorbed by the body. In recent years, with the in-depth study of extracorporeal shock wave therapy at home and abroad, it has been found that it has good therapeutic effect on osteoarthritis, bone marrow edema, tibial tuberosus osteochondritis, talus osteochondral injury, tenosynovitis, scapula bursitis, etc, and reduces pain.[22]

Table 1

Comparison of pain degree between the 2 groups ($\bar{x} \pm s$).

Groups	N	Pre-treatment	One month after treatment	Two months after treatment	Five months after treatment
Extracorporeal shock group	41	7.12 ± 1.31	5.24 ± 1.21*	3.21 ± 1.03*	2.12 ± 0.65*
Control group	40	7.22 ± 1.03	6.02 ± 1.23*	4.25 ± 1.14*	2.65 ± 0.87*
t		0.414	3.115	4.663	3.358
P		.681	.002	.001	.001

*$P < .05$, compared with before treatment.

Table 2

Comparison of serum levels between the 2 groups ($\bar{x} \pm s$).

		TNF-α (pg/mL)		HIF-1α (pg/mL)		VEGF (μg/L)	
Groups	N	Pre-treatment	Five months after treatment	Pre-treatment	Five months after treatment	Pre-treatment	Five months after treatment
Extracorporeal shock group	41	44.45 ± 5.67	24.69 ± 3.36*	20.23 ± 4.11	14.56 ± 4.98*	3.39 ± 3.21	5.01 ± 0.81*
Control group	40	44.43 ± 5.78	28.56 ± 3.52*	20.56 ± 4.79	17.98 ± 3.82*	3.40 ± 3.20	4.46 ± 0.79*
t		0.004	5.355	0.027	9.963	1.505	5.178
P		.997	<.001	.979	<.001	.136	<.001

HIF-1α = hypoxia-inducible factor-1α, TNF-α = tumor necrosis factor-α, VEGF = vascular endothelial growth factor.

*$P < .05$, compared with before treatment.

VEGF can promote the proliferation of vascular endothelial cells and promote angiogenesis. VEGF receptor 2 is a tyrosine receptor with high affinity to VEGF and plays an important role in promoting angiogenesis and increasing vascular permeability.[23] In hypoxia, HIF-1α is rapidly degraded, and in hypoxia, a large amount of VEGF is synthesized and activated, which then activates endothelial cells, induces inflammation, and ultimately leads to pathological angiogenesis and joint inflammation.[13] In this study, after 5 months of treatment, the expressions of TNF-α and HIF-1α were decreased in both groups, and the extracorporeal shock group was lower than the control group, VEGF was increased, and the extracorporeal shock group was higher than the control group ($P < .05$), and the western blot expression levels of TNF-α, HIF-1α and VEGF in the extracorporeal shock group were higher than the control group ($P < .05$). The dorsiflexor and plantar flexor of both groups increased, and the extracorporeal shock group was higher than the control group ($P < .05$), indicating that extracorporeal shock wave therapy can regulate subchondral bone homeostasis through TNF-α/HIF-1α/VEGF signaling pathway to treat talus bone marrow edema and improve ankle joint function. Shock wave therapy at the ultrasound boundary, through mechanical stress, acoustic boundary energy release, enhance cell permeability, promote and promote the production and secretion of growth factors, so as to achieve the purpose of inhibiting bacterial infection; At the same time, unmyelinated nerve tissue can also be selectively destroyed to promote vascularization, promote bone healing, improve microcirculation, and relieve joint adhesion.[24] At present, this technology has been widely used in rehabilitation training and has a good clinical application prospect. Studies have shown that extracorporeal shock wave therapy can improve motor function after SCI, relieve joint pain, and delay cartilage degeneration. Extracorporeal shock wave therapy can inhibit the expression of HIF-1α and VEGF protein in the synovial tissue of ankle in patients with talus bone marrow edema, and the higher the intensity of extracorporeal shock wave therapy, the more obvious the inhibitory effect on protein.

The weakness of this study is that the number of cases included is relatively small, and case studies will be carried out in the future. Therefore, we must use big data to conduct a comprehensive and comprehensive evaluation of it, and conduct a comprehensive and comprehensive evaluation of it, so as to establish an indicator system that can objectively and accurately predict its occurrence and development, which is also a problem worthy of in-depth study.

Table 3

Comparison of western blot expression levels between the 2 groups ($\bar{x} \pm s$).

Groups	N	TNF-α	HIF-1α	VEGF
Extracorporeal shock group	41	16.76 ± 3.45	15.71 ± 2.11	16.71 ± 3.13
Control group	40	4.15 ± 1.23	8.08 ± 1.45	12.08 ± 1.24
t		12.132	15.352	11.124
P		<.001	<.001	<.001

HIF-1α = hypoxia-inducible factor-1α, TNF-α = tumor necrosis factor-α, VEGF = vascular endothelial growth factor.

5. Conclusions

In summary, extracorporeal shock wave therapy can regulate subchondral bone homeostasis through TNF-α/HIF-1α/VEGF

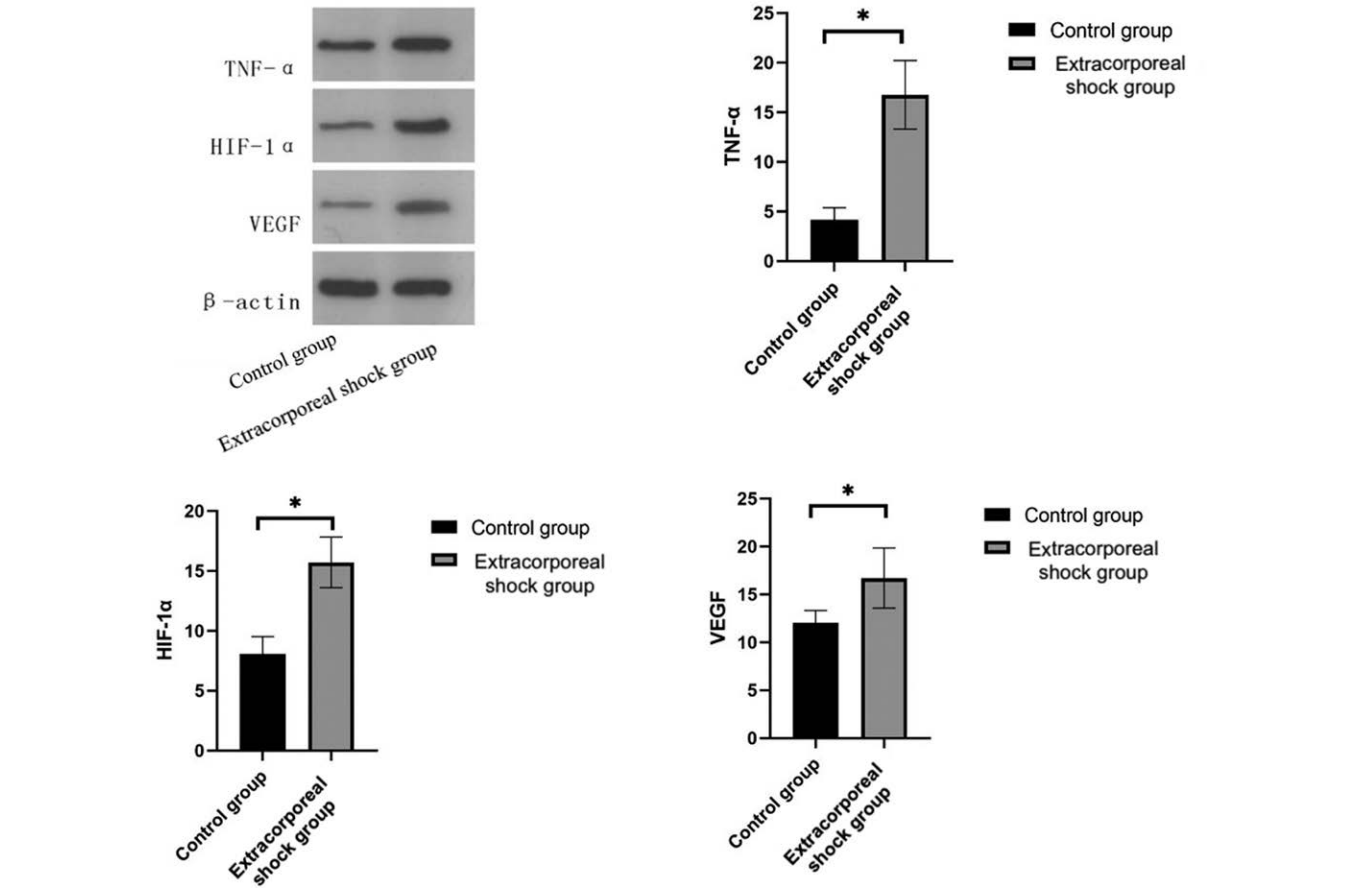

Figure 1. Comparison of western blot expression levels between the 2 groups. HIF-1α = hypoxia-inducible factor-1α, TNF-α = tumor necrosis factor-α, VEGF = vascular endothelial growth factor.

Table 4

Activity level of dorsiflexion and plantar flexion between the 2 groups ($\bar{x} \pm s$).

Groups	N	Dorsiflexion range of motion		Plantar flexion range of motion	
		Pre-treatment	Five months after treatment	Pre-treatment	Five months after treatment
Extracorporeal shock group	41	11.58 ± 3.01	23.67 ± 4.27*	21.60 ± 4.34	37.69 ± 4.21*
Control group	40	11.24 ± 2.97	19.37 ± 3.37*	21.57 ± 4.18	31.97 ± 4.21*
t		0.123	15.981	0.072	11.266
P		.903	<.001	.943	<.001

*indicates statistical significance between the extracorporeal shock group and the control group.

signaling pathway to treat talus bone marrow edema, reduce the pain degree of talus bone marrow edema, and improve ankle joint function.

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