High-energy focused extracorporeal shock wave prevents the occurrence of glucocorticoid-induced osteonecrosis of the femoral head: A prospective randomized controlled trial

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ABSTRACT

Background: Studies have shown that high-energy focused extracorporeal shock wave therapy (HF-ESWT) has a certain therapeutic effect on glucocorticoid-induced osteonecrosis of the femoral head (ONFH). This study aimed to observe the efficacy and safety of HF-ESWT as a precautionary measure to reduce the probability of glucocorticoid-induced ONFH.

Methods: A prospective randomized controlled trial was designed to evaluate whether HF-ESWT (Group A) can significantly prevent the incidence of glucocorticoid-induced ONFH relative to a control group without shock-wave intervention (Group B). MRI was used to assess whether all participants experienced ONFH at 3, 6, and 12 months after the intervention. Continuous scoring was used to evaluate the intervention results: the 10-cm visual analog scale (VAS) was used to evaluate pain, and the hip Harris score (HHS) was used to evaluate the function of the hip joint. Any adverse events were recorded.

Results: 153 patients (89 females and 64 males) who had been allocated to group A (75 patients) or Group B (78 patients) were included in the final analysis. The patients were 45.0 ± 13.0 years old. There were significant differences between the two groups in MRI diagnosis of ONFH patients (2 cases in Group A, 9 cases in Group B; p = 0.034). Significant differences between groups were found in bilateral hip function measured using the HHS at 6 months (Left p = 0.026; Right p = 0.033) and 12 months (Left p = 0.018; Right p = 0.038). However, there was no difference in the functional results measured at 3 months and the VAS at any points.

Conclusions: This study confirms that HF-ESWT can be successfully used to reduce the probability of glucocorticoid-induced ONFH. Pain and hip dysfunction are common clinical manifestations when ONFH is unavoidable. Therefore, HF-ESWT can be recommended for the prevention and intervention of ONFH high-risk populations receiving high-dose glucocorticoid therapy.

The Translational potential of this article: The effective prevention of HF-ESWT on ONFH after high-dose glucocorticoid application demonstrated its transformation potential as a preventive method in the clinical prevention of glucocorticoid-induced ONFH.
1. Introduction

Glucocorticoid-induced osteonecrosis of the femoral head (ONFH) has a high disability rate and disability rate, which seriously affects the daily life of patients. The root cause is the blood supply disorder of the femoral head, and the damage to the bone microvascular endothelial cells is the key link of the damaged blood supply to the femoral head [1, 2]. At present, ONFH is divided into two categories: traumatic and non-traumatic. Nontraumatic ONFH usually affects adults under the age of 50 and often progresses to a collapsed femoral head [3,4], about half of which are caused by glucocorticoids [5,6]. Osteonecrosis occurs in 9–40% of patients receiving long-term glucocorticoid therapy [7], and the incidence of glucocorticoid-induced ONFH has been increasing in recent years due to the widespread use or inappropriate abuse of glucocorticoids.

An estimated 20,000 to 30,000 new patients are diagnosed with osteonecrosis each year [8–10], and individuals between the ages of 30 and 50 were identified as the most susceptible group [11,12]. The number of new ONFH cases in China is increasing year by year. During the treatment of COVID-19 in Wuhan in 2020, the use rate of hormone drugs was as high as 44.9% [13,14]. In addition, some scholars have found that some patients with new coronary pneumonia who receive glucocorticoid therapy will have early ONFH manifestations within an average of 58 days after receiving treatment [15]. ONFH may be asymptomatic in the early stage, but when clinical presentations appear, it means that ONFH may have entered the middle or late stages [11]. At this point, osteonecrosis will be treated surgically and the opportunity for early therapeutic intervention will be lost.

Extracorporeal shock wave therapy (ESWT) is a special form of waves, which is an effective mechanical stimulation. ESWT spreads through alternating media of decompression and compression (sparse and dense), applying cavitation, stretching, and shearing forces to achieve non-destructive mechanical stimulation of tissue cells, thereby activating the self-healing mechanism of tissue cells [16]. According to the different working mechanisms, shock wave therapy is divided into focused shock wave therapy (FSWT) and radial shock wave therapy (RSWT) [17]. There are two important differences in wave characteristics between focused and radial shock waves. Radial shock wave velocity is lower and the destructive mechanical stimulation of tissue cells, thereby activating the self-healing mechanism of tissue cells [16]. According to the different working mechanisms, shock wave therapy is divided into focused shock wave therapy (FSWT) and radial shock wave therapy (RSWT) [17]. There are two important differences in wave characteristics between focused and radial shock waves. Radial shock wave velocity is lower and the effect is more superficial. By contrast, focused shock wave is faster and reaches its maximum energy at a focal point located deeper in body tissue [17]. Many researchers have conducted many studies on the role of high-energy focused extracorporeal shock wave therapy (HF-ESWT) in the treatment of ONFH. Most researchers believe that HF-ESWT can effectively promote osteogenic repair of ONFH [18], relieve ONFH pain, and improve hip joint function, especially in the treatment of early patients [19–21]. Yu et al. [22] even found that HF-ESWT is the most effective way to improve hip Harris scores (HHS). Our center had also carried out a single-center case series study of HF-ESWT treatment of early ONFH [23]. The results show that HF-ESWT can significantly improve early ONFH, effectively relieve pain, and improve hip joint function. For glucocorticoid-induced ONFH, a 12-year follow-up study also confirmed the good effect of combination therapy including HF-ESWT in the treatment of ONFH [24]. Some patients had to use high doses of glucocorticoids due to interference from other diseases, which also means that these patients are at higher risk of developing ONFH. Based on the beneficial effects of HF-ESWT on early ONFH, we hypothesize that HF-ESWT could effectively prevent glucocorticoid-induced ONFH. This will potentially prevent the incidence of ONFH at the source or reduce the area of osteonecrosis, thereby reducing the disability rate, saving medical resources, and improving patients’ medical compliance.

2. Materials and methods

2.1. Study design

This was a prospective, randomized, parallel, controlled study conducted at our single institution from August 2018 to May 2021. This study was approved by the Clinical Research Ethics Committee of China–Japan Friendship Hospital (2018-84-K39-1). This study has been registered with the Chinese Clinical Trial Registration Center (CHICTR1800016283). In this study, all subjects recruited were randomly divided into two groups by random table: the intervention group with HF-ESWT (Group A) and a control group without shockwave intervention (Group B). The primary aim of this study is to observe the occurrence of ONFH during the follow-up period of the two groups of subjects, combined with the clinical experience of our center. The sample size of the intervention group and the control group was calculated by PASS 11.0 software, and the value of each group was 61. Taking into account the 15% loss to follow-up rate, the sample size was set to 144. However, in the actual research process of this study, we moderately increased the calculated value of the sample size. A total of 158 steroid-induced ONFH high-risk groups were eventually recruited. After the participants received high-dose glucocorticoid therapy, the attending doctor registered after evaluating the inclusion and exclusion criteria (R.M. or A.P.). All included patients signed an informed consent form to participate in this study.

2.2. Inclusion and exclusion criteria

Inclusion criteria: 18–65 years old, regardless of gender. It is expected to use high-dose glucocorticoid, and the amount of glucocorticoid should meet one of the following three items [3,5,7,11,25,26]: The cumulative dose of prednisone is greater than 2000 mg; Prednisone exceeds 30 mg/day for more than 1 month; Use high-dose glucocorticoid shock therapy (methylprednisolone ≥800 mg/day for 3 consecutive days and above); Those who can understand this study and sign the informed consent.

Exclusion criteria: The primary disease is severe and is not suitable for participating in this study;Those who have been diagnosed with ONFH before being selected; Pregnant or lactating women; People with allergies and allergies to multiple drugs; Combined with severe heart and cerebrovascular diseases, liver and kidney dysfunction, hematopoietic system disease, serious digestive tract disease, serious underlying diseases of the mental and central nervous system; People with bleeding tendencies or vascular insufficiency; Those who are not suitable for MRI examination; Other situations that the researcher thinks are not suitable for participating in this study.

2.3. Intervention regimen

Group A: HF-ESWT orthopedic settings were prepared and used according to the methods described by Gao et al. [23] and Wang et al. [27–30] as follows: number of layers, level 3–4; Select the layer according to the patient’s feelings. And if the patient feels uncomfortable, it will be reduced to level 3; choose 6 points of the femoral head, each point receives 500 pulses with an energy flux density >0.44 mJ/mm² (level 3); and a total of 3000 pulses with a frequency of 2 Hz. Each treatment time is about 25–30 min. Each patient received one treatment. All cases in group B did not receive shock wave intervention. Alendronate sodium tablets (Trade name: Fushanmei, Hangzhou Merck & Co., Ltd.) [31] (70 mg p. o. q. w. for 6 weeks) and Chinese herbal Fufang Xian Ling Gu Bao胶囊 (Main ingredient: Icariin, Tongjitang (Guizhou) Pharmaceutical Co., Ltd. of Sinopharm Group) [32] (3 capsules p. o. b. i.d. for 6 weeks)
were administered to patients in two groups. Both drugs have been approved by China's State Drug Administration.

2.4. Assessment

Hip magnetic resonance imaging (MRI) scan is the accepted gold standard for the diagnosis of ONFH [3,11]. In this study, a 3.0T magnetic resonance scanner (GE DISCOVERY MR750, China-Japan Friendship Hospital) was used for hip MRI scans. The recommended sequence is T1WI, T2WI, and T2WI fat suppression coronal and axial MRI scans, TR/TE = 1300 ms/36 ms, slice thickness 1 mm, slice spacing 0. The scanned data is stored as a Dicom format file. The between-group difference of dichotomous data, such as gender, sick side, ARCO stage, and CJFH classification type (Fig. 1) was evaluated [23,33,34].

This study uses a single-blind method. Professional doctors used MRI to assess whether all participants had ONFH before intervention and during the follow-up period of 3 months, 6 months, and 12 months after the intervention. Constant score evaluation function result: The 10 cm VAS was used to evaluate the pain, and the HHS was used to evaluate the hip joint function [11].

2.5. Statistical analysis

All data analyses were performed using SPSS version 25.0.0 software (SPSS; Chicago, IL, USA). Quantitative variables from baseline to 12 months, including patient age, glucocorticoid dose, VAS, and HHS, were presented as mean ± standard deviation (SD) and assessed using t-tests. Gender, primary disease, and the number of patients diagnosed with ONFH were assessed by a positive chi-square test. P-values < 0.05 were considered statistically significant.

3. Results

There were 158 patients enrolled. Four of them did not meet inclusion criteria and were excluded, leaving 154 to be randomized. After randomization, 75 patients were assigned to group A and received the allocated intervention and 79 patients were assigned to group B and received the allocated intervention. One randomized patient was lost during the follow-up, leaving 153 patients to be analyzed (Fig. 2). One patient in Group B lost telephone contact within 3 months of follow-up.

The average age of the 153 selected patients was 45.0 ± 13.0 years (19–65 years). There were 89 women and 64 men. The average glucocorticoid dose is 2.07 ± 0.72 (0.96–7.59)g. The two groups are comparable in terms of age, gender, glucocorticoid dosage, and primary disease, and there is no significant difference. No significant differences were found between the two groups in bilateral hip pain measured using the VAS before the intervention (Left p = 0.154; Right p = 0.113). Bilateral hip function measured by HHS before intervention showed no significant difference between groups (Left p = 0.664; Right p = 0.603) (Table 1).

During the follow-up period, 11 people were diagnosed with bilateral ONFH by MRI (Fig. 3), accounting for 7.19%. There was a significant difference between the two groups (2 cases in Group A and 9 cases in Group B; p = 0.034) (Table 2). The eleven cases of ONFH found were all treated according to the principle of individualized treatment, which did not belong to the scope of this study and was not mentioned.

No significant differences were found between the two groups in bilateral hip pain measured using the VAS at 3 months (Left p = 0.891; Right p = 0.924), 6 months (Left p = 0.158; Right p = 0.135), 12 months (Left p = 0.061; Right p = 0.088).

There were no significant differences between groups in bilateral hip function measured using the HHS at 3 months (Left p = 0.890; Right p = 0.536) (Table 2). Significant differences between groups were found in bilateral hip function measured using the HHS at 6 months (Left p = 0.026; Right p = 0.033) and 12 months (Left p = 0.018; Right p = 0.038).

There were no adverse drug reactions in all cases. Group A cases had no systemic or nociceptive complications. Eleven (14.7%) patients developed complications during follow-up in Group A. All adverse events occurred at the shock wave site, manifested as ecchymosis or hemorrhage, and all symptoms disappeared within 2 weeks.

4. Discussion

At the end of the follow-up in this study, the number of patients diagnosed with ONFH in the HF-ESWT group was significantly lower than that in the control group. This suggests that HF-ESWT has a significant effect on preventing glucocorticoid-induced ONFH. HF-ESWT can effectively prevent the incidence of glucocorticoid-induced ONFH. When ONFH is unavoidable, patients experience hip pain and
dysfunction, manifested by increased VAS and decreased HHS. This also explains why patients in group A had higher HHS than group B after HF-ESWT at the 6- and 12-month follow-up assessments. There was no significant difference in bilateral hip VAS and HHS in the early follow-up (p > 0.05), but there were significant differences between the groups in bilateral hip HHS at 6 months (Left p = 0.026; Right p = 0.033) and 12 months (Left p = 0.018; Right p = 0.038) of treatment. This may be related to an increase in the number of patients diagnosed with ONFH in the control group, and patients using crutches to reduce weight to protect the hip joint when they had ONFH symptoms or became aware of the condition.

Currently, there are few clinical studies on the prevention of glucocorticoid-induced ONFH. Li et al. [32] demonstrated through a multicenter clinical study that the herbal Fufang (formula) XLGB, rich in antiadipogenic compounds, can effectively prevent glucocorticoid-induced ONFH in patients with immune-inflammatory diseases. However, many studies have confirmed that icariin, alendronate, acetylsalicylic acid [35], ESWT, and multiple drilling can delay the progression of early glucocorticoid-induced ONFH. Compared with traditional surgical intervention, ESWT has the advantages of non-invasiveness, adjustable stimulation intensity, no side effects, low risk, and fewer complications. A large number of scholars on the mechanism of ESWT have shown that ESWT has new application prospects in the prevention and treatment of ischemic diseases [36,37]. Recent studies have shown that glucocorticoid-induced ONFH is closely related to the damage of bone microvascular endothelial cells (BMECs) of the femoral head [38]. Icariin in XLGB can significantly reduce the killing effect of glucocorticoids on BMECs [39]. Alendronate can inhibit the activity of osteoclasts and improve bone formation [31]. The use of HF-ESWT in combination with these hip-sparing drugs can more effectively prevent the progression of ONFH [11,23,36,40].

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram outlining patient recruitment, allocation, and follow-up.

Table 1
The patients’ characteristics, pre-intervention VAS, and HHS for Groups A and B.

| Variable                        | Group A (n = 75) | Group B (n = 78) | V^2  | P-Value |
|---------------------------------|-----------------|-----------------|------|---------|
| Age (yr)                        | 50.83 ± 13.10   | 52.18 ± 12.85   | 0.785 | 0.434   |
| Sex (no.)                       |                 |                 |      |         |
| Females                         | 46              | 43              |      |         |
| Males                           | 29              | 35              |      |         |
| Glucocorticoid dosage (mg/day)  | 2.08 ± 0.74     | 2.06 ± 0.72     | 0.215 | 0.820   |
| Intersitial pneumonia           | 20              | 17              |      |         |
| Systemic lupus erythematosus    | 9               | 10              |      |         |
| Dermatomyositis                 | 16              | 23              |      |         |
| Connective tissue disease (CTD) | 10              | 8               |      |         |
| Nephrotic syndrome              | 4               | 5               |      |         |
| Glomerulonephritis              | 10              | 9               |      |         |
| Others                          | 6               | 6               |      |         |
| Clinical assessment             |                 |                 |      |         |
| VAS Before intervention         |                 |                 |      |         |
| Left hip                        | 0.20 ± 0.40     | 0.12 ± 0.32     | 1.433 | 0.154   |
| Right hip                       | 0.23 ± 0.42     | 0.13 ± 0.34     | 1.593 | 0.113   |
| HHS Before intervention         |                 |                 |      |         |
| Left hip                        | 99.76 ± 0.94    | 99.83 ± 0.81    | 0.435 | 0.664   |
| Right hip                       | 99.78 ± 0.73    | 99.84 ± 0.69    | −0.521 | 0.603   |

After ESWT acts on the tissue, it will produce cytokine release, stem cell recruitment, angiogenesis, and other self-healing mechanisms to activate tissue cells, and it has the effect of antagonizing glucocorticoid on the damage of bone microcirculation endothelial cells [16,37,41]. In animal experiments, ESWT can increase the mRNA and protein levels of...
enhanced in ESWT-treated hip bone marrow stromal cells [41,44], and runt-related transcription factor 2 (Runx2), and osteocalcin was ing necrotic bone, suggesting the ingrowth of new blood vessels and Vascular endothelial growth factor (VEGF) in the bone tissue surround-
ing.

In conclusion, this study confirms that HF-ESWT can be successfully used to reduce the probability of glucocorticoid-induced ONFH. Pain and hip dysfunction are common clinical manifestations when ONFH is unavoidable. Therefore, HF-ESWT can be recommended for the prevention and intervention of ONFH high-risk populations receiving high-dose glucocorticoid therapy.

Table 2
The results of clinical and MRI radiological outcomes by two groups.

| Variable                  | Group A (n = 75) | Group B (n = 76) | V/² | P-Value |
|---------------------------|------------------|------------------|-----|---------|
| Clinical assessment of left hip VAS |                   |                   | 0.095 | 0.924 |
| 3 months                  | 0.12 ± 0.37      | 0.13 ± 0.37      | -0.137 | 0.891 |
| 6 months                  | 0.17 ± 0.42      | 0.29 ± 0.63      | -1.420 | 0.158 |
| 12 months                 | 0.17 ± 0.38      | 0.37 ± 0.84      | -1.895 | 0.061 |
| HHS (0-100)               |                   |                   |       |         |
| 3 months                  | 99.73 ± 0.85     | 99.75 ± 0.75     | -0.139 | 0.890 |
| 6 months                  | 99.63 ± 1.39     | 98.91 ± 2.43     | 2.256  | 0.026 |
| 12 months                 | 99.79 ± 0.79     | 98.77 ± 3.65     | 2.404  | 0.018 |
| Clinical assessment of right hip VAS |                   |                   |       |         |
| 3 months                  | 0.16 ± 0.40      | 0.15 ± 0.40      | 0.095  | 0.924 |
| 6 months                  | 0.19 ± 0.43      | 0.32 ± 0.65      | -1.505 | 0.135 |
| 12 months                 | 0.21 ± 0.44      | 0.41 ± 0.90      | -1.721 | 0.088 |
| HHS (0-100)               |                   |                   |       |         |
| 3 months                  | 99.78 ± 0.74     | 99.71 ± 0.68     | 0.620  | 0.536 |
| 6 months                  | 99.64 ± 1.19     | 98.99 ± 2.35     | 2.154  | 0.033 |
| 12 months                 | 99.61 ± 1.49     | 98.63 ± 3.84     | 2.101  | 0.038 |
| MRI radiological assessment |                   |                   |       |         |
| Number of confirmed ONFH  | 2                 | 9                 | 4.510  | 0.034 |

Bone morphogenetic protein 2 (BMP-2), thereby promoting osteoblast differentiation [42]. In addition, ESWT can up-regulate the expression of Vascular endothelial growth factor (VEGF) in the bone tissue surrounding necrotic bone, suggesting the ingrowth of new blood vessels and improving the blood supply to the femoral head [43]. In vitro experiments, the mRNA expression of VEGF, alkaline phosphatase, BMP-2, runt-related transcription factor 2 (Runx2), and osteocalcin was enhanced in ESWT-treated hip bone marrow stromal cells [41,44], and the mineralized nodules were more mature.

The mechanism by which HF-ESWT prevents glucocorticoid-induced ONFH may be similar to its mechanism for treating ONFH. On the one hand, it induces the activation of early necrotic bone tissue, activates cell proliferation, promotes the formation of callus, and achieves the purpose of repair. On the other hand, it improves blood circulation in the bones and surrounding tissues. Osteonecrosis can be prevented or repaired at an early stage through the above mechanism. In addition, Li et al. [32] found that XLGB could prevent glucocorticoid-induced coagulation and fibrinolysis, thereby preventing glucocorticoid-induced ONFH. Glucocorticoid-induced ONFH is manifested by osteoclast hyperactivity [45], and the purpose of alendronate in this study was to inhibit osteoclasts and increase bone mineral density [31,46].

The study also has some limitations. This study mainly observes the incidence of femoral head necrosis. The total follow-up time is short, and the results of long-term follow-up observation are lacking. The number of patients enrolled in this study was small. Considering bias factors, the size and location of necrotic foci were not compared between the two groups of ONFH patients, and it is difficult to study the role of HF-ESWT in reducing osteonecrotic areas. The included cases are high-risk groups of ONFH caused by the application of hormones such as interstitial pneumonia, SLE, dermatomyositis, etc. There is no direct evidence reported in the literature that the primary disease may affect the occurrence of ONFH, and further research will be refined in the future. There was no statistically significant difference between the two groups in terms of primary disease (p > 0.05). This study involved the local intervention of HF-ESWT and did not consider the observation of systemic bone metabolism or changes in the blood index of the internal environment.

5. Conclusions

In conclusion, this study confirms that HF-ESWT can be successfully used to reduce the probability of glucocorticoid-induced ONFH. Pain and hip dysfunction are common clinical manifestations when ONFH is unavoidable. Therefore, HF-ESWT can be recommended for the prevention and intervention of ONFH high-risk populations receiving high-dose glucocorticoid therapy.

Authorship

Xu Yang: Conception and design of study, analysis and/or interpretation of data, Drafting the manuscript. Lijun Shi: acquisition of data, analysis and/or interpretation of data, Drafting the manuscript. Tao Zhang: acquisition of data, analysis and/or interpretation of data, Drafting the manuscript. Peixu Wang: Conception and design of study, analysis and/or interpretation of data, Drafting the manuscript. Mengda Wang: acquisition of data, Drafting the manuscript. Chun Sun: acquisition of data, Drafting the manuscript. Zirong Li: Conception and design of study.
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Institutional review board statement
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Clinical Research Ethics Committee of China–Japan Friendship Hospital (2018-84-K59-1; date 2018-06-28).

Informed consent statement
Not applicable.

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

Declaration of competing interest
The authors declare no conflict of interest.

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