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Original Article

Combination of neuromuscular electrical stimulation and ibuprofen to reduce pain in femoral head necrosis

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Abstract: Objective: The combinative effects of neuromuscular electrical stimulation and ibuprofen on pain in patients with femoral head necrosis were discussed and analyzed. Method: This retrospective study analyzed data of 60 patients with femoral head necrosis hospitalized during Oct. 2020 to Oct. 2021. According to different treatment methods, the patients were divided into an observation group and a control group (30 cases in each group). The control group took oral ibuprofen sustained-release capsules, and the observation group was treated with neuromuscular electrical stimulation in addition to ibuprofen. Both groups received a 4-week treatment course. The therapeutic efficacy, Harris scale scores, Visual Analogue Scale (VAS) score, MRI hip imaging stage, SF-36 scale score, serum plasminogen activator inhibitor 1 (PAI-1), leptin and osteopontin levels before and after treatment were compared between the two groups. Results: After treatment, the overall response rate in the observation group was higher than that in control group ($P<0.05$). The post-treatment scores of Harris scale were higher in both groups than those pre-treatment ($P<0.05$), and were higher in the observation group than in the control group ($P<0.05$). The VAS scores were decreased in both groups ($P<0.05$), and the decrease was more significant in the observation group than in the control group ($P<0.05$). After treatment, there were more patients with 0-I MRI hip imaging stage in the two groups than before treatment ($P<0.05$), and more in the observation group than in the control group ($P<0.05$). The SF-36 scores in both groups were increased ($P<0.05$), and the increase was more significant in the observation group than in the control group ($P<0.05$). The serum levels of PAI-1, leptin and osteopontin were decreased in both groups ($P<0.05$), and the decreases were more significant in the observation group than in the control group ($P<0.05$). Conclusion: The combinative treatment of neuromuscular electrical stimulation and ibuprofen has a significant effect on patients with femoral head necrosis. The treatment can remarkably reduce patients' pain, improve their hip function and quality of life, and decrease the PAI-1, leptin and osteopontin levels.

Keywords: Neuromuscular electrical stimulation, ibuprofen, femoral head necrosis, curative effect, pain

Introduction

Necrosis of the femoral head refers to the death of bone marrow components and bone cells due to damage or interruption of the blood supply to the femoral head [1]. Clinical studies have confirmed that treatment of pain caused by femoral head necrosis is the key to the therapeutic effect [2]. In addition, it is also an important factor affecting the functional recovery of patients. Angiogenesis and formation of new bone in femoral head necrosis area are crucial factors of pathological reversal [3-5]. Multi-mode analgesia has become the focus of clinical research on hip joint diseases, especially on femoral head necrosis, which provides scientific data and research basis for the maximum preservation of hip function [6]. Ibuprofen is an anti-inflammatory and analgesic drug which has been widely adopted in orthopedic treatment of motor diseases or injuries due to its high efficacy and has few side effects [7]. The combination of ibuprofen and neuromuscular electrical stimulation improves blood circulation to the femoral head and restores blood supply to the blood vessels, thus improving the pain of patients.

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Myoelectric biofeedback technique excites the depolarisation and repolarization of cells through repeated electromyography stimulation, and can promote the release of morphine-like substances from the central nervous system. In addition, the stimulation of excitable and unexcitable cells can produce intracellular ions and molecular oscillations to form a continuous depolarization state, thus promoting the recovery of neuromuscular function [8, 9]. Neuromuscular electrical stimulation can inhibit or interrupt nerve conduction to achieve analgesia. The combined electrical stimulation can release polypeptide substances, which are stronger than morphine in analgesia. It can also adjust neuromuscular tissue and human body function, improve local blood circulation, eliminate edema between nerve fibers, and promote the rapid removal of pain-causing substances and local acidic metabolites, thus relieving the pain of patients [10, 11]. In addition, neuromuscular electrical stimulation can stimulate the regular contraction of the leg muscle group caused by the common peroneal nerve, improve venous stasis and blood circulation by speeding up the venous blood flow of lower extremities, avoid the aggregation of blood clots, thus accelerating the metabolism of the wound tissue and reducing the pain caused by the femoral head.

Currently, there are few studies that have analyzed the combination of neuromuscular electrical stimulation and ibuprofen for the treatment of pain in patients with femoral head necrosis. In order to improve the analgesic effect for patients with femoral head necrosis, this study discussed and analyzed the influence of the above combined therapy on the pain.

Data and methods

Subjects and grouping

This retrospective study analyzed data of 60 patients with femoral head necrosis hospitalized during Oct. 2020 to Oct. 2021. According to different treatment methods, the patients were divided into an observation group and a control group (30 cases in each group). The study was approved by ethics committee of Affiliated Hospital of Hebei Engineering University.

Diagnostic code

The diagnosis of femoral head necrosis was based on the criteria in Practical Osteology [8]. (1) The frog leg lateral view showed early uneven femoral head density with small cystic shadows. X-ray of intermediate stage showed crescent sign and collapse of femoral head. In the late stage, the femoral head showed collapse, deformation, hyperplasia and hardening of the bone socket, as well as narrowing of joint space. (2) According to MRI, early-stage patients presented with a uniform or uneven localized linear or patchy abnormal signal shadow on the anterior superior margin of the femoral head. T1 weighted image showed low or slightly low signal, and T2 weighted image showed high or slightly high signal parallel to the lateral low signal band, which formed a “double-line sign”.

Inclusion criteria

(1) Patients met the diagnostic criteria of femoral head necrosis. (2) Patients were aged between 18 and 85 years old. (3) Patients did not have severe metabolic disease.

Exclusion criteria

(1) Patients with rheumatoid arthritis, gout, joint tuberculosis, suppurative arthritis or Kashin-Beck disease. (2) Patients with pain caused by diseases other than the femoral head. (3) Patients with serious mental illness. (4) Females in pregnancy or lactation. (5) Patients with contraindications to the trial.

Methods

The control group took ibuprofen sustained-release capsules orally (TSKF, H20013062) with a single oral dose of 300 mg, twice a day (morning and evening). The observation group was treated with neuromuscular electrical stimulation in addition to ibuprofen. Am-800 neural network reconstruction instrument (Danmeter, Denmark) was applied for the electrical stimulation of the patients. Two detection electrodes and two treatment electrodes were affixed to the surface of the extensor muscle of the healthy side and the affected side, respectively, and the auxiliary ground electrode was affixed to the affected limb (**Figure 1**). The treatment parameters were as follows: stimula-

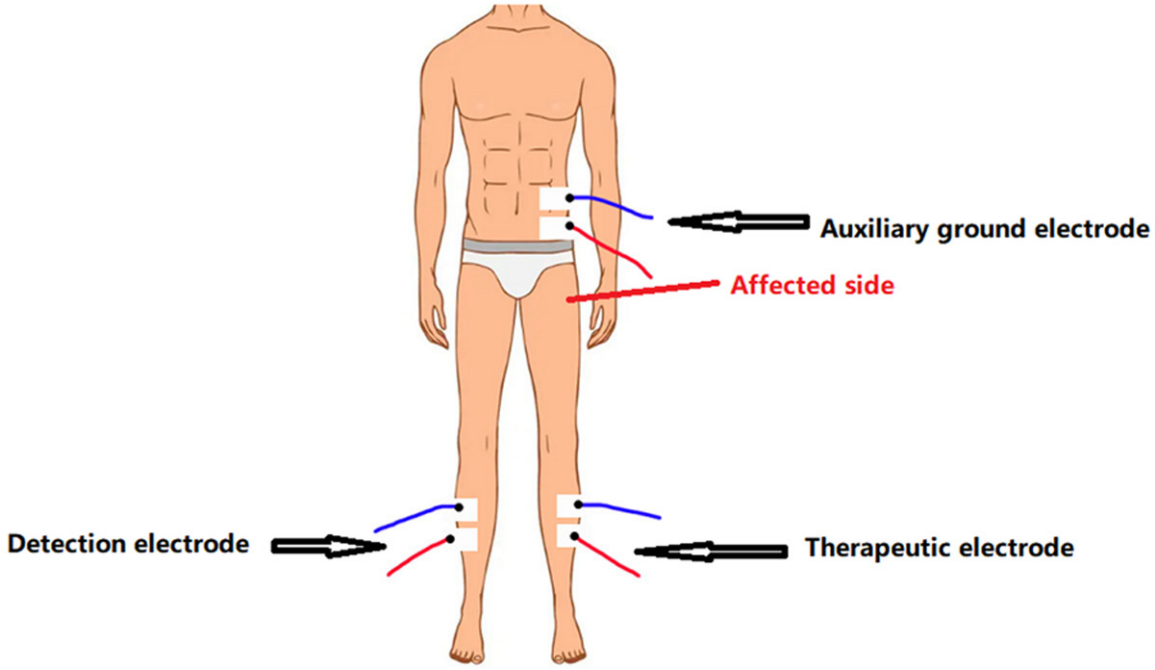

Figure 1. Schematic diagram of neuromuscular electrical stimulation.

tion mode: automatic mode, stimulation intensity: 20-30 mA, output waveform: unidirectional square wave, output pulse frequency: 50 Hz, and pulse width: 0.2 ms. The stimulation lasted for 5 to 10 seconds, with an interval of 10 to 15 seconds. Patients were treated for about 20 to 30 min each time, 5 times a week. The treatment course was 4 weeks for both groups.

Evaluation criteria of efficacy

(1) Markedly effective: The patient's hip pain disappeared with restored basic movement and walking functions, also, their hip joints were normal or only slightly changed on imaging. (2) Effective: The patients expressed improved hip pain and were able to walk with limited mobility, also imaging showed that the osteonecrosis was improved. (3) Ineffective: The patients' hip pain did not improve and there was no change in radiographic images. The overall response rate (%) = cases of (remarkable effective + effective)/total number of cases.

Outcome measures

(1) The Harris scores were observed before and after treatment. The evaluation dimensions included pain (44 points), function (47 points), range of motion (5 points) and deformity (4 points). A higher Harris score indicated better hip function of patients. (2) The changes of Visual Analogue Scale (VAS) score pre- and post-treatment were observed in the two groups, and the score range was 0 to 10 points. A higher score referred to more obvious pain. (3) MRI hip imaging were observed before and after treatment. The femoral head necrosis was divided into 5 stages according to the staging methods recommended by the International Bone and Joint Association [12]. (4) The changes in quality of life before and after treatment were observed. The evaluation was conducted using Health Survey Brief Form-36 (SF-36), which has 8 dimensions and 36 items. Each item was rated on a scale of 1 to 5, and a higher score referred to better quality of life. (5) The serum levels of plasminogen activator inhibitor type 1 (PAI-1), leptin and osteopontin were observed. Both before and after treatment, 3 ml venous blood was collected and centrifuged for 10 min at a radius of 10 cm and a speed of 1500 r/min. The serum was collected and the levels of PAI-1, leptin and osteopontin were determined by enzyme-linked immunosorbent assay (ELISA) using PAI-1 ELISA kit (Abcam, ab270375), leptin ELISA kit (Abcam, ab179884) and osteopontin ELISA kit (Abcam, ab269374).

Table 1. Comparison of clinical data

Group	Number of cases	Sex		Age (years, $\bar{x}$ ± s)	Course of disease (d, $\bar{x}$ ± s)	BMI (kg, $\bar{x}$ ± s)
		Male	Female			
Observation group	30	17	13	52.63±13.49	23.12±3.76	61.08±7.65
Control group	30	18	12	51.26±10.81	21.97±4.04	60.56±8.23
t/χ^2	-	0.069		0.434	1.141	0.254
P	-	0.793		0.666	0.258	0.801

BMI: Body Mass Index.

Table 2. Comparison of efficacy between the two groups (%)

Group	Number of cases	Markedly effective	Effective	Ineffective	Overall response rate
Observation group	30	18 (60.00)	10 (33.33)	2 (6.67)	28 (93.33)
Control group	30	11 (36.67)	11 (36.67)	8 (26.67)	22 (73.33)
χ^2	-	-	-	-	4.320
P	-	-	-	-	0.038

Table 3. Comparison of Harris scores between two groups ($\bar{x}$ ± s, points)

Index	Observation group (n=30)				Control group (n=30)			
	Before treatment	After treatment	t	*P*	Before treatment	After treatment	t	*P*
Pain	25.37±3.24	36.89±4.65*	11.133	<0.001	24.85±3.32	31.27±3.47	7.322	<0.001
Function	26.38±4.13	40.37±5.65*	10.949	<0.001	26.61±3.25	35.42±4.16	9.141	<0.001
Joint range of motion	1.25±0.65	3.98±0.76*	14.952	<0.001	1.31±0.42	3.17±0.54	14.892	<0.001
Joint deformity	1.47±0.67	3.78±0.58*	14.278	<0.001	1.50±0.54	3.10±0.45	12.467	<0.001

Note: Compared with the control group, **P<0.05*.

Statistical analysis

SPSS 26.0 was adopted for data processing. The measurement data were expressed in ($\bar{x}$ ± sd), and the counting data were expressed in percentage. The comparisons of measurement data were done by *t*-test, and of counting data by χ^2 test. *P<0.05* indicated that the difference was statistically significant.

Results

Clinical data

There was no significant difference in baseline data between the two groups (P>0.05). See **Table 1**.

Comparison of efficacy

The overall response rate in the observation group was higher than that in control group (*P<0.05*) (**Table 2**).

Comparison of Harris scores

The post-treatment scores of Harris scale were higher in the two groups than those pre-treatment (*P<0.05*), and were higher in the observation group than in the control group (*P<0.05*) (**Table 3**).

Comparison of VAS scores

The post-treatment VAS scores were lower in both groups than those pre-treatment (*P<0.05*), and the score in the observation group was lower than that in the control group (*P<0.05*) (**Figure 2**).

Comparison of MRI hip imaging stages

There were more cases with 0-I MRI hip imaging stage in the two groups after treatment than those before treatment (*P<0.05*), and the observation group had more than the control group (*P<0.05*) (**Table 4**).

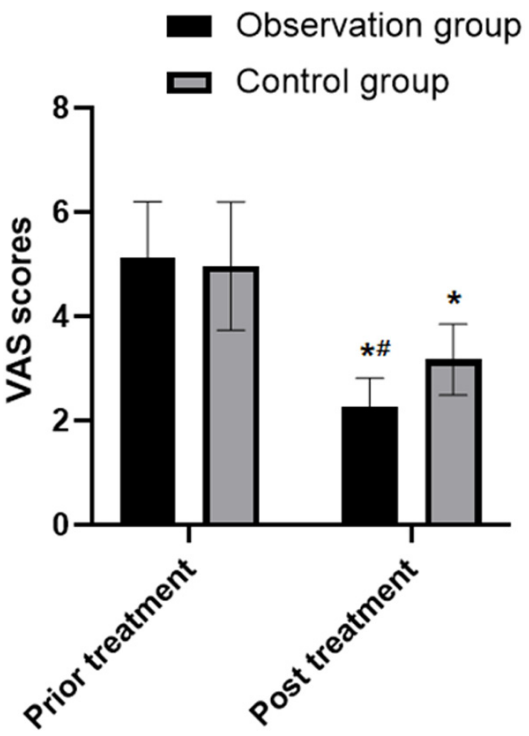

Figure 2. Comparison of Visual Analogue Scale (VAS) scores between the two groups. Note: Compare with prior treatment, *$P<0.05$; Compare with the control group, #$P<0.05$.

Comparison of SF-36 scores

The post-treatment SF-36 scores were higher in both groups than the pre-treatment scores ($P<0.05$), and the observation group had higher post-treatment score than the control group ($P<0.05$) (**Table 5**).

Comparison of PAI-1, leptin and osteopontin levels

The post-treatment serum levels of PAI-1, leptin and osteopontin in two groups were lower than those pretreatment ($P<0.05$), and the post-treatment levels in the observation group were lower than those in the control group ($P<0.05$) (**Table 6**).

Discussion

Femoral head necrosis, also known as avascular necrosis of the femoral head, is divided into two categories: traumatic and non-traumatic. Osteonecrosis of the femoral head is a pathological process in which the local blood circulation of the femoral head is impaired due to a variety of diseases, resulting in the loss of active components of bone [13, 14]. It is a common and refractory chronic orthopedic disease, and the patients may suffer from loss of joint function, trabecular destruction in femoral head, articular cartilage fracture and femoral head collapse, etc. [15]. Osteonecrosis of the femoral head initially presents as indistinct pain or dull pain in the hip or surrounding joints, which becomes worse after movement. This disease can result in dysfunction of the hip joint, which seriously affects patient's ability to work and quality of life, and may cause disability if not treated timely and effectively [16-18]. Pain is the biggest difficulty in the treatment of femoral head necrosis. Generally, multi-stage analgesia cannot be achieved by a single treatment, and more adverse reactions can occur with the increase of drug dosage [19]. Therefore, multi-mode analgesia has become the first choice for femoral head necrosis.

Ibuprofen sustained-release capsules can peak 4-5 h after administration. This drug is easily absorbed by oral administration, with an absorption rate of over 90%. Ibuprofen is a commonly used analgesic drug. The protein binding of ibuprofen sustained-release capsule is 99%. It is metabolized by the liver, with 60%-90% excreted by the kidney through the urine, and 100% excreted within 24 hours. The mechanism of osteonecrosis of the femoral head in different pathological states has a certain correlation with pain, and affects the disease progress. The neuromuscular electrical stimulation is applied through two electrodes on the healthy side and the affected side, respectively, which stimulates conduction of the central nervous system to synchronize with the low-frequency pulse current. Combined with reflex movement, it promotes the formation of correct motor responses, reduces the resistance of synapses in conduction, causes rhythmic muscle contractions, and accelerates the recovery and regeneration of nerve conduction functions. The combination therapy of ibuprofen and neuromuscular electrical stimulation can promote the recovery of motor function of denervated muscles, regulate and promote the recovery and reconstruction of limb motor reflex arc, gradually recover the central nervous system, facilitate the blood circulation of the affected side, promote the metabolism of muscle cells, thus promoting the healing of fractures and the recovery of joint function [20].

Table 4. Comparison of MRI hip imaging staging of femoral head necrosis between two groups cases (%)

Group	Time	Stage 0-I	Stage II	Stage III	Stage IV
Observation group (n=30)	Before treatment	2 (6.67)	6 (20.00)	15 (50.00)	7 (23.33)
	After treatment	21 (70.00)	7 (23.33)	2 (6.67)	0 (0)
Control group (n=30)	Before treatment	1 (3.33)	8 (26.67)	16 (53.33)	5 (16.67)
	After treatment	13 (43.33)	11 (36.67)	5 (16.67)	1 (3.33)

Note: Comparison was made by rank sum test. The comparison of observation group before and after treatment Z=-5.628, P<0.001. In the control group, Z=-4.273, P<0.001. The comparison between the two groups before treatment Z=-0.594, P=0.646; after treatment, Z=-2.179, P=0.029.

Table 5. Comparison of SF-36 scores ($\bar{x}$ ± s, points)

Group	Number of cases	Prior treatment	Post treatment
Observation group	30	45.62±12.31	78.98±9.74*
Control group	30	46.21±12.73	63.54±8.85*
t	-	0.183	6.426
P	-	0.856	<0.001

Note: Compared with prior treatment, **P<0.05*.

Table 6. Comparison of serum PAI-1, leptin and osteopontin levels between the two groups ($\bar{x}$ ± s)

Index	Observation group (n=30)				Control group (n=30)			
	Before treatment	After treatment	t	*P*	Before treatment	After treatment	t	*P*
PAI-1 (pg/ml)	53.24±6.76	25.85±4.34*	18.675	<0.001	52.48±7.27	37.74±7.18	7.901	<0.001
Leptin (μg/L)	45.45±7.86	24.87±4.36*	12.541	<0.001	44.61±8.59	32.12±5.57	6.682	<0.001
Osteopontin (μg/L)	10.85±2.16	3.75±1.08*	16.103	<0.001	10.57±2.23	5.98±1.56	9.238	<0.001

Note: Compared with the control group, **P<0.05*. PAI-1: Plasminogen Activator Inhibitor type 1.

This study demonstrated that the overall response rate, SF-36 score and Harris scores were higher, and VAS score was lower in the observation group than those in control group. Also, the number of patients with imaging stage 0-I was higher in the observation group than that in the control group. These results confirmed that the combination of neuromuscular electrical stimulation and ibuprofen can improve the therapeutic efficacy and hip function, reduce pain and imaging stage, and improve patients' quality of life.

PAI-1 is a glycoprotein which is composed of 379 amino acids. Its abnormal expression breaks the system balance and affects the blood supply of the femoral head, thus participating in the occurrence of femoral head necrosis [21]. Leptin is mainly produced in white adipose tissue and can also be secreted and formed by bone, cartilage and skeletal muscle. The abnormal levels of leptin or its receptor can cause pathological reactions such as osteoporosis and obesity [22]. Osteopontin can be secreted and formed by osteoclasts, osteoblasts, osteocytes and other cells in the human body, and also exists in human body fluids such as serum [23]. Osteopontin promotes the adhesion of osteoclasts to bone matrix and induces the osteoclast process during bone resorption [24]. This study demonstrated that the post-treatment serum levels of PAI-1, leptin and osteopontin in the observation group were lower than those in control group, which indicates that neuromuscular electrical stimulation combined with ibuprofen could reduce PAI-1, leptin and osteopontin levels. Yet its specific mechanism of action has not been fully defined.

Overall our results may be biased due to the limited sample size. Therefore, this is only a preliminary observation and analysis of the

treatment plan. In later research, the sample size needs to be expanded to obtain more reliable clinical research data.

To summarize, the combinative treatment of neuromuscular electrical stimulation and ibuprofen has a significant effect on patients with femoral head necrosis. This treatment can remarkably reduce patients' pain, improve their hip function and quality of life, and decrease PAI-1, leptin and osteopontin levels.

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Disclosure of conflict of interest

None.

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