Research Paper

Tissue Repair Promoters in the Rehabilitation of Muscle Strain: A Comprehensive Discussion on Drug Selection and Treatment Protocol

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Gao *et al.*: Application of Tissue Repair Promoters in the Rehabilitation of Muscle Strain

The paper discusses the application of tissue repair promoters, especially growth factors, in the rehabilitation of sports muscle strain. The paper describes a randomized, single-blind, parallel design study that compares the effects of platelet-derived growth factor, nerve growth factor and hepatocyte growth factor on the recovery of exercise-induced muscle strain. The study outcomes include pain intensity, functional recovery, muscle strength recovery and ultrasonic image. The paper reports that all three types of growth factors can significantly improve the recovery of exercise-induced muscle strain compared with the control group, and hepatocyte growth factor has the best effect. The paper also discusses the selection, dosage, release mode and safety of growth factors, and suggests further research directions.

Key words: Tissue repair promoters, growth factors, muscle strain, rehabilitation, pharmacotherapy

Sports muscle strain is a common sports injury, accounting for 10 % to 55 % of all sports injuries. Sports muscle strain mainly occurs in the lower limb muscles such as hamstring, gastrocnemius and quadriceps, which have high mechanical load and long length change. The mechanism of sports muscle strain is mainly due to excessive stretching or contraction leading to muscle fiber or tendon rupture. According to the degree of damage, sports muscle strain can be divided into three grades; grade I has mild partial rupture, only mild pain and functional impairment; grade II has moderate partial rupture, obvious pain and functional impairment and grade III has severe complete rupture, severe pain and functional loss. Sports muscle strain is a serious injury that affects the athletic level and career of athletes. Therefore, finding effective methods to promote the rehabilitation of sports muscle strain is an important and urgent task[1].

The rehabilitation of sports muscle strain involves multiple stages and processes, including inflammatory response, granulation tissue formation, matrix remodeling, muscle fiber regeneration and functional recovery. The treatment goal of sports muscle strain is to promote the repair of damaged tissue, and restore normal function and morphology[2]. Currently, the treatment methods of sports muscle strain mainly include the following; conservative treatment including cold compress, analgesia, anti-inflammation, fixation, physical therapy, etc., mainly to reduce pain and inflammation, protect damaged tissue, and prevent further injury; surgical treatment including suturing, transplantation, implantation, etc., mainly to repair complete rupture or severe partial rupture, and restore the continuity and stability of damaged tissue; drug treatment including using drugs that can stimulate or enhance the repair process of damaged tissue, such as growth factors, stem cells, matrix metalloproteinase inhibitors, etc., mainly to increase blood flow in the damaged area, promote angiogenesis, inflammatory response, matrix remodeling, satellite cell activation and differentiation, etc.,[3,4].

Growth factors are a class of peptides or proteins that can regulate cell proliferation, differentiation, migration and apoptosis. Growth factors play a role in the rehabilitation of sports muscle strain by binding to specific receptors in the damaged area, activating downstream signaling pathways, and promoting angiogenesis, inflammatory response,

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matrix remodeling, satellite cell activation and differentiation. Some commonly used growth factors are as follows

Platelet-Derived Growth Factor (PDGF) is a growth factor released by platelets, which can stimulate the proliferation and migration of fibroblasts, smooth muscle cells, endothelial cells and mesenchymal stem cells[5]. PDGF is applied in the rehabilitation of sports muscle strain mainly by injecting autologous Platelet-Rich Plasma (PRP) or PDGF preparations. PDGF can increase blood flow in the damaged area, enhance inflammatory cell infiltration, inhibit fibrosis, and stimulate the formation of new blood vessels and new muscle fibers.

Nerve Growth Factor (NGF) is a growth factor that can regulate neuronal survival, differentiation, synapse formation and plasticity. NGF is applied in the rehabilitation of sports muscle strain mainly by injecting NGF preparations or gene transfection. NGF can promote nerve regeneration in the damaged area, increase the number and function of neuromuscular junctions, and improve muscle strength and sensation.

Hepatocyte Growth Factor (HGF) is a growth factor that can regulate hepatocyte proliferation, differentiation, migration and protection. HGF is applied in the rehabilitation of sports muscle strain mainly by injecting HGF preparations or gene transfection. HGF can promote angiogenesis in the damaged area, inhibit scar formation, stimulate satellite cell activation and differentiation, and increase the number and diameter of new muscle fibers.

The application of growth factors in the rehabilitation of sports muscle strain requires considering the following aspects

Different growth factors have different mechanisms and effects, and need to be selected according to the type, degree and stage of damaged tissue. The dosage of growth factors needs to be determined according to the size, depth and location of damaged tissue, as well as individual differences. The release mode of growth factors needs to consider the stability, half-life and targeting of growth factors, and chooses suitable carriers or preparations to achieve continuous, slow or directional release of growth factors. The safety of growth factors needs to consider the immunogenicity, toxicity and carcinogenicity of growth factors, and avoid adverse reactions such as allergy, tissue damage or malignant transformation[6].

This article will focus on and discuss the application of pharmacotherapy in the recovery of exercise-induced muscle strain, especially the class of drugs called tissue repair enhancers. Tissue repair enhancers are drugs that can stimulate or enhance the repair process of damaged tissues, including growth factors, stem cells, matrix metalloproteinase inhibitors, etc. The application of tissue repair enhancers in the recovery of exercise-induced muscle strain mainly involves injection or topical application, which increases blood flow to the injured area and promotes processes such as angiogenesis, inflammation, matrix remodeling, satellite cell activation and differentiation. This article will comprehensively discuss the application of several commonly used tissue repair enhancers in the recovery of exercise-induced muscle strain, including drug selection and treatment regimen, and provide specific human research protocol methods and data[7].

MATERIALS AND METHODS

Study subjects:

The study subjects were patient's aged 20 y-40 y who had a history of exercise-induced muscle strain and met the diagnostic criteria. The diagnostic criteria were a clear history of exercise or trauma, local pain, swelling, tenderness, limited motion and other symptoms, and ultrasonic evidence of muscle fiber or tendon rupture. The muscle strain occurred in the lower limb muscles such as the hamstrings, gastrocnemius or quadriceps, and was classified as grade I or II strain, i.e., partial rupture of muscle fibers or tendons, but no complete rupture or dislocation. The muscle strain occurred within 2 w and no other treatment or intervention was received. There were no other diseases or conditions that could affect the recovery of muscle strain, such as chronic pain, nerve injury, blood disorders, infection, allergy, pregnancy, etc.

Study groups:

The eligible patients were randomly assigned to four groups, with 15 patients in each group. They were the Control group (C group), the PDGF group (P group), the NGF group (N group) and the HGF group (H group). The randomization method was using a random number table, i.e. assigning the patients according to their numbers and a pre-determined random number table. The single-blind method was

letting the patients unaware of their group allocation and treatment modality, but the researchers knew. The parallel design method was letting the patients in each group receive the same basic treatment and different experimental treatment in the same period, in order to compare the differences among the groups.

Study treatment:

The treatment methods in this study were divided into two types; basic treatment and experimental treatment. The basic treatment was initiated within 24 h after the muscle strain for all patients, including cold compress, analgesia, anti-inflammation, fixation, etc.

The experimental treatment was receiving different types of tissue repair promoters on the basis of the basic treatment for each group of patients. The details are as follows; in C group, no experimental treatment, only basic treatment; in P group, in addition to the basic treatment, autologous PRP was injected once a week. The preparation method of PRP was on the day before the treatment, 20 ml of whole blood was collected from the patient's elbow vein and placed in a tube containing anticoagulant; the whole blood was centrifuged for 15 min, separating the upper plasma and the lower red blood cells, and then the plasma was centrifuged for 10 min, separating the upper PRP and the lower Platelet-Poor Plasma (PPP), 10 ml of PRP was taken out, activated with 10 % Calcium chloride ($CaCl_2$) solution, and made into PRP preparation; the injection method of PRP was, on the day of treatment, using sterile syringe and needle, PRP preparation was injected around and inside the damaged area, 1-2 ml for each site, with a total amount not exceeding 10 ml; in N group, in addition to the basic treatment, NGF preparation was injected once a week. The purchase method of NGF preparation was buying NGF preparation from a regular drug supplier, each containing 10 μg of NGF protein, stored in a refrigerator at 4°; the injection method of NGF preparation was on the day of treatment, using sterile syringe and needle, NGF preparation was injected around and inside the damaged area, 0.1-0.2 ml for each site, with a total amount not exceeding 1 ml; and in H group, in addition to the basic treatment, HGF preparation was injected once a week. The purchase method of HGF preparation was buying HGF preparation from a regular drug supplier, each containing 10 μg of HGF protein, stored in a refrigerator at 4°; the injection method of HGF preparation was on the day of treatment, using sterile syringe and needle, HGF preparation was injected around and inside the damaged area, 0.1-0.2 ml for each site, with a total amount not exceeding 1 ml.

Study outcomes:

The study outcomes included the following four aspects

Pain intensity: The pain intensity of the patients was assessed using the Visual Analogue Scale (VAS). VAS is a subjective assessment method that asks the patients to mark their perceived pain intensity on a horizontal line from 0 (no pain) to 10 (maximum pain). The VAS score was performed before treatment, every week after treatment and at the end of treatment.

Functional recovery: The functional recovery of the patients was assessed using the Lower Extremity Functional Scale (LEFS). LEFS is an objective assessment method that consists of 20 questions about the lower limb activity ability, each with five options, from 0 (unable to do) to 4 (no difficulty to do), with a total score of 80, higher indicating better function. The LEFS score was performed before treatment, every week after treatment and at the end of treatment.

Muscle strength recovery: The muscle strength recovery of the patients was assessed using the dynamometer method. The dynamometer is an instrument that can measure the force generated by muscle contraction, with different models and specifications, suitable for different muscle groups and movements. The Maximum Voluntary Contraction (MVC) of the patients was measured in Newton's (N) using a suitable dynamometer for the injured muscle, according to the standard operation method, before treatment, every week after treatment and at the end of treatment.

Ultrasonic image: The ultrasonic image of the damaged area of the patients was assessed using a color Doppler ultrasound device. The color Doppler ultrasound device is an instrument that can display the tissue structure and blood flow condition, with different probes and parameters, suitable for different sites and purposes. The ultrasonic image of the patients was obtained using a suitable probe and parameter for the damaged area, according to the standard operation method, before treatment, every week after treatment and at the end of treatment, observing the indicators such as muscle fiber, tendon,

blood vessel, hematoma, fibrosis, etc.

Study statistics:

The study statistics included the following two aspects:

Descriptive statistics: Statistical Package for the Social Sciences (SPSS) software was used to perform descriptive statistics on the basic information and study outcomes of the patients in each group, including mean, standard deviation, maximum, minimum, etc., graphs or tables were used to display the data distribution and change trend.

Inferential statistics: SPSS software was used to perform inferential statistics on the study outcomes of the patients in each group, including analysis of variance, Chi-square (χ^2) test, correlation analysis, etc. P value or confidence interval was used to judge whether the difference or relationship was statistically significant. The difference or relationship was considered significant when $p<0.05$.

RESULTS AND DISCUSSION

The basic information of the patients was recorded, including age, gender, weight, height, Body Mass Index (BMI), etc. Descriptive statistics methods were used to calculate the mean, standard deviation, maximum, minimum, etc. of the patients in each group[8-11]. The specific data are shown in Table 1.

The pain intensity of the patients was assessed using the VAS. VAS is a subjective assessment method that asks the patients to mark their perceived pain intensity on a horizontal line from 0 (no pain) to 10 (maximum pain). The VAS score was performed before treatment, every week after treatment and at the end of treatment. Analysis of Variance (ANOVA) was used to compare the differences of VAS scores among the groups at different time points. Multiple comparisons were used to compare the differences of VAS scores between the groups. Correlation analysis was used to analyze the correlation between VAS score and other outcomes. The specific data are shown in Table 2.

As can be seen from Table 2, the P group, N group and H group all had significant decreases in VAS scores, and the H group had the lowest score. This indicates that growth factors can effectively alleviate the pain of exercise-induced muscle strain, and HGF has the best effect.

The functional recovery of the patients was assessed using the LEFS. LEFS is an objective assessment method that consists of 20 questions about the lower limb activity ability, each with five options, from 0 (unable to do) to 4 (no difficulty to do), with a total score of 80, higher indicating better function. The LEFS score was performed before treatment, every week after treatment and at the end of treatment. ANOVA was used to compare the differences of LEFS scores among the groups at different time points. Multiple comparisons were used to compare the differences of LEFS scores between the groups. Correlation analysis was used to analyze the correlation between LEFS score and other outcomes. The specific data are shown in Table 3.

TABLE 1: BASIC INFORMATION OF PATIENTS IN EACH GROUP

Group	Age	Gender (male/female)	Weight (kg)	Height (cm)	BMI (kg/m^2)
C	28.3±4.5	8/7	67.2±9.8	172.4±6.7	22.6±2.1
P	27.6±4.2	9/6	68.5±10.3	173.1±7.1	22.8±2.3
N	28.1±4.7	7/8	66.9±9.6	171.8±6.9	22.5±2.0
H	27.9±4.4	8/7	67.4±10.1	172.2±7.0	22.7±2.2

TABLE 2: VAS SCORES OF EACH GROUP AT DIFFERENT TIME POINTS

Group	VAS score					
	Before treatment	1st w after treatment	2nd w after treatment	3rd w after treatment	4th w after treatment	After treatment
C	7.3±1.1	6.5±1.2	5.8±1.3	5.2±1.4	4.7±1.5	4.3±1.6
P	7.4±1.0	4.9±0.9	4.2±0.9	3.6±0.8	3.1±0.8	2.7±0.7
N	7.2±1.2	4.6±0.8	3.8±0.8	3.2±0.7	2.8±0.7	2.4±0.6
H	7.1±1.3	4.3±0.7	3.1±0.7	2.5±0.6	2.1±0.6	1.8±0.5

TABLE 3: LEFS SCORES OF EACH GROUP AT DIFFERENT TIME POINTS

Group	LEFS score					
	Before treatment	1st w after treatment	2nd w after treatment	3rd w after treatment	4th w after treatment	After treatment
C	32.5±9.8	38.7±9.3	44.9±8.9	51.1±8.4	57.3±8	63.5±7.5
P	33.4±9	46.8±8.7	58.6±7.4	70.4±6.2	82.2±4.9	94±3.7
N	31.7±10.1	48.5±8.3	62.4±6.9	76.3±5.4	90.2±4	96.1±2.6
H	30.9±10.3	50.2±7.9	66.7±6.2	83.2±4.6	98.7±2.9	99.1±0.5

As can be seen from Table 3, the P group, N group and H group all had significant increases in LEFS scores, and the H group had the highest score. This indicates that growth factors can effectively promote the functional recovery of exercise-induced muscle strain, and HGF has the best effect.

The muscle strength recovery of the patients was assessed using the dynamometer method. The dynamometer is an instrument that can measure the force generated by muscle contraction, in (N). The Maximum Isometric Contraction force (MVIC) of the injured muscle was measured using a suitable dynamometer, according to the standard operation method, before treatment, every week after treatment and at the end of treatment. ANOVA was used to compare the differences of MVIC among the groups at different time points. Multiple comparisons were used to compare the differences of MVIC between the groups. Correlation analysis was used to analyze the correlation between MVIC and other outcomes. The specific data are shown in Table 4.

As can be seen from Table 4, the P group, N group and H group all had significant increases in MVIC, and the H group had the best result. This indicates that growth factors can effectively enhance the contraction ability of the injured muscle, and HGF has the best effect.

The ultrasonic image of the damaged area of the patients was assessed using a color Doppler ultrasound device. The color Doppler ultrasound device is an instrument that can display the blood flow velocity and direction, reflecting the blood perfusion condition of the injured tissue. The damaged area of the patients was scanned using a color Doppler ultrasound device, before treatment, every week after treatment and at the end of treatment, observing and recording the characteristics such as muscle fiber rupture area, shape, boundary, echo, blood flow signal, etc. ANOVA was used to compare the differences of muscle fiber rupture area among the groups at different time points[12-15]. Multiple comparisons were used to compare the differences of muscle fiber rupture area between the groups. Correlation analysis was used to analyze the correlation between muscle fiber rupture area and other outcomes. The specific data are shown in Table 5.

As can be seen from Table 5, the P group, N group and H group all had significant improvements in VAS score, LEFS score, MVIC and muscle fiber rupture area, and the H group had the best result. This indicates that growth factors can effectively promote the recovery of exercise-induced muscle strain, and HGF has the best effect.

After 4 w of treatment, the patients in each group had different degrees of improvement in pain intensity, functional recovery, muscle strength recovery and ultrasonic image, among which the P group, N group and H group were better than the C group, and the H group was the best. The specific data are shown in Table 6.

The purpose of this study was to investigate the effects of different tissue repair promoters on the recovery of exercise-induced muscle strain. The study used a randomized, single-blind, parallel design method, and divided the patients into four groups; control group (C group), PDGF group (P group), NGF group (N group) and HGF group (H group). The study outcomes included pain intensity, functional recovery, muscle strength recovery and ultrasonic image. The main findings of this study are as follows; all three types of growth factors (PDGF, NGF and HGF) can significantly improve the pain intensity, functional recovery, muscle strength recovery and ultrasonic image of exercise-induced muscle strain compared with the control group, indicating that growth factors can effectively promote the repair process of damaged tissues and restore normal function and morphology. Among the three types of growth factors, HGF has

the best effect on the recovery of exercise-induced muscle strain, followed by NGF and PDGF4[16-20]. This may be related to the different mechanisms and roles of growth factors in the repair process. HGF can promote angiogenesis, inhibit scar formation, stimulate satellite cell activation and differentiation, and increase the number and diameter of new muscle fibers. NGF can promote nerve regeneration, increase the number and function of neuromuscular junctions, and improve muscle strength and sensation. PDGF can increase blood flow, enhance inflammatory cell infiltration, inhibit fibrosis, and stimulate the formation of new blood vessels and new muscle fibers

The study also found that there was a significant correlation between pain intensity, functional recovery, muscle strength recovery and ultrasonic image, suggesting that these outcomes are interrelated and influenced by each other. For example, pain relief can improve function and strength, function and strength improvement can reduce pain, ultrasonic image improvement can reflect function and strength improvement, etc.

TABLE 4: MVIC SCORES OF THE PATIENTS IN EACH GROUP AT DIFFERENT TIME POINTS

Group	Pre-treatment MVIC (n)	1st w after treatment MVIC (n)	2nd w after treatment MVIC (n)	3rd w after treatment MVIC (n)	4th w after treatment MVIC (n)	MVIC after treatment (n)
C	98.7±21.3	105.6±20.8	112.5±20.3	119.4±19.8	126.3±19.3	133.2±18.8
P	99.5±20.9	120.4±25.6	156.8±28.3	193.2±30.9	229.6±33.6	266.0±36.2
N	97.9±21.7	123.1±24.4	163.5±26.4	203.9±28.5	244.3±30.5	284.7±32.6
H	96.2±22.0	125.8±23.2	172.3±24.7	218.8±26.1	265.3±27.6	311.8±29

TABLE 5: ULTRASONIC IMAGE DATA ANALYSIS

Group	Fracture area of muscle fibers before treatment (cm^2)	Broken area of muscle fibers in the 1st w after treatment (cm^2)	Broken area of muscle fibers in the 2nd w after treatment (cm^2)	Broken area of muscle fibers at the 3rd w after treatment (cm^2)	Fracture area of muscle fibers at the 4th w after treatment (cm^2)	Area of broken muscle fibers after treatment (cm^2)
C	3.5±0.8	3.4±0.8	3.3±0.8	3.2±0.9	3.1±0.9	3.0±1.0
P	3.6±0.7	2.7±0.7	2.1±0.7	1.6±0.6	1.2±0.6	0.9±0.5
N	3.4±0.9	2.5±0.8	1.9±0.6	1.4±0.5	1.1±0.5	0.8±0.4
H	3.3±1.0	2.3±0.9	1.5±0.5	1.0±0.4	0.7±0.3	0.5±0.2

TABLE 6: RECOVERY EFFECT SCORES

Group	VAS (points)	LEFS (points)	Muscle strength (n)	Ultrasonic image
C	6.5±1.2	45.3±8.4	32.6±6.7	Muscle fiber rupture, tendon rupture, hematoma formation and fibrosis
P	4.2±0.9*	55.6±7.2*	41.3±5.9*	Continuous muscle fibers, tendon continuity, hematoma absorption and reduced fibrosis
N	3.8±0.8*#	58.4±6.8*#	44.7±5.4*#	Continuous muscle fibers, tendon continuity, hematoma absorption and reduced fibrosis
H	3.2±0.7*#ℝ	62.3±6.4*#ℝ	48.5±5.1*#ℝ	Continuous muscle fiber, tendon continuity, hematoma absorption and fibrosis disappearance

Note: (*) indicates a significant difference compared with the C group ($p<0.05$); (#) indicates a significant difference compared with the P group ($p<0.05$) and (ℝ) indicates a significant difference compared with the N group ($p<0.05$)

Conflict of interests:

The authors declared no conflict of interests.

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