Effect and Evaluation of Long-term Isokinetic Training of Knee Joint Under the Influence of Stiffness

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1 Summary of the study

The present study is a randomized controlled trial with a sample size of 10 control group and 10 experimental group for 6 weeks of seated kicking rehabilitation training for postoperative knee patients, applying the rehabilitation training intervention of portable isokinetic trainer to the experimental group, and the control group training with the same posture unarmed, and comparing the rate of change of the main indexes, such as isokinetic peak moment, between the control group and the experimental group by the t-test method.

2 Full text

6.1 Research overview/background and rationale for the project

(1) Knee injuries have a serious impact on a person's quality of life. Globally, there are 178 million fracture cases and 42 million lower extremity fractures[1][2] , nearly 25% of adults suffer from knee pain disorders[3] 87 million people aged 20 years and older suffer from osteoarthritis of the knee.[4] All of these patients can be rehabilitated or restored to function after surgery with a plyometric device.[5][6] The following are some examples of the types of rehabilitation and post-surgical functional restoration programs available to these patients Anterior cruciate ligament (ACL) rupture is one of the most common sports injuries and its incidence is increasing worldwide. Surgical reconstruction is an effective treatment for patients with complete ligament rupture, but the surgical failure rate can be as high as 20%, there are more than 400,000 ACL reconstruction surgery cases in the United States every year, and the population of our country is about 4.28 times that of the United States. With the implementation of the national fitness movement and the strategy of Healthy China, the number of people who take part in sports and the intensity of sports are increasing year by year, which makes the number of people with ACL rupture of the knee joint increase rapidly! In the near future, when the amount of exercise and sports habits of our population is close to those of Americans, the annual number of ACL reconstructions will exceed 1 million cases. The large number of people with ACL ruptures requires rehabilitation resources and effective rehabilitation methods.

(2) During the rehabilitation process, patients are often advised to use isokinetic plyometrics for rehabilitation or postoperative functional recovery training due to the high efficiency of isokinetic training and the ability to quantify muscle strength.[7] In addition to knee disorders, isokinetic training is also used for stroke[8] In addition to knee disorders, it is also used for stroke, traumatic spinal cord injury[9] and orthopedic diseases[10] In addition to knee disorders, it is also used for stroke, traumatic spinal cord injury and orthopedic disorders.

(3) However, the scarcity of rehabilitation training resources, the scarcity of professional

physiotherapists and the expensive cost of training equipment have hindered the promotion and popularization of isokinetic training. In addition, the existing commercial isokinetic training devices, such as Biodex, Cybex and IsoMed, are fixed devices that are large, bulky, high energy consumption, and cannot be worn at any time and trained at any time to meet the needs of multi-occasion rehabilitation training, such as home travel and other occasions.[11] The following are some examples of such devices.

(4) From the safety point of view, the commercial isokinetic trainer provides a large minimum impedance torque and the joints are completely rigid, so it is not suitable for postoperative bedridden patients or long-term bedridden people with weak muscle strength.[11] Therefore, it is not suitable for the rehabilitation training of postoperative bedridden patients or people with weak muscle strength who have been bedridden for a long time. A lightweight and wearable knee portable isokinetic training robot with variable joint stiffness can meet the needs of portability, multi-scene use and personalized human-computer interaction[13] , which together with the energy regeneration technology can effectively solve the above high energy consumption and low energy utilization efficiency problems.[14][15][16][17] The following are some examples of the use of the robot.

Isokinetic plyometric training robots require energy supply for their work, and the application of joint stiffness regulation and energy regeneration methods can improve the energy utilization efficiency of isokinetic plyometric training robots and reduce the requirement of energy supply for isokinetic plyometric training robots. The applicant proposed a dynamic power regeneration method in the early stage, realizing that 1/3 of the power can be obtained by the energy regeneration method.[18] . However, there are still some limitations in the previous research, the previous work mainly focuses on the regulation of joint damping (accompanied by dynamic power regeneration) method, whether the characteristics of isokinetic plyometric training robots, through the synergistic regulation of joint stiffness and joint damping (accompanied by dynamic energy regeneration and reverse energy regeneration), to further improve the efficiency of energy utilization, or even completely rely on regenerated power (100% self-supply) powering the robot remains to be further investigated. Due to the large differences in the condition of the subjects, how to establish a differentiated training model for plyometrics, adjust the joint stiffness of the plyometrics training robot and regulate the joint damping in the process of human-machine energy conversion, so as to reveal the matching mechanism between the differentiated functional requirements of plyometrics training and the stiffness of the plyometrics training robot and the human-machine energy conversion, and to promote faster and better recovery of the subjects has become the focus of the research in the present project.

6.2 Current status of domestic and foreign research

(1) Current status of variable stiffness actuator research

Rigid drive compared to flexible drive force control accuracy and energy utilization efficiency is lower, the buffer capacity is weaker, human-computer interaction safety and comfort is poor, isokinetic plyometric training equipment is often faced with the problem of the user's larger impact, the introduction of flexible drive joints can reduce the impact and improve the efficiency of energy utilization. According to the driver elastomer stiffness characteristics and whether it is controllable or not, the flexible driver can be divided into series elastic actuator (SEA) with constant stiffness and variable stiffness actuator (VSA), which can be specifically divided into passive VSA with nonlinear stiffness characteristics and active VSA with adjustable stiffness.

(a) Passive variable stiffness actuators

The stiffness (force/torque-displacement/angular displacement) curve of a passive VSA is determined by the structure of the actuator itself. The stiffness of the actuator can be varied with the load or with the output angle of the joints, and the need for different stiffness variation characteristics requires the design of different mechanical structures. Passive VSA developed by the Italian Institute of Technology team[19] utilizes an internal meshing planetary wheel system planetary wheel mechanism to stretch a linear spring in a nonlinear manner, producing a nonlinear force-displacement curve, as shown in Fig. 1(a). Unlike the planetary gear mechanism, Schmit N. et al.[20] proposed a passive VSA based on a cam-wound coil mechanism, which nonlinearly stretches a linear spring by cam-driven flexible ropes to obtain nonlinear spring characteristics, and can be applied to drive a 3-degree-of-freedom robotic arm to reduce the power requirement of the motor. In addition, Schepelmann A. et al.[21] have used a similar scheme to that of Schepelmann A. et al.[20] similar scheme utilizing rubber material to design a passive VSA with incremental stiffness characteristics, which reduces the structural size of the actuator and balances the contradiction between torque resolution and control bandwidth, but also has the disadvantage of hysteresis. In addition, also utilizing the cam mechanism, some research progress has been made by domestic university teams, and the Nankai University team[22][23] proposed a passive VSA, the actuator uses a spatial cam mechanism to compress three mold springs in a nonlinear manner to obtain nonlinear spring characteristics, as shown in Fig. 1(b). Hong Kong University team[24] A passive VSA with rigid, flexible, and free working states is designed using a combination of cam mechanism and linear compression springs, as shown in Fig. 1(c), and the actuator can be applied to human-computer interaction scenarios to enhance safety. The rotary passive VSA designed by the

Tianjin University team[25] A nonlinear spring with a given stiffness curve can be obtained by changing the shape of the curved surface of the contact part between the roller and the leaf spring and the dimensions of the leaf spring structure, as shown in Fig. 1(d). In addition, the team also designed a passive VSA with a helical torsion spring.[26] that can achieve the desired nonlinear spring characteristics by designing convex contour lines.

(b) Active variable stiffness actuator

Active VSA relies on its own mechanical structure or material properties to freely change the output stiffness of the drive, and can realize that the control of the drive position change and the control of the drive stiffness change are independent of each other (two motors are required), which has more usage scenarios compared to passive VSA. According to the layout of the two motors for variable stiffness and variable joint position, active VSAs can be categorized into parallel (antagonistic) and series (variable preload, variable structure, and variable ratio) types.

ETH Zurich Petit F. et al.[27] The active bi-directional antagonistic variable stiffness joint BAVS-Joint developed combines a cam mechanism with a linear compression spring to design a nonlinear spring with bi-directional actuation capability, which results in an improved torque output capability of the actuator and is a typical case study for antagonistic VSAs, as shown in Fig. 1 (e). Different from the antagonistic variable stiffness principle, Vanderborght B. et al.[28] proposed the MACCEPA variable stiffness method based on the variable preload method, which realizes the adjustment of the actuator stiffness by changing the spring preload, as shown in Fig. 1 (f) for the active variable stiffness joints designed by the team, which have been applied to bipedal robots, exoskeleton robots and prosthetics[28][29][30] The joint has been used in bipedal robots, exoskeleton robots and prosthetics.

In addition, for the variable structure approach, the Korea Advanced Institute of Science and Technology (Choi J. et.al.,)[31] designed a variable stiffness joint VSJ, which utilizes a two-degree-of-freedom linkage mechanism to adjust the effective action length of the cantilever beam leaf spring, as shown in Fig. 1(g). The actuator requires two motors to work in tandem and is relatively complex to control, but has an enhanced torque output capability. Further, Chalvet V. et al. of Singapore University of Technology and Design[32][33] proposed a variable-structure VSA variable-stiffness mechanism with a large stiffness adjustment range, high stiffness adjustment efficiency and low energy consumption, as shown in Fig. 1(h).

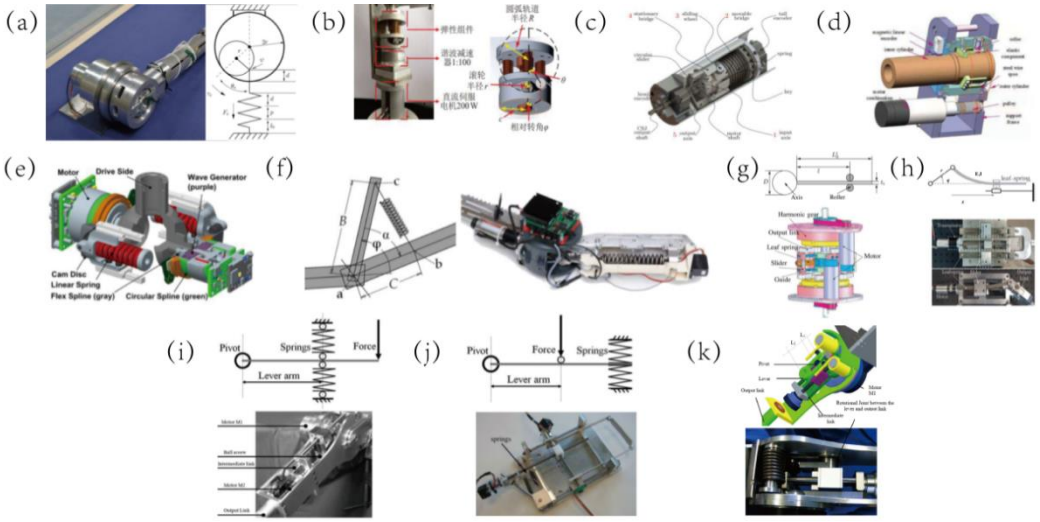

Figure 1 Variable stiffness actuator (a) Italian Institute of Technology[19] (b) Nankai University, China[22][23] (c) University of Hong Kong[24] (d) Tianjin University[25] (e) ETH Zurich[27] (f) MACCEPA[28] (g) Korea Advanced Institute of Science and Technology (KAIST)[31] (h) Singapore University of Technology and Design[32][33] (i) AwAs [34] (j) University of Twente, Netherlands[35] (k) AwAs-II[36]

Based on the principle of variable transmission ratio, three kinds of active VSAs can be obtained by adjusting the position of the elastic element, the position of the force application point and the position of the fulcrum point respectively. Tsagarakis N.G. et al.[34] The developed actuator AwAs shown in Fig. 1(i) can theoretically realize the stiffness adjustment in the range of [0, k] by adjusting the spring position through the ball screw mechanism, and the external load of the stiffness-adjusted motor is theoretically zero when the stiffness of this type of actuator is adjusted at the equilibrium position, which results in a high stiffness-adjusted energy utilization efficiency. Visser L.C., University of Twente, Netherlands, et al.[35] The proposed active VSA, as shown in Fig. 1(j), then has a theoretical stiffness adjustable range of [k, ∞) by adjusting the position of the force application point, which enhances the stiffness-regulated energy efficiency with the stiffness adjustable range, but the energy storage effect is general and the structure size is large. As in Fig. 1(k) based on changing the pivot position, Tsagarakis N.G. et al.[36] Based on AwAs and proposed a wider range of stiffness adjustment drive AwAs-II, the theoretical stiffness adjustment range of [0, ∞), but also has a high stiffness adjustment energy utilization efficiency.

6.2 Purpose

1. Use the portable knee isokinetic trainer to find the joint flexibility that maximizes the force applied by the patient, i.e., the optimal stiffness, and observe and evaluate the effect of long-term isokinetic rehabilitation training under the influence of the optimal stiffness.

2. Training with a portable knee isokinetic trainer was used to compare the long-term (6-week) training effects of isokinetic training under the influence of optimal stiffness with those of conventional unarmed training.

6.3 Design

6.3.1 Study site or study population

Inclusion criteria.

1. Age 20-60 years.

2. Patients undergoing unilateral knee ligament and/or meniscus surgery, including initial reconstruction for anterior cruciate ligament rupture, initial reconstruction for posterior cruciate ligament rupture, and initial medial patellofemoral ligament reconstruction for patellofemoral dislocation in conjunction with meniscus injury.

3. 3-6 months after the patient's operation.

4. There is no impairment of knee extension or flexion.

Exclusion criteria.

1. Suffer from other major diseases or conditions such as coronary heart disease, myocardial infarction, heart failure, cerebral infarction, cerebral hemorrhage and malignant tumors.

2. Special groups such as pregnant women and nursing mothers.

3. Refusal to sign the informed consent form or inability to complete the entire study, etc.

4. Ongoing infection with Human Immunodeficiency Virus (HIV), infectious Hepatitis B or Hepatitis C, or a history of such infection.

5. concurrent medical problems, including but not limited to the following:

(1) Uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg), congestive heart failure (New York Heart Association status class III or IV).

(2) The patient is mentally incapacitated or unable to understand the requirements for participation in the study.

Exit criteria:

1. Subject withdraws informed consent;

2. Serious violations of clinical trial protocols;

3. Those who, in the opinion of the investigator, are no longer suitable for continuation of the clinical trial;

4. Women who become pregnant during clinical trials;

5. Death of the subject;

6. Subjects were lost to interviews.

Treatment of withdrawn subjects:

1. All withdrawing subjects should retain all source data and source files. When a subject withdraws, the investigator should contact the subject in as many forms as possible, such as by phone, e-mail, etc., to inquire about the reason;

2. Record the time and reason for termination of the clinical trial in detail on the case report form;

3. Injuries due to adverse events must be documented on the case report form if a causal relationship with the test device is conclusively determined after follow-up. Patients whose trials are terminated due to an adverse event must be followed until the adverse event is resolved or stabilized.

6.3.2 Grouping of patients (randomization or not, method of randomization, blinding or not, etc.)

This trial is a randomized controlled trial to further validate the safety and efficacy of the portable isokinetic device in this study. The experimental group was 10 patients who met the inclusion criteria and were rehabilitated with the portable isokinetic device. While the control group was 10 patients who met the inclusion criteria and underwent unarmed rehabilitation. The randomization method was performed using the REDCap system without blinding.

6.3.3 Interventions (what kind of intervention, choice of control, etc.)

Postoperative plyometric training criteria:

According to the experience of a large number of patients' rehabilitation training, isokinetic muscle strength training can be carried out after 3 months postoperatively, and the criteria for being able to carry out the training are normal knee joint movement and no obvious swelling and pain.

Experimental group trial process:

Patients were invited to come to the hospital to sign the informed consent form and other documents, to carry out pre-trial data recording and mechanical assessment (isokinetic muscle strength of the patient's knees on both sides) and imaging assessment (cross-sectional MRI scan of the patient's thigh muscles on both sides). The base duration of the trial was 6 weeks, with two training sessions per week for a total of 12 sessions, ensuring that the interval between two consecutive training sessions was greater than 48 h in order to eliminate the effects of fatigue and allow sufficient recovery time, and that the total duration of each training session was controlled to be around 30 min. Patients were required to perform optimal stiffness determination before the start of training in weeks 1, 3 and 5, and the corresponding optimal stiffness conditions were used in the training after the determination was completed. During each training session, the patient wore the isokinetic robot with the affected leg in a seated

position, fixed the healthy leg, extended and then flexed the knee, set the angular velocity to 60°/s, the initial angle of the knee joint was 90° before the start of the test, and extended and flexed the knee for 15 consecutive times as a group, with 5 groups, and each group was separated by 2-5 min, during which the patient took off the isokinetic robot and lay down on the bed to fully relax and rest. Depending on the patient's condition, the number of knee extensions and flexions, the number of groups and the length of rest between groups were fine-tuned appropriately. At the same time, the upper computer software recorded the whole training data in real time, obtained the knee extension parameters (peak torque PT_{ext} , average torque AT_{ext} , average work AW_{ext}) and knee flexion parameters (peak torque PT_{fle} , average torque AT_{fle} , average work AW_{fle}), and took the average value to eliminate the random error to get the six indicators of the training, respectively, to calculate the correlation coefficient within the group ICC, and to determine the comprehensive index I. The average value was calculated as follows:

$$I = \sum ICC_X X$$

The data of the patients in the experimental group were recorded throughout each training session and used for their own control, the I-value of each training session was calculated, and the date-I curve was plotted. the trial was ended after 6 weeks, and at the end of the session, thigh MRI scanning and isokinetic muscle strength were performed again, and the subjects were asked about their subjective feeling according to the safety indexes, and the patients were observed for any adverse reactions (gait body posture).

Observational indicators for the experimental group:

Quadriceps and hamstring cross-sectional area (pre-test start and post-test comparison), and knee isokinetic muscle strength (peak flexion-extension knee torque, average flexion-extension knee torque, and flexion-extension knee work, pre-test start and post-test comparison).

Control group trial process:

For the control group, patients were invited to come to the hospital to sign the informed consent and other documents, carry out pre-trial data recording and perform mechanical assessment (isokinetic muscle strength of the patient's knees on both sides) and imaging assessment (cross-sectional MRI scan of the patient's thigh muscle groups on both sides). The patient did unarmed rehabilitation twice a week, each lasting about 30 min at intervals greater than 48 h. The rehabilitation maneuvers were also seated knee flexion and extension without the use of a portable isokinetic trainer. After the completion of all the training at the base duration of 6 weeks, the thigh MRI scan and isokinetic muscle strength were performed again,

and the subjects were asked about their subjective feelings and observed for any adverse reactions (gait body posture) according to the safety indexes.

Control Group Observational Indicators:

Quadriceps and hamstring cross-sectional area (comparison between before the start of the test and at the end of the test), and knee isokinetic muscle strength (peak flexion-extension knee torque, average flexion-extension knee torque, and flexion-extension knee work, comparison between before the start of the test and at the end of the test).

The specific SOP is shown in Figure 6.9:

6.3.4 Follow-up plan (periodicity and content of follow-up visits)

The study will last for 6 weeks, with 2 training sessions per week, during which follow-up visits will be made and information will be collected in order for the patients to get better rehabilitation results, as detailed below:

Time: Before the start of the trial and at the end of weeks 2, 4 and 6 of training.

METHODS: Telephone follow-up visits were conducted.

Content: Consultation on training feelings (knee pain, discomfort relief, subjective feeling of muscle strength).

6.3.5 Selection and validation of key measurement or endpoint indicators

Primary Indicators:

Cross-sectional area of the quadriceps, cross-sectional area of the hamstrings, peak flexion and extension knee torque, average flexion and extension knee torque, and flexion and extension knee work.

Secondary indicators.

high circumference (10 cm proximal to the superior pole of the patella) and knee pain score (VAS score).

Security Indicators:

Skin temperature of the suprapatellar bursa of the knee, angle of joint mobilization, and degree of knee pain.

6.3.6 Sample size calculation and inference

In this study, which involved a new intervention method, a pretest with a sample size of 6 was set up to evaluate the safety of the new method, and the effectiveness and other aspects were evaluated based on the confirmation of safety. Since the main index in the pretest was isokinetic mean moment, according to the results of the pretest, the mean and standard

deviation of the experimental group was 40.1±20.9, and that of the control group was 9.5±10.6, and the ratio of the sample size of the experimental group to that of the control group was 1 :1, and the hypothesis tests were set up with a type I error α=0.05 and a type II error β=0.1, according to the sample size calculation formula: $n_2 = \frac{(z_{1-\alpha/2}+z_{1-\beta})^2(sd_1^2+sd_2^2)(1+1/k)}{2(mean_1-mean_2)^2}$,,,,,, and$n_1 = k \times n_2$, where$z_{1-\alpha/2}$ = 1.96, and$z_{1-\beta}$ = 1.28, obtaining a sample size of 7 for the experimental group and 7 for the control group. Assuming a failure rate of 30%, a sample size of at least 10 is required for the experimental group and 10 for the control group, so 20 patients need to be enrolled to ensure that 14 patients complete the trial, and the total number of samples is determined to be 20.

6.4 Data management

6.4.1 Data entry (choice of paper/electronic record forms, double entry or not, electronic data capture system or not, etc.)

Dual paper/electronic form entry.

6.4.2 Content and modalities of data verification and management

A database of patient training indicators has been established, for the patient's basic information, training raw data, assessment and analysis indicators and curve images are stored in the cloud database, users can store a large amount of patient data in the cloud, real-time uploading and reading, preventing data loss, and facilitating multi-person, multi-location operation and verification.

6.4.3 Data archiving

Case report forms are filed and stored in numbered order with search catalogs, etc., filled in for reference after data entry and verification are completed as required. Electronic data files including databases, examination procedures, analytical procedures, analytical results, code books and description documents are kept in categories with multiple backups saved on different disks or recording media, and properly preserved to prevent damage. All original files should be kept for the period within the corresponding regulations.

6.5 Statistical analysis

After completing the test, we performed T-tests on the mean quadriceps cross-sectional area increase, the mean hamstring cross-sectional area increase, the mean knee isokinetic peak torque increase, the mean knee isokinetic mean torque increase, and the mean knee isokinetic work-effort increase before and after carrying out the test for the experimental group and the control group to observe the significance of changes in the indexes after the imposed

intervention, so as to evaluate the effects of the knee isokinetic training under the optimal stiffness intervention in comparison with the rehabilitation training effect of traditional unarmed training was evaluated. Specifically, MATLAB and SPSS26.0 software (SPSS, Inc., IBM, USA) were used to compare the rate of improvement of the above five main indexes in the experimental group and the control group using the t-test method (95% confidence interval), and the indexes were measured using the mean±standard deviation (percentage), with $P \leq 0.05$ being considered as a significant difference. The muscle strength of healthy adults is relatively stable under the conditions of daily life exercise level, so the main indicators on the healthy side generally do not have significant changes, according to the pre-test situation showed that there are cases in which patients participate in other rehabilitation programs (such as the gym) at the same time and do not inform the researcher, which leads to a significant increase in the indicators on the healthy side. Considering the elimination of the effect of additional exercise by the patients themselves during the conduct of the trial, and assessing the effect of the intervention on the balance of the strength of the two thigh muscles on the healthy side of the affected side of the body, the difference between the ratio of the indexes on the affected side of the subject to the main indexes on the healthy side before and after the conduct of the training, or the rate of improvement in the ratio (mean ±standard deviation), was standardized, and a t-test was used to see the significance of the difference in this statistic between the experimental group and the control group.

For the experimental group, all the impedance torque data during each training session were recorded, and the main indicators of mechanics mentioned above (peak torque of leg lifting/retracting, average torque of leg lifting/retracting, and leg lifting/retracting work) were extracted for the before and after self-checking, and the date-I curves of the training sessions were analyzed according to the specific conditions of the subjects, and the reasons for the differences in the rehabilitation effects of different patients were explored.

Using the paired-samples t-test (95% confidence interval), the isokinetic peak moments, average moments and work done, and the composite index I of the first and last training sessions of the subjects in each experimental group were compared, thus verifying the effectiveness of the training for postoperative rehabilitation of the knee, and a significant difference was considered to exist at $P \leq 0.05$.

After each measurement of optimal stiffness, the isokinetic peak moments, average moments and work done, and the composite index I of subjects trained at optimal stiffness and at maximum stiffness in each experimental group were compared separately using a paired-samples t-test (95% confidence interval) to measure the effect of isokinetic training at optimal stiffness on the rehabilitation effect relative to traditional purely rigid isokinetic training, with

$P \leq 0.05$ being considered a significant difference. Secondly, the secondary indexes were used as an auxiliary basis for drawing experimental conclusions.

6.6 Security evaluation

Isokinetic training is a non-invasive means of rehabilitation, which has been shown in a large number of clinical case studies to improve the level of muscle strength without the occurrence of serious adverse reactions, indicating that its clinical application is safe. Prior to this project, this robot has been tested and verified many times, and a study based on this robot has been approved by the Medical Science Research Ethics Committee of the Third Hospital of Peking University (Approval No. (2024) Medical Ethics Review No. (419-04)), and its safety can be guaranteed due to its non-invasive characteristics and the application of flexible joints, and the results showed that the patient's mechanical indexes (average moment, peak moment, and average work in flexion and extension) can be improved. moment, peak moment, and average work) and imaging indexes (cross-sectional area of quadriceps muscle, cross-sectional area of hamstring muscle) were better improved.

The portable isokinetic trainer used in this test can realize isokinetic impedance torque provision of 60, 120 and 180°/s, with the maximum impedance torque of 24 Nm and the minimum impedance torque of 0.3 Nm. When the trainer is used, the user needs to take the initiative to send out force to kick the leg, and if the user does not send out force, then the trainer does not produce damping, and will not actively exert force on the limb in the process of using the trainer, which ensures the safety of the training process. In addition, because the damping device of the training instrument and the user's limbs are connected in series with an elastic element, avoiding direct contact between the limbs and the damper, and the elastic element can play a role in buffering and damping, absorbing the force generated by the emergency stop, so it can further increase the safety of the isokinetic equipment. When the damper fails, because the damping source is a brushless DC motor, the motor stops blocking the rotation, at this time the resistance is the minimum resistance of 0.3Nm, 0.3Nm is much smaller than the human knee joint isokinetic torque, so as to ensure that the failure does not cause harm to the human body.

Risks that may occur:

Risks that may occur in the use of this isokinetic robot for rehabilitation include:

1. Any instrumental means of rehabilitation carries risks.

2. Any overtraining may produce side effects, including muscle soreness, joint pain, muscle strains or sprains, and fatigue.

3. The effectiveness of rehabilitation training may be compromised if the patient is not in the proper position or posture and does not follow medical advice.

4. If the patient suffers from hypertension, hyperlipidemia, obesity, heart disease, diabetes mellitus, vital organ insufficiency, venous thrombosis, etc.; these risks may be increased.

5. Other unforeseen circumstances.

In the event of such risks and accidents, the doctor will take proactive measures to deal with them, but cannot guarantee the desired results, and the amount (total) of all expenses incurred as a result of the occurrence of the risks will be paid by BHU. Ethical considerations can be found in (2024) Medical Ethics Review No. (419-04) and BHU Bio and Medical Ethics Committee 2024-04-22 BM20240173.

6.6.1 Concepts of Adverse Events (AE) and Serious Adverse Events (SAE)

Definition of adverse events in this trial: during the training period and follow-up at the end of the trial, if the subject has knee pain for no reason, or has pain on a daily basis but the pain worsens for no reason, and does not get better after two weeks after the occurrence of the above conditions, it will be considered as an adverse event. The trial can be continued if recovery occurs after a certain period of rest and without affecting the observation of efficacy. Serious adverse events are events that require hospitalization, prolonged hospitalization, disability, work ability, permanent damage to organ function, life-threatening or death during the clinical trial. Adverse events were evaluated according to five levels: definitely related to training, probably related, probably related, probably unrelated, and definitely unrelated, with the first three counted as the incidence of adverse reactions. The occurrence of any serious adverse event or significant adverse event, whether or not related to the study intervention and whether or not the intervention operation had been carried out, had to be reported to the clinical trial organization and the ethics committee within 24 hours of occurrence or knowledge.

Qualifying criteria for clinical trial results:

1. Relevant information of each subject should be recorded in the case record form designed according to the requirements of the trial, and ensure the accuracy and completeness of the data, as well as traceability.

2. Key points such as the date of signing the informed consent, the date of enrollment, and the time of each visit should be noted for data collection to avoid missing as much as possible.

3. The efficacy data recorded for each visit period should be those obtained when the subject arrives in strict compliance with the time window specified in the protocol.

Some subjects who go against the above should be discussed by the principal investigator and the statistical professional to decide on specific treatment measures, as well as to assess whether there will be a greater impact on the trial.

6.6.2 Reporting of Adverse Events

The sponsor must be notified by telephone/fax within 24 hours of occurrence/knowledge of any serious adverse event or significant adverse event, whether or not related to the study intervention and whether or not an intervention manipulation has been performed.

6.7 Subject protection (informed consent, subject benefits and risks, confidentiality, conflict of interest, and other ethical considerations)

The trial should not be started until the trial protocol and subject informed consent forms have been submitted and approved by the ethics committee. If a protocol revision is carried out, it may only be started after the corresponding revised section and the revised informed consent form (if it exists) have been reviewed and approved by the Ethics Committee, and a copy of the Ethics Committee's approval is required to be provided to the Clinical Supervisor. If the revision of the protocol is intended to reduce the clear risk to the subjects, it can be implemented immediately, but it must be submitted to the relevant authorities and the ethics committee for record as soon as possible.

According to the relevant regulations in China, before the start of the trial, the investigator shall provide the subjects with written and oral explanations of the background, nature, significance, steps, benefits, risks, compensation, injury compensation, withdrawal, etc., and must obtain an informed consent form signed by each subject (or the subject's legal representative). The informed consent form should be dated, and the informed consent form and its copy should be kept separately by the investigator and the subject. The design of the informed consent form can be referred to the Informed Consent Form Template provided by the Ethics Committee.

If the trial process results in physical or psychological injuries to the participant, BUAA will be responsible for paying all related medical expenses and will provide necessary medical counseling and support from the Third Hospital of Peking University when needed. If a participant suffers permanent physical or psychological injuries due to trial-related factors, BUAA will provide appropriate compensation in accordance with relevant laws and regulations and bear further treatment and rehabilitation costs.

Each subject is not required to pay for the examination costs involved in the trial, all of which will be borne by BUAA. In addition, subjects participating in the trial are given a basic transportation subsidy of 50 yuan per trip, and the amount of the subsidy is increased to a maximum of 150 yuan per trip, depending on the distance of the trip and the degree of active participation.

6.8 Research management

Before the trial started, the test equipment had to be tested repeatedly to confirm its reliability. The researchers were trained in the Department of Sports Medicine of Peking University Third Hospital to familiarize themselves with the trial process, practice the equipment, and assign specific tasks, including subject recruitment, patient guidance, communication, equipment maintenance, data recording, data entry, and data processing, among others.

6.8.1 Program modification (define the principles and process of program modification after the start of the project)

If the results of the trial still did not show significant differences after inclusion of the planned sample. Then the sample size was re-estimated based on the data already available in this trial and the sample was further increased. The trial protocol was strictly followed, and if serious adverse reactions due to device defects occurred, the trial was immediately suspended, evaluated for the defects, and ethical approval needed to be renewed as to whether it could be continued.

6.8.2 Quality management (PMP)

During the course of the trial study, clinical supervisors are assigned by the sponsor to conduct regular on-site supervisory visits to the research unit to ensure that all elements of the study protocol are strictly adhered to, as well as the correctness of the completed information. The trial center should objectively and truthfully record and retain all data and protocol implementation and modifications during the trial study. Consistency of inclusion/exclusion criteria should be ensured as far as possible during the patient recruitment phase.

The specific inspections are:

1. The validation program was submitted to the Ethics Committee for approval.

2. Researchers participating in this validation before, during and after the validation carefully implement the standard operating procedures for clinical validation.

3. The validation process accepts the monitoring of the correctness and completeness of the data in the CRF by the monitors of the clinical trial research units and implementers.

4. Participating researchers must undergo uniform training and harmonization of recording methods and standards of judgement.

5. The investigator should record the contents of the CRF truthfully, in detail and carefully according to the requirements for completing the case report form, so as to ensure that the contents of the case report form are true and reliable.

6. All observations and findings in the clinical verification should be verified to ensure

the reliability of the data, to ensure that the conclusions in the clinical verification come from the original data, and that there are corresponding data management measures in the clinical verification and data processing.

6.8.3 Early termination

If one serious adverse event related to product quality occurs, the clinical trial is judged to have failed, and the clinical trial should be terminated in a timely manner; if a serious deviation is found in the implementation of the clinical trial, and it is difficult to evaluate the effect of rehabilitation training, the applicant will request the termination of the trial or the administrative department will request the termination of the trial.

6.9 Organizational management

6.9.1 Project organizational framework

6.9.2 Participating units (basic information on each participating unit, description of the division of tasks on the subject)

The Department of Sports Medicine of the Third Hospital of Peking University provided the test site, examination and evaluation, as well as the rehabilitation movement specifications, and the Beihang University provided the portable isokinetic trainer in order to provide maintenance services, database construction, data entry and analysis.

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Informed consent

Effect and Evaluation of Long-term Isokinetic Training of Knee Joint Under the Influence of Stiffness

You are being invited to participate in this study because you are eligible for enrollment in a study to evaluate the effectiveness of a portable isokinetic knee trainer in the rehabilitation of the thigh muscle group. Your study doctor or investigator will fully explain the contents of the informed consent form to you. Please read this informed consent form carefully and make your decision to participate in the study carefully. If you are participating in another study, please let your study doctor or investigator know.

The content/nature, risks and other important information about this study are listed below:

Fuzhen Yuan will lead the study, which is being conducted jointly by Peking University Third Hospital and Beihang University.

1.Why was this study conducted?

Portable knee isokinetic trainer refers to the use of robotics to assist humans in the process of rehabilitation treatment and training, can collect and observe all biological data of the human body and provide assistance in coordinating the movement of the human body, and the robot can also provide movement support for patients with motor dysfunction. This kind of robot will bring a great transformation to human life and perception. In the current robotics research, portable, lightweight, and wearable are the hotspots of current research. The biological data of human movement is characterized by strong coupling and complexity, which leads to a relatively large difficulty in its measurement and processing, and puts forward great requirements for sensor measurement, data fusion processing and control algorithms, and is also a difficult point in current research. Ultimately, this project intends to clarify whether the treatment means for patient groups with obvious differentiation should be different, and to observe and evaluate the long-term isokinetic rehabilitation training effect under the influence of stiffness for postoperative patients with ACL reconstruction under the premise of fixing the angular velocity and the range of motion. And compare the long-term (6-week) training effect of isokinetic training under the influence of stiffness with that of traditional unarmed training. In order to provide better ACL treatments with evidence-based medical evidence for the majority of patients with knee injuries, so that they can return to normal life, work and physical activity faster, better and with less surgery.

2.Number of participants in the study and method of grouping

Twenty people were included in this trial, divided into Group A and Group B, where Group A was instrumental training and Group B was unarmed training. This trial is a randomized controlled trial, which needs to verify the safety and validity of wearable isokinetic robots. The test group is 10 patients who meet the inclusion criteria, and the method of randomized controlled trial is used to study the effect of long-term knee joint on isokinetic rehabilitation training under the influence of stiffness, and to record the rehabilitation indexes of the patients in the process of training for their own control.

The control group consisted of 10 patients who met the inclusion criteria and underwent unarmed rehabilitation.

The investigator will use the REDCap system to randomize subjects without knowing their information, thus assigning a test group (A) versus a control group (B), where you have a 50% chance of being in group A and a 50% chance of being in group B. The investigator will use the REDCap system to randomize subjects to a test group (A) versus a control group (B).

3.Inclusion and exclusion criteria for this study

Inclusion criteria:

1. Age 20-60.
2. Patients with unilateral knee ligament and/or meniscus surgery, including patients with initial reconstruction for anterior cruciate ligament rupture, initial reconstruction for posterior cruciate ligament rupture, and initial medial patellofemoral ligament reconstruction for patellar dislocation versus meniscus injury.
3. Patients were 3-6 months postoperative.
4. There was no impairment of knee extension and flexion movement.

Only those who met all of the above criteria were included in the study.

Exclusion Criteria:

1. Suffering from other major diseases or conditions such as coronary heart disease, myocardial infarction, heart failure, cerebral infarction, cerebral hemorrhage and malignant tumors.
2. Special populations such as pregnant and lactating women.
3. Refusal to sign the informed consent or inability to complete the full study, etc.
4. Ongoing infection with Human Immunodeficiency Virus (HIV), infectious Hepatitis B or Hepatitis C, or a history of corresponding medical conditions.
5. Also suffering from medical problems, including but not limited to the following:
   (1) Uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg), congestive heart failure (New York Heart Association status class III or IV).
   (2) The patient is mentally incapacitated or unable to understand the requirements for participation in the study.

4. Research process:

If you agree to participate in this study and sign the informed consent form, you will undergo trial-related tests and procedures to confirm your suitability to participate in this study, according to the protocol, and the frequency of training will be twice a week in both the trial and control groups:

5.Follow-up visits and information collection?

The study will last for 6 weeks, with 2 training sessions per week, during which follow-up visits

will be made and information will be collected in order for the patients to get better rehabilitation results, as detailed below:

Time: Before the start of the trial and at the end of weeks 2, 4 and 6 of training.

METHODS: Telephone follow-up visits were conducted.

Content: Consultation on training feelings (knee pain, discomfort relief, subjective feeling of muscle strength).

6.Benefits of participating in the study?

The discomfort associated with your knee injury may be greatly relieved during this program, and there may be no direct benefit to you from participating in this study, but we hope that the information gained from your participation in this study will benefit patients with your condition in the future, and that this program may be used for others with similar conditions, to guide future clinical examinations, treatment, rehabilitation, and follow-up visits. You will receive good medical care during this period, and the follow-up may reveal patterns that were not previously recognized, and we will inform you of these in detail if you wish.

7.Risks of participating in this study

Isokinetic training is a non-invasive means of rehabilitation, which has been shown in a large number of clinical case studies to improve the level of muscle strength without the occurrence of serious adverse reactions, indicating that its clinical application is safe. Prior to this project, this robot has been tested and verified many times, and a study based on this robot has been approved by the Medical Science Research Ethics Committee of the Third Hospital of Peking University (Approval No. (2024) Medical Ethics Review No. (419-04)), and its safety can be guaranteed due to its non-invasive characteristics and the application of flexible joints, and the results showed that the patient's mechanical indexes (average moment, peak moment, and average work in flexion and extension) can be improved. moment, peak moment, and average work) and imaging indexes (cross-sectional area of quadriceps muscle, cross-sectional area of hamstring muscle) were better improved.

The portable isokinetic trainer used in this test can realize isokinetic impedance torque provision of 60, 120 and 180°/s, with the maximum impedance torque of 24 Nm and the minimum impedance torque of 0.3 Nm. When the trainer is used, the user needs to take the initiative to send out force to kick the leg, and if the user does not send out force, then the trainer does not produce damping, and will not

actively exert force on the limb in the process of using the trainer, which ensures the safety of the training process. In addition, because the damping device of the training instrument and the user's limbs are connected in series with an elastic element, avoiding direct contact between the limbs and the damper, and the elastic element can play a role in buffering and damping, absorbing the force generated by the emergency stop, so it can further increase the safety of the isokinetic equipment. When the damper fails, because the damping source is a brushless DC motor, the motor stops blocking the rotation, at this time the resistance is the minimum resistance of 0.3Nm, 0.3Nm is much smaller than the human knee joint isokinetic torque, so as to ensure that the failure does not cause harm to the human body.

Risks that may occur in the use of this isokinetic robot for rehabilitation include:

1. Any instrumental means of rehabilitation carries risks.

2. Any overtraining may produce side effects, including muscle soreness, joint pain, muscle strains or sprains, and fatigue.

3. The effectiveness of rehabilitation training may be compromised if the patient is not in the proper position or posture and does not follow medical advice.

4. If the patient suffers from hypertension, hyperlipidemia, obesity, heart disease, diabetes mellitus, vital organ insufficiency, venous thrombosis, etc.; these risks may be increased.

5. Other unforeseen circumstances.

8.If a research-related injury occurs

In the event of such risks and accidents, i.e., physical or psychological injuries to the participants during the trial, BUAA will be responsible for paying all related medical expenses, and the Third Hospital of Peking University will provide necessary medical counseling and support when needed. If a participant suffers permanent physical or psychological injuries due to trial-related factors, BUAA will compensate the participant in accordance with relevant laws and regulations, and bear further treatment and rehabilitation costs.

9.Other medical options available?

You will be guided by a healthcare professional who will provide you with the most appropriate treatment for your specific condition, including but not limited to: physical therapy such as cold therapy, heat therapy, massage, medication used to reduce pain or inflammation, and more.

10.Confidentiality

Your medical records will be kept intact at Peking University Third Hospital, and we will ensure that the confidentiality of your identifying documents, specimens, and test results will be maintained. No organization or individual will have access to this information without your permission. Your identity will not be disclosed when the research information and data obtained from this program are published in scientific conferences or journals. However, your records may be reviewed to ensure compliance with relevant laws and regulations. The reviewers will include the relevant national regulatory authorities, the Ethics Committee of Peking University Third Hospital, and the team of Peking University Third Hospital project staff directly involved in the collection of materials.

11.Related costs and financial compensation

Costs related to medical examinations: Each subject will not be required to pay for the costs of the examinations involved in the trial, which will be borne entirely by BUAA, including the costs of MRI examinations and follow-up visits (you will need to participate in the full trial in order to be reimbursed for the costs of the examinations).

Additional financial compensation: A basic transportation subsidy of RMB 50/trip will be given to subjects participating in the trial, and the amount of the subsidy will be increased depending on the distance traveled and the degree of active participation, up to a maximum of RMB 150/trip.

You can consult with a study doctor or researcher for more information about costs.

12.Refusal to participate or withdrawal

Before you accept the trial, you need to make sure that your participation is completely voluntary, that you have the option to refuse to participate or to withdraw from the trial at any stage of the trial (you will be considered to have withdrawn from the trial automatically after you miss a visit), that you will not be discriminated against or retaliated against for doing so, and that your healthcare treatment and rights will not be affected.

In order to ensure participation compliance, financial compensation and examination fees will be paid only if you have participated in all 12 training sessions and completed all examinations; if you withdraw from the program, you will have to pay for the examination fees out of your own pocket, and additional financial compensation will be settled and paid depending on your cooperation prior to withdrawing from the program.

If you have a serious adverse reaction, or if your study doctor feels that it is not in your best interest to continue participating in the study, he/she may decide to withdraw you from the study. You will be notified promptly if this happens, and your study doctor will discuss other options for you. If your doctor feels that sudden discontinuation of the trial will affect your health, you may be asked to come to the hospital for a check-up before stopping the trial.

13.Related Consultations

If you have any questions related to your rights and interests, or if you would like to reflect your dissatisfaction and worries in the process of participating in this program, please contact the direct person in charge of this program at 010-82266876 (Ethics Committee Office), 15034655724, 15896503639.

Notification statement

"I have informed the subject and the subject's guardian of the background, purpose, steps, risks and benefits of the trial, and given him/her enough time to read the informed consent form, discuss it with others, and answer his/her questions about the project; I have informed the subject that when he/she encounters problems related to the project, he/she can contact the Department of Sports Medicine of Peking University Third Hospital or the School of Mechanical Engineering and Automation of Beihang University, and to contact the General Office of Research Ethics of the Third Hospital of Peking University at any time when encountering problems related to his/her rights/interests and to provide accurate contact information; I have informed the subject and the subject's guardian (that he/she may withdraw from the study at any time without any reason; I have informed the subject that he/she will be provided with a copy of this informed consent form, which contains my and his/her consent to participate in the study. It contains my signature and his/her signature."

Signature of the researcher: Contact number: Date:

Statement of informed consent

"I was informed about the background, purpose, steps, risks and benefits of the trial. I was given plenty of time and opportunity to ask questions and I was satisfied with the answers to my questions. I have also been told who to contact when I have questions, complaints, concerns, or want further information. I have read this informed consent form and agree to participate in this program. I know that I can withdraw from this study at any time and without any reason. I am told that I will be given a copy of this informed consent form that contains my signature and that of the researcher.

Subject Signature: Contact phone number: Date: