Far Eastern Memorial Hospital
Human subject research study protocol

I. Title

Effects of individualized exercise intervention combined with manual therapy on the musculoskeletal system, cardiorespiratory endurance and quality of life in severe hemophilia patients with polyarthropathy.

II. Principal Investigator

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IV. Background

Hemophilia is clinically characterized by acute bleeding, more than 80% of which occur in specific joints (commonly occurring in ankle joints, knee joints and elbow joints, followed by hip joints, shoulder joints and wrist joints) and muscles (iliopsoas and gastrocnemius). Joint bleeding worsens joint damage in hemophilia patients, increasing the risk of chronic synovitis and hemophilic arthropathy in the long term. Improper treatment of intramuscular bleeding cause muscle contracture, especially in muscles that cross joints (such as calf muscles and psoas muscles), bleeding sites in these muscles are related to neurovascular damage and require immediate treatment to prevent permanent damage and loss of function [1].

For hemophilia patients with chronic synovitis who cannot take routine prophylaxis, the World Federation of Hemophilia recommends non-surgical treatment, including short-term prophylaxis for 6-8 weeks to control bleeding, selective COX-2 inhibitors, or physical therapy improves muscle strength and joint function to reduce pain and inflammation [6]. In addition, past studies have also recommended that patients with hemophilia receive physical therapy evaluation and intervention to improve muscle strength, balance, cardiorespiratory fitness, reduce the risk of falls, and improve quality of life [7].

A complete assessment of acute joint bleeding and physical therapy based on the clinical status of the case is necessary [3]. Past studies have shown that individualized exercise significantly improve muscle strength, upper and lower limb mobility [10], so individualized physical therapy should develop treatment plans and content based on the individual's abilities and goals [6].

Many literatures have discussed the safety and effectiveness of different physical therapy interventions for hemophilia patients and found that exercise therapy, manual therapy, electrotherapy and hydrotherapy, etc. improve muscle strength and

joint mobility [6][10][11]. Coupled with appropriate physical therapy, it can also strengthen muscles, increase joint stability, avoid joint contracture, and reduce the possibility of re-bleeding [2][4][7][8]. Past literature has recommended that exercise therapy should be provided to patients with hemophilia. However, there is currently no consensus on the type, severity, and frequency of safe exercise programs, especially for hemophilia patients with polyarthropathy [12][13]. In addition, manual therapy is another effective physical therapy intervention to increase biomechanical extensibility and joint function by mobilizing and stretching joints and soft tissues (including muscles and nerves). Although the use of manual therapy for patients with hemophilia is increasing, most studies focus on exploring the mobility of single joint [12][13], and the number of studies on manual therapy for multiple joints in the past literature is limited. As hemophilia patients' life expectancy increases, workforce participation, overall functioning, and independent activity daily living have become current issues and challenges. Therefore, much more evidence-based research is needed on manual therapy and exercise programs in hemophilia patients with polyarthropathy. Therefore, this study intends to investigate the impact and effectiveness of individualized physical therapy based on case conditions (severe hemophilia with polyarthropathy) [3]. It is hoped to try to combine different physical therapy techniques (manual therapy and exercise intervention) to improve pain, muscle strength, joint health, cardiopulmonary endurance, and thereby enhance the overall quality of life [5][7][8][9].

V. Purpose

Whether the use of individualized physical therapy combined with manual therapy and exercise intervention effectively improve joint status, muscle strength, pain, cardiopulmonary endurance, etc. for severe hemophilia patients with polyarthropathy, and at the same time prevent the possibility of recurrence of bleeding.

VI. Methods

A. Selection criteria and number of people.

1. Number of subjects: It is expected that 10 subjects.
2. Inclusion criteria:
   a. Over 20 years old and diagnosed with severe hemophilia
   b. Those who receive prophylaxis regularly
   c. There are more than 2 target joints (arthrosis)
3. Exclusion criteria:
   a. Unable to sign the informed consent form
   b. Any neurological disease or major musculoskeletal system disease (such

as fracture) one year ago

c. Have had more than 3 (excluding 3) joint replacement surgeries (different joints)

d. Unable to walk due to hemophilic arthropathy or any other disease

e. Major bleeding events that pose risks or hinder research

f. Unable to follow instructions due to cognitive impairment

4. Recruitment methods: through the Rehabilitation Department of Far Eastern Memorial Hospital, the Hemophilia Center and relevant hemophilia associations. Recruitment is open and a promotional leaflet has been given.
5. Method of consent of research subjects: After the assessment and confirmation of inclusion and before the start of the research, fully inform the experiment content. and process, and ask the subjects to sign the human subject clinical trial consent form.

B. Design

1. Research conduct method

a. The physical therapists of the research team will evaluate whether they meet the inclusion criteria to recruit subjects who meet the conditions of this trial.

b. Fully inform the experiment content and process, and ask the subjects to sign the subject informed consent form.

c. Study location: Rehabilitation department

d. The execution content is as follows:

(i) Manual treatment: including fascia release, progressive passive stretching, joint mobilization, etc., and adjustments will be made according to the subject's current condition.

(ii) Exercise therapy: including upper and lower limbs muscle strengthening, trunk (spine) exercise, and adjustments based on the subject's current condition.

Upper extremity strengthening	• Shoulder external rotation (with theraband): 10 repetitions per set Position the upper arm and forearm at a 90-degree angle, holding the theraband with both hands. Rotate outward while keeping the upper arms close to the sides of the body throughout the movement. • Shoulder flexion (with theraband): 10 repetitions per set Hold the theraband in one hand, extend the arm upward to lift it straight, and then slowly lower it back down. • Shoulder abduction (with sandbag or theraband): 10 repetitions per set Hold a sandbag or theraband in one hand, and slowly lift

	the arm outward to the side until it is parallel to the floor. • Elbow flexion / extension (with theraband): 10 repetitions per set While seated, pull the theraband with one hand, performing elbow flexion and extension movements.
Lower extremity strengthening	• Hip & knee flexion/extension (with sandbag): 10 repetitions per set Stand with both hands supporting a stable table or chair. Attach a sandbag to one leg, perform hip and knee flexion, and then slowly extend the leg backward. • Hip abduction (with theraband): 10 repetitions per set Lie on your side with a theraband secured around both feet for resistance. Perform hip abduction by lifting the top leg outward against the resistance. • Ankle dorsiflexion/plantarflexion (with theraband): 10 repetitions per set While seated, attach a theraband to one ankle for resistance. Perform ankle dorsiflexion (lifting the foot upward) and plantarflexion (pointing the foot downward). • Ankle eversion/inversion (with theraband): 10 repetitions per set While seated, attach a theraband to one ankle for resistance. Perform ankle eversion (turning the foot outward) and inversion (turning the foot inward).
Trunk(spine) exercise	• Pelvic tilting: 10 repetitions per set Lie flat on your back with your knees bent and feet flat on the bed. Inhale as you tilt your pelvis forward, creating a hollow in the lower back; exhale as you tilt your pelvis

	backward, pressing your lower back flat against the bed. • Thoracic spine rotation: 10 repetitions per set Lie on your side, and rotate the shoulder joint backward and outward as far as possible. This movement can be coordinated with breathing. • Abdominal core training: 10 repetitions per set While seated, lift your feet off the ground with both knees bent. • Dynamic neuromuscular stabilization: 10 repetitions per set Lie flat on your back with your hips and knees at a 90-degree angle. If it's difficult to maintain this position, use a ball or chair for support. Slowly inhale, allowing your abdomen to expand. Exhale slowly, trying to maintain the abdominal expansion without letting it collapse.

(iii) Exercise prescription settings:

(1) Frequency: 10 times/time, 1~2 times/day, 3~5 days/week.

(2) The time is 10 minutes, and the time can be gradually increased depending on the situation.

(3) The intensity is adjusted in time according to the patient's condition: the sandbag can be gradually increased from 0.5 kg, and the elastic band can be gradually increased starting from the lightest resistance coefficient (from light to dark according to the color).

e. Intervention schedule: Once a week for three months (about 12 weeks), 30 minutes of traditional physical therapy plus 30 minutes of individualized physical therapy intervention, about 1 hour.

f. Questionnaires and scales were conducted before intervention, at the 6th week after intervention (mid-term intervention) and at the 12th week (end of intervention) to evaluate changes in joint status, pain, cardiopulmonary endurance, functional level, and quality of life.

g. The patient daily note includes exercise duration and content, intensity, manual

therapy techniques, bleeding, and remark on special situations.

(i) Exercise duration and content, intensity, and manual therapy techniques: Gradually increase according to the current situation and ability, as mentioned above.

(ii) Bleeding: It can be determined by the range of motion of the joint, the severity of the pain, and the appearance of redness, swelling and heat.

(iii) Notes on special circumstances: If there are any special things in this study, please note them down.

h. Subjects will be given NT$500 each in the 6th and 12th weeks respectively, for a total of NT$1,000 in traffic allowance.

2. Subject follow-up or necessary rehabilitation plan:
   During the study period, subjects will come to the treatment room for individualized physical therapy once a week, and safety status will be tracked regularly.
   After the study is completed, if necessary (depending on subject's opinion and therapist's judgment), rehabilitation plan will be arranged based on the actual situation.
3. Treatment effect evaluation and statistical analysis methods:
   This study employed the non-parametric statistical software SPSS version 20.0, with a significance level set at $p<0.05$. Descriptive statistics were used to describe the characteristics and distribution of the basic data variables. Furthermore, the Wilcoxon signed-rank test was utilized to examine differences in joint condition, muscle strength, pain, and cardiopulmonary endurance before intervention, and at 6 and 12 weeks post-intervention. The statistical analysis included comparisons between pre-test and mid-test, as well as pre-test and post-test, to mitigate the risk of incomplete data due to participants dropping out before completing the final test. Additionally, sample size calculations were performed using G*Power. The effect size was based on the visual analogue scale measuring perceived pain in patients with hemophilic knee joint disease, set at $d = -1.30$ [20]. With an alpha level of 0.05 and a power value of 0.95, the required sample size was determined to be 9 participants. To account for potential sample attrition, a 10% increase in sample size was applied, resulting in a projected total sample size of 10 hemophilia patients [12].

4. Questionnaires or other research-related scales:
   This study utilized the following scales and questionnaires to assess changes in joint condition, pain, cardiopulmonary endurance, functional level, and quality of life in patients before intervention, and at 6 and 12 weeks post-intervention, in order to confirm treatment efficacy:
   a. **Hemophilia Joint Health Score (HJHS)**: This scale is designed to monitor joint

changes over time in hemophilia patients. It evaluates the swelling of the elbow, knee, and ankle joints, duration of persistent swelling, muscle atrophy, presence of crepitus during movement, reduction in range of motion, joint pain level, muscle strength, and overall gait performance. **Validity**: The scale has high evidence of both convergent validity and discriminant construct validity for detecting joint damage in adults with hemophilia, making it suitable for this population. **Reliability**: The scale demonstrates excellent reliability, with test-retest (ICC=0.89) and inter-observer (ICC=0.83) values.[14] The scale was assessed and completed by physical therapists.

b. **Visual Analog Scale (VAS)**: This scale evaluates pain in target joints of hemophilia patients, converting the results into scores to provide a clearer understanding of overall pain experience. **Reliability**: The scale exhibits high reliability with an ICC of 0.97 (95% CI 0.96 to 0.98). Research indicates that it is a reliable and valid instrument. [15]

c. **6-Minute Walk Test (6MWT)**: This test assesses the overall cardiopulmonary endurance of patients. **Reliability:** The reliability is good, with test-retest values ranging from 0.88 to 0.94. **Validity**: It has moderate convergent validity, with a correlation of 0.71 to 0.82 with treadmill performance. [16] The assessment and completion of this scale are performed by physical therapists.

d. **Hemophilia Activity List (HAL):** This scale evaluates functional activities in hemophilia patients across seven domains: lower limb function, upper limb function, transportation, self-care, household tasks, leisure activities and exercise, and modification or use of assistive devices. **Validity:** The HAL demonstrates good construct and convergent validity. **Reliability:** It shows good internal consistency, with a Cronbach's alpha ranging from 0.61 to 0.96. [17] This scale is completed by the patients themselves.

e. **EQ-5D-5L**: This scale assesses patients' quality of life, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. **Validity:** It exhibits satisfactory construct validity for measuring quality of life in hemophilia patients. Research indicates that this scale has both good reliability and validity. [18] [19] The scale is completed by the patients themselves.

f. **Patient Diary Card:** This card assesses patient status, including basic information and daily living activities, and records the content of each treatment session. The documentation is completed by physical therapists.

VII. Handling of Research Materials:

A. Collection and processing of paper, electronic data / samples during the study:

The principal investigator is responsible for explaining the experimental procedures and distributing consent forms. The principal investigator also oversees the execution of exercise and manual therapy, while the co-investigator handles clinical

assessments and data statistics and analysis. All data is collected and processed by the research team. Paper records are securely locked in the principal investigator's personal filing cabinet, and electronic data is temporarily consolidated and stored on a personal computer.

B. Post-study processing, storage, and retention of paper and electronic data / samples:
To ensure the appropriate handling and security of the data, the research team will utilize a lockable filing cabinet to store paper records securely. Electronic data, once consolidated, will be saved on a personal computer. Upon completion of the study, all research data will be retained for five years. After this period, the principal investigator will be responsible for the destruction of electronic data to ensure privacy. Additionally, paper records containing personal information will be destroyed by incineration through a process managed by Far Eastern Memorial Hospital, to mitigate the risk of data leakage.

VIII. Protection of subjects' rights

A. Potential physical, psychological, and social harm and mitigation measures:
Although the likelihood is low, this study may still cause physical discomfort such as muscle soreness or joint bleeding due to the testing procedures. Therefore, prior to testing, participants will be asked if they regularly receive prophylaxis. If any discomfort occurs during the testing, the procedure will be immediately halted, and appropriate management will be taken. Should the discomfort occur three times, the subject will be withdrawn from the study ahead of schedule. During the testing period, professionals will assist in enhancing the safety of the subjects.

B. Conditions and mechanisms for study suspension / termination or early withdrawal:
Since rehabilitation outcomes may vary among individuals, the therapist will continuously monitor the subject's condition throughout the intervention period. Additionally, subjects may withdraw their consent to participate in the study at any time, and this decision will not affect the therapist's future medical care of the subject. Subjects need not worry about the impact of withdrawal on subsequent rehabilitation treatment (this will be explicitly stated in the consent form), thereby minimizing any psychological pressure or burden.

C. Subject compensation:
Subjects will receive transportation expenses of 500 TWD each at the 6th and 12th weeks, totaling 1000 TWD.

IX. Outcomes

A. Expected results and major benefits:

This study aims to investigate the therapeutic benefits of individualized physical therapy approach, combined with manual therapy and exercise interventions, for severe hemophilia patients with polyarthropathy. Based on previous research, manual therapy and exercise intervention have been shown to effectively improve musculoskeletal conditions. It is anticipated that this study will also enhance subjects' pain management, muscle strength, joint health, and cardiopulmonary endurance, ultimately improving overall quality of life.

B. Ownership and utilization of results:
Upon completion of the research, the results will be owned by Far Eastern Memorial Hospital.

X. Funding requirements and sources:
The funding for this study will be sourced from an internal project grant provided by Far Eastern Memorial Hospital.

XI. Conflicts of interest:
This trial is not sponsored by any manufacturers and does not have any commercial interests.

XII. References or domestic and international literature:

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