Clinical trial study protocol template involving humans

The clinical study of bone-patellar tendon-bone and quasi-anatomical meniscus allograft transplantation technique

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Basic information about the project				
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The body of the study protocol

1. Background:

1.1 Purpose and significance of the study

1.1.1 Purpose

The application of bone-patellar tendon-bone and anatomical meniscus human allogeneic transplantation technology aims to solve the shortcomings of traditional treatment methods, restore the function of the knee joint, reduce postoperative complications, and delay the process of knee degeneration through advanced transplantation technology. Specific objectives include:

- Ligament transplantation : Restore the mechanical stability and normal function of the anterior/posterior cruciate ligament through bone-patellar tendon-bone allografting.
- Meniscus transplantation : Repair or replace the damaged meniscus through anatomical allogeneic meniscus transplantation techniques to improve the biomechanical environment of the joint.

1.1.2. Significance

- Addressing donor site injury: Avoid donor site injury from traditional autografts, especially in complex cases or patients who require multiple surgeries.
- Improve clinical efficacy: through anatomical reconstruction, the joint function can be restored to the maximum extent and the degeneration of the knee joint can be delayed.

- Promoting the development of precision medicine: combining personalized treatment plans to improve the functional recovery and quality of life of postoperative patients.
- Filling treatment gaps: Provide more treatment options for patients with moderate to severe knee injuries, especially to delay the need for joint replacement surgery while preserving joint function

1.2 Research status at home and abroad

Sports medicine in China began in 1955 by Professor Qu Mianyu, a pioneer of sports medicine in China and the mentor of Professor Yu Jiakuo. In 1959, Professor Qu founded the first Institute of Sports Medicine in China and served as its first director, and later Professor Yu Jiakuo became the fourth director. In 1959 and 1960, Professor Qu Mianyu completed the first meniscus surgery and knee cruciate ligament reconstruction surgery for professional athletes in China, and his technical level was at the forefront of the world. However, since then, due to various reasons, the development of sports medicine in China has stagnated, and the gap between China's sports medicine and the international advanced level at that time has become wider and wider. After unremitting efforts, we have innovatively proposed allogeneic bone-patellar tendon-bone reconstruction anterior cruciate ligament and minimally invasive anatomical human allogeneic meniscus transplantation, once again leading the global technological frontier. This technology not only greatly improves the accuracy and minimally invasive surgery, but also effectively preserves the anatomical structure and biomechanical function of the grafted ligament and meniscus, and significantly improves the patient's recovery outcome. Through this minimally invasive procedure, the patient's postoperative recovery period is greatly shortened, and the motor function is rapidly rebuilt, making an outstanding contribution to the technological development of the global field of sports medicine.

1.3 The conditions for our hospital to carry out this research are guaranteed

1.3.1 Technical platform and equipment support:

High-end laboratory and operating room equipment, including tissue engineering, transplant surgery, microsurgical techniques and other facilities.

Special imaging equipment (e.g., MRI, CT scan, etc.) is used for preoperative evaluation and postoperative monitoring.

Precise surgical instruments and robot-assisted surgical equipment to ensure the delicate operation of the transplant process.

1.3.2 Allogeneic transplantation resource guarantee:

A source of high-quality bone-patellar tendon-bone and anatomical meniscus-like allogeneic

material. There is a need to ensure that the graft is of good quality, that it is of legal origin, and that there is no risk of immune rejection. This product has obtained the national class III registration certificate, which guarantees the effectiveness and safety

1.3.3 Senior surgeons and technicians perform bone-patellar tendon-bone and anatomical meniscus transplantation surgery to ensure the accuracy and safety of the operation. Led by Professor Yu Jiakuo, a well-known expert in sports medicine in China, he has more than 40 years of experience in athlete medical security, more than 37 years of medical-engineering interdisciplinary and more than 24 years of experience in medical-enterprise collaborative R&D and achievement transformation.

Ethics Approval and Regulatory Protection:

1.3.4 Funding and resource guarantee: Sufficient financial support to ensure the long-term sustainable development of research. Investments in related facilities, such as cold storage, tissue preservation technology, etc., ensure that the storage and handling of samples during the research process are standardized.

The above conditions can provide strong support for the research on bone-patellar tendon-bone and anatomical meniscus human allogeneic transplantation technology.

2. Research objectives and content

2.1 Research Objectives:

Knee ligament injury and meniscus injury are common sports injuries in clinical practice, and although traditional treatment methods can alleviate some symptoms, there are certain limitations in restoring knee joint function and protecting cartilage. In recent years, allogeneic transplantation techniques have shown significant advantages in ligament and meniscus reconstruction, providing patients with new treatment options. The application of osteo-patellar tendon-bone and anatomical meniscus allogeneic transplantation technology aims to solve the shortcomings of traditional treatment methods, restore the function of the knee joint, reduce postoperative complications, and delay the process of knee degeneration through advanced transplantation technology.

2.2 What to study

The main contents of this study include the following aspects:

1. Objective: To explore the clinical application effect of bone-patellar tendon-bone and anatomical meniscus allogeneic transplantation technology, and to evaluate its safety, effectiveness and long-term effect in knee injury repair.

2. Research subjects: Select patient groups that meet specific criteria, such as knee injury, meniscus injury, etc., for clinical trials and follow-up observation.

3. Treatment plan: The patient was treated with surgery and postoperative rehabilitation using bone-patellar tendon-bone and anatomical meniscus-like allogeneic transplantation technology, and the treatment effect was evaluated through regular follow-up.

4. Evaluation indicators: The treatment effect was evaluated through clinical symptoms, knee function, imaging examination and other dimensions, including pain relief, joint range of motion recovery, functional recovery, etc.

5. Ethical review: Ensure that all patients sign the informed consent form before participating in the study, ensuring the privacy and safety of patients.

6. Data analysis: Collect data on surgical results, postoperative recovery and complications, and use statistical methods to analyze the data to evaluate the clinical effect and risks of the technique.

The purpose of this study is to provide clinical evidence support for the bone-patellar tendon-bone and anatomical meniscus human allogeneic transplantation technology, and to provide a reference for the treatment of related fields.

3. Research protocols

3.1 Study design

Briefly clarify the type of scheme design (such as parallel group design, crossover design, factorial design, group sequential design, etc.), randomization grouping method, blinding form (single-blind, double-blind, open-ended), multi-center or single-center, etc.

Design Type:

In this study, a parallel-group design was used to compare the effects of different transplant techniques on the postoperative recovery of patients. In this design, participants were randomly assigned to different treatment groups, received corresponding treatment regimens, and underwent data collection and effect evaluation during the same time period.

Non-Randomization Method:

This is a Non-Randomization trial.

Blinded form:

This study uses a single-blind design. Specifically:

Blinding (to assessors): Researchers do not know the treatment group to which the patient belongs during data collection and postoperative evaluation, so as to ensure the objectivity and

fairness of the evaluation results.

Center Type:

This study is multicenter. Participating centers use uniform standard operating procedures, the same treatment protocols, and evaluation methods to ensure consistency and comparability of data collection across centers, increasing the applicability and external validity of study results. The sites include multiple hospitals and research institutes, and all sites will strictly adhere to the approval and requirements of the Ethics Committee.

Summary:

The study design protocol ensures the scientificity, reliability and wide applicability of the results through parallel-group, non-randomization, single-blind format and multicenter study. This design method can effectively compare the efficacy of bone-patellar tendon-bone and anatomical meniscus transplantation techniques, and provide strong support for future clinical applications.

3.2 Subjects of the study

The research subjects of this study mainly include the following screening criteria:

1. Inclusion Criteria:

- Age requirement: The age of the study participants is usually set between 18 and 60 years old to ensure that the patient's physiological condition is suitable for surgical treatment and postoperative rehabilitation.
- Diagnostic criteria: Patients should be diagnosed with knee injury or meniscus injury, and meet the indications for transplant surgery, including but not limited to knee ligament injury, meniscus tear and other diseases.
- Disease course requirements: The patient's course of disease should usually be more than 6 months, and no good results can be achieved with conservative treatment.
- Functional assessment: the patient's knee function is poor, daily activities are significantly affected, and the expected goals of transplant surgery are met.

2. Exclusion Criteria:

- Severe cardiovascular and cerebrovascular diseases: patients with a history of uncontrollable hypertension, diabetes and other diseases.
- Immune system disorders: Patients with immunosuppression or immune system disorders who are not candidates for transplantation.

- History of severe infection: If the patient has a severe systemic or localized infection, it may affect surgery and recovery.
- History of allergies: Patients with a history of anaphylaxis to allogeneic grafts.
- Mental disorder or non-cooperative: the patient is unable to understand the content of the study or is unable to cooperate with the research process.

3. Special cases of patient selection:

- Patients with a history of surgery: for example, those who have had knee surgery and have not responded well may be included in the study, provided that the impact of surgical history on current surgery is acceptable.
- Age-specific patients: Although predominantly between the ages of 18 and 60, younger or older patients with specific medical conditions such as athletes may also be considered for inclusion if they meet the requirements for surgery and are assessed by their physician to be suitable.

4. Patient informed consent: All study subjects are required to sign an informed consent form prior to participation to ensure that they fully understand the risks of surgery, the purpose of the study, and postoperative recovery requirements

3.3 Sample size and calculation basis

Indicate the total number of cases and grouping of the sample size, and explain the basis for the measurement.

In clinical research, the determination of sample size is essential to ensure the scientific and reliable results of the study. Sample size needs to be calculated based on factors such as expected effect size, study design, level of statistical significance (α values), and statistical power (1-β values). The following is the basis and method of sample size measurement in this study:

1. Effect Size

The primary objective of this study is to evaluate the clinical effect of the osteo-patellar tendon-bone with anatomical meniscus human allograft technique in patients with knee injury. Based on the existing literature and the results of previous studies, it is expected that the main effect indicators of this study will be the improvement of knee joint function, pain relief, and the improvement of patients' quality of life. It is assumed that there will be a moderate difference between the treatment and

control groups, with an effect size of 0.5 (moderate effect), which is a commonly used assumption in clinical studies.

2. Statistical significance level (α value).

The significance level in the study was typically set at 0.05, indicating that we accepted a 5% risk of false rejection of the null hypothesis. That is, if the p-value is less than 0.05, the results of the study are considered statistically significant.

3. Statistical power (1-β value).

The efficacy of this study was set at 80% (i.e. 1-β = 0.8), meaning that if the treatment did work, there was an 80% probability that the study would detect this effect. This is a commonly used power value in most clinical trials to ensure the reliability of the results.

4. Study design

This study is a prospective randomized controlled trial, which was divided into treatment group and control group. To ensure that the differences between the groups are statistically significant, it is assumed that the differences between the two groups can be detected by statistical analysis.

5. Formula for calculating sample size

The sample size is usually calculated using the following formula:

n=2×($Z\alpha$/2+$Z\beta$)2×(σ2)d2n=d22×(Zα/2+Zβ)2×(σ2)

Thereinto:

- nn is the sample size for each group.
- Zα/2Zα/2 is the cut-off value for the standard normal distribution with a significance level of α, typically 1.96 (corresponding to α = 0.05).
- ZβZβ is the critical value of a standard normal distribution with a power value of 1-β, typically 0.84 (corresponding to β = 0.2).
- σσ is the expected standard deviation (the standard deviation of the knee function score is assumed here).

- dd is the expected effect size (0.5 here).

6. Expected effect size vs. standard deviation

According to the relevant literature and pre-experimental results, the standard deviation of the knee function score in this study was estimated to be 10 points, and the effect size d was set to 0.5 (i.e., moderate effect).

7. Sample size calculation results

Calculated using the above formula, the resulting sample size required for each group is approximately 40 cases. In order to account for possible loss to follow-up, missing data, etc., the study increased the sample size in each group by 10%, i.e., the final sample size for each group was 44 cases.

Therefore, the sample size of the entire study was 100 cases (50 treatment group and 50 control group), which fully met the case count requirement.

8. Basis for sample size measurement

- The sample size for this study was based on a moderate effect size (0.5), 80% statistical power, a significance level of 5%, and reasonable standard deviation estimates.
- Through this sample size, the differences in knee joint function and pain relief between the treatment group and the control group can be effectively detected, so as to evaluate the clinical effect of the bone-patellar tendon-bone and anatomical meniscus allogeneic transplantation technique.
- This study also took into account potential factors such as loss to follow-up rate and data loss, and ensured a high degree of confidence and representativeness of the results through appropriate sample size increases.

9. Limitations of sample size

- The sample size is calculated based on the expected effect size and the statistical distribution of assumptions, but in actual studies, the effect size may deviate from the expectation, so the sample size needs to be adjusted according to the actual situation.

- The sample size calculation of this study mainly took into account the changes in knee function score and pain relief, and further sample size measurements may be required for other possible clinical outcomes (e.g., patient quality of life scores, postoperative complications, etc.).

Through a reasonable sample size design, this study can obtain statistically significant conclusions and provide a scientific basis for clinical practice.

3.4 Inclusion Criteria

Bone-patellar tendon-bone allograft reconstruction of anterior/posterior cruciate ligaments is indicated for the following study populations

1. Anterior/posterior cruciate ligament injuries: These include complete rupture or severe injuries that affect the stability and functional recovery of the knee joint.
2. Recurrent knee instability: a sensation of displacement associated with joint flexion, particularly in patients who interfere with daily activities or sports.
3. Knee dysfunction: including unsteady gait and inability to bend or extend the knee, which can seriously affect exercise ability.
4. Younger, high-activity patients: want to regain exercise and reduce the risk of long-term knee degeneration.

Minimally invasive anatomical human allogeneic meniscus transplantation is suitable for the following study populations

1. Extensive or complete meniscus extraction: resulting in long-term pain, instability, and degeneration of the knee.
2. Articular cartilage lesions: patients with early-stage degenerative arthritis may be treated with meniscus transplantation to slow progression.
3. Knee biomechanical abnormalities: patients who wish to return to normal knee load distribution after surgery.
4. Young or middle-aged patients: high level of joint mobility and long-term recovery of function.
5. Conservative treatment and failure of conventional surgery: Patients whose symptoms persist and do not improve.

3.5 Exclusion Criteria:

1. Severe osteoarthritis of the knee joint.
2. There is a risk of active infection or severe immune rejection.

3. The patient has irreparable ligament damage or deformity correction needs.

3.6 Methods of intervention

Arthroscopic treatment

3.7 Observational indicators and follow-up plan

1. Observe the metrics

The observations included the following aspects and were designed to evaluate the effects of the two treatments on knee function recovery, pain relief, and quality of life improvement:

(1) Clinical function assessment

- Knee Society Score (KSS): Used to assess the function and pain level of the knee joint. Pain scores (0-100 points) and functional scores (0-100 points) are included, with higher scores indicating better knee function and less pain.
- International Association for the Study of Knee (IKDC) score: This score evaluates the mobility, pain, function and daily living ability of the knee joint, and is widely used in the clinical evaluation of the treatment effect of the knee joint.
- Lysholm Knee Score: It is used to evaluate the function of the knee joint, including knee stability, range of motion, exercise ability in daily life, etc.

(2) Imaging evaluation

- X-rays: Knee x-rays are performed regularly before and after surgery to assess joint space, bone alignment, cartilage damage, and possible complications (such as fractures or graft failure).
- Magnetic Resonance Imaging (MRI): An MRI scan is performed postoperatively to assess the recovery of the graft site, the stability of the meniscus, the repair of the cartilage, and possible graft complications.

(3) Pain assessment

- Visual Analogue Score (VAS): Used to assess the patient's pain level at various points postoperatively. A score of 0 is no pain and a score of 10 is the worst pain.
- Duration and frequency of pain: Record the number and duration of pain occurrences.

(4) Quality of life assessment

- SF-36 Health Survey Scale: To evaluate the overall improvement before and after treatment by investigating the patient's quality of life, including physical health, mental health, social activity ability, etc.

(5) Complications and adverse events

- Postoperative complications such as infection, graft failure, joint instability, deep vein thrombosis, etc., are observed.
- Adverse events and their treatment were recorded.

2. Follow-up plan

In order to track the progress of patients' recovery and assess the effectiveness of treatment, a detailed follow-up plan was set up. Each patient will be examined and evaluated at different points postoperatively, as follows:

(1) 1st week after surgery

- Assessment: postoperative recovery, pain management, mobility, and start of physical therapy.
- Examination items: basal pain score (VAS), KSS score, Lysholm score.

(2) 6th week after surgery

- Assessment: range of motion of the knee, recovery of joint function, preliminary effect of meniscus transplantation.
- Examination items: IKDC score, KSS score, imaging examination (X-ray and MRI), to evaluate the stability of the transplanted tissue.

(3) The 3rd month after surgery

- Evaluation content: the patient's knee joint function recovery, pain relief progress, and rehabilitation effect.

- Examination items: Lysholm score, VAS score, SF-36 quality of life assessment.

(4) 6th month after surgery

- Assessment content: Comprehensively evaluate the recovery of the knee joint, function, pain, range of motion, quality of life, etc.
- Examination items: KSS score, IKDC score, MRI examination, to check the stability of the meniscus and the recovery of cartilage.

(5) The 12th month (1 year) after surgery

- Evaluation content: Long-term effect evaluation, check whether the knee joint is stable, and whether the patient has returned to normal daily activities.
- Examination items: Lysholm score, KSS score, imaging tests (X-ray and MRI) to observe whether there are joint changes or complications.

(6) The second year after surgery

- Evaluation content: Long-term efficacy evaluation, including knee function, pain, activity level, quality of life, complications, etc.
- Examination items: KSS score, IKDC score, X-ray and MRI examination to evaluate the long-term effect.

3.8 Methods of statistical analysis

All assessment data will be collected at each follow-up time point and analysed by a dedicated research team. Data analysis will compare the differences between the two groups by statistical methods (such as paired t-test, chi-square test, etc.) to ensure that the results are statistically significant and clinically significant.

3.9 Data collection and management methods

1. Data collection

The data collection process will be carried out in strict accordance with the study design to ensure the accuracy, completeness and timeliness of the data.

(1) Data collection tools and methods

- Questionnaires and rating scales: The main assessment tools in the study include the Knee Society score (KSS), the International Society for Knee Research (IKDC) score, the Lysholm knee score, the SF-36 quality of life assessment scale, etc. These scales will be filled out by the investigator or trained staff in a standardized questionnaire form.
- Imaging examination: All imaging data (such as X-ray, MRI, etc.) will be collected in the clinical imaging department and evaluated by professional imaging physicians. The results of all imaging examinations will be recorded in an electronic database.
- Patient self-reported data: Patient's pain score (VAS), functional recovery, quality of life, etc., will be self-reported by patients based on specific time points.
- Surgical records: All surgical procedures, types of transplanted tissues, intraoperative conditions and complications will be recorded by the attending physician in the surgical log to ensure accurate recording of data.

(2) Data collection time points

- Preoperative: including the patient's basic medical history, imaging examinations, rating scales (KSS, IKDC, Lysholm, VAS, etc.), and quality of life assessment.
- Postoperatively: Regular follow-up visits were conducted at the 1st week, 6th week, 3rd month, 6th month, 12th month, and 24th month after surgery, and relevant evaluations and examinations were conducted.

2. Data management

The management and storage of data needs to ensure that data is confidential, complete, and ethical.

1. Data confidentiality: The personal information and medical data of all patients and study participants should be encrypted and stored to ensure that access to the data is restricted to authorized personnel. Data encryption technology, access control, and identity authentication mechanisms can be used to prevent data breaches.
2. Data integrity: The data checksum backup mechanism is used to back up data regularly, and the hash algorithm is used to ensure that the data is not tampered with or damaged during storage and transmission. At the same time, regular data quality checks are carried out to ensure that the data is accurate.
3. Ethical requirements: All data management processes should follow the review and approval of the relevant ethics committee to ensure that the collection, storage and use of data comply

with the patient's informed consent requirements. The data is limited to research purposes and should be processed in strict compliance with privacy regulations such as GDPR or HIPAA.

4. Data traceability: Ensure that each data set can be traced back to a specific source, including patient information, experimental data, processing flows, and more, so that it can be audited and verified when needed.

Through these measures, the security, legitimacy and ethical compliance of data can be ensured, the rights and interests of patients can be protected, and reliable data support can be provided for scientific research.

4. Evaluation indicators

In this study, the evaluation measures will be divided into primary and secondary outcomes. These indicators will help to comprehensively evaluate the efficacy and safety of interventions, and provide an important basis for clinical application.

1. Primary outcome measures

The primary outcome measure was to assess the impact of the intervention on the patient's primary health outcomes, reflecting the core effects of the treatment intervention.

(1) Knee function score

- Knee Society Score (KSS): A composite score that assesses knee function and knee health, including pain, motor function, and physiological function of the knee. The KSS consists of a two-part score: a pain score and a functional score. The pain score is 0-50 points, the functional score is 0-50 points, and the total score range is 0-100 points.
    - Data presentation method: The KSS score is presented as a total score, and the higher the score, the better the knee function.
    - Time points: preoperative, postoperative week 6, month 3, month 6, month 12 and month 24.

(2) Knee quality of life score

- Lysholm Knee Score: Used to assess a patient's recovery after knee surgery, including pain, function, activity level, knee stability, etc. Scores range from 0-100, with higher scores indicating better knee recovery.
    - Data Presentation Method: The Lysholm score is presented as a total score, with higher levels indicating better knee function and quality of life.
    - Time points: preoperative, postoperative week 6, month 3, month 6, month 12 and month 24.

(3) Quality of life assessment

- SF-36 Health Survey Scale: Assesses the overall health status and quality of life of patients, covering multiple aspects such as physical function, emotional state, social functioning, etc., the scale is divided into 8 dimensions, with a total score from 0 to 100, with higher scores indicating better quality of life.
    - Data Presentation: The SF-36 score is described by each dimension and the total score is calculated.
    - Time points: preoperative, postoperative week 6, month 3, month 6, month 12 and month 24.

2. Secondary outcomes

Secondary outcome measures complement the primary outcome and further assess the multidimensional effects of treatment, including safety assessment and other relevant clinical measures.

(1) Pain score

- Visual Analogue Score (VAS): Assesses the patient's level of pain on a scale of 0 to 10, with 0 being no pain and 10 being the most severe pain. The VAS score reflects the patient's pain level and is an important indicator to evaluate the effect of treatment.
    - Data presentation: The VAS score is presented as a score, with lower scores indicating less pain.

- Time points: preoperative, postoperative week 6, month 3, month 6, month 12 and month 24.

(2) Knee range of motion

- Knee flexion and extension range: The functional recovery of the knee joint is assessed by measuring the maximum flexion and extension angle of the knee joint.
  - Data Presentation Method: Range of motion is expressed in the number of angles, and the larger the knee joint mobility, the better the mobility.
  - Time points: 1st week, 6th week, 3rd month, 6th month, 12th month and 24th month after surgery.

(3) complication rate

- Surgery-related complications: including infection, bleeding, joint instability, thrombosis, etc.
  - Data presentation method: The number and proportion of complications were counted, and the incidence rate was calculated (complication rate = number of complications / total number of cases × 100%).
  - Time point: The whole process of follow-up was carried out within 24 months after surgery, and the occurrence of complications at each time point was recorded.

3. Clinically relevant interpretation of efficacy and safety indicators

- Effectiveness Indicators:
  - The primary outcome measures KSS, Lysholm and SF-36 will directly reflect the improvement of knee joint function, and assess the quality of life and functional recovery of patients after surgery. Pain relief and functional recovery of the knee joint are the most important concerns of patients, so these indicators are the core basis for evaluating the treatment effect.
  - Pain score (VAS) and knee range of motion as secondary outcomes will provide additional information on treatment effectiveness clinically. Pain relief and restoration of knee range of motion are important criteria for the success of treatment.
- Safety Indicators:

- The complication rate will reflect the potential risks during the treatment process and the safety of the treatment. A high complication rate may indicate a safety hazard to the treatment and therefore requires close attention.

4. Timeline and Data Collection

All evaluation indicators will be collected according to the time point of the clinical trial design. The preoperative data will be used as the baseline, and the functional recovery, pain improvement, quality of life and other indicators will be evaluated at each postoperative time point (1st week, 6th week, 3rd month, 6th month, 12th month, and 24th month after surgery). These data will help analyse the long-term impact of interventions on patient recovery and whether they provide lasting treatment outcomes.

5. Safety reporting and adverse event management

5.1 Definition of adverse events and serious adverse events

1. Adverse events (AEs).

Adverse events refer to negative health reactions experienced by any patient while undergoing a bone-patellar tendon-bone with anatomical meniscus allotransplantation. They are not necessarily directly related to treatment, but need to be documented and evaluated. Common adverse events include:

- Postoperative pain: Constant or intermittent pain at the surgical site, which may be caused by trauma or the post-operative recovery process.
- Mild swelling and hematoma: Mild swelling or localized hematoma may occur in the surgical area or around the knee joint.
- Inflammation: Mild inflammation of the transplanted area, such as redness, swelling, fever, inflammation, etc.
- Wound infection: Although not serious, the wound may have slight redness, swelling, discharge, or healing problems.
- Slow functional recovery: patients may have a slower recovery of knee function and mild limitation of motion.
- Mild post-activity discomfort: Patients may experience joint discomfort or slight movement limitation during postoperative rehabilitation.

2. Serious adverse events (SAEs).

Serious adverse events are those that pose a significant threat to a patient's health and usually require immediate medical intervention or hospitalization. For bone-patellar tendon-bone and anatomical meniscus allograft techniques, serious adverse events may include the following:

- Transplant failure or rejection: The patient's immune system may experience rejection of the transplanted meniscus or patellar tendon bone tissue, resulting in transplant failure. Such reactions can cause severe pain, swelling, and loss of function.
- Severe infection: If the surgical site infection is severe, it can lead to extensive soft tissue injury, abscess, or sepsis that requires urgent treatment.
- Fracture or nonunion at the graft site: During surgery, fractures may occur in the graft area, or the graft site may not be securely engaged, resulting in dysfunction.
- Deep vein thrombosis (DVT) or pulmonary embolism (PE): During recovery, patients may develop deep vein thrombosis, which can become life-threatening if left untreated.
- Joint dislocation or ligament injury: After the transplant, patients may experience knee dislocation or other ligament damage, resulting in joint instability and the need for further surgical treatment.
- Nerve damage: During surgery, the nerves around the knee joint may be damaged, resulting in loss of sensation or muscle weakness.

5.2 Main AEs and SAEs and how to deal with them

1. Major adverse events (AEs) and how they were handled

1.1 Postoperative pain

- Symptoms: Patients may experience pain at the surgical site, especially in the early postoperative period, which may be accompanied by mild swelling and discomfort.
- What to do: Use over-the-counter or prescription pain relievers, such as ibuprofen or acetaminophen, and cold compresses to relieve swelling. If necessary, use of local anesthetic drugs or short-term use of strong analgesics.

1.2 Mild swelling and hematoma

- Symptoms: Mild local swelling or hematoma may occur postoperatively.
- Treatment: Use ice to relieve swelling, elevate the affected limb appropriately, avoid weight-bearing, and if the hematoma is not absorbed, drainage or local massage can be used to help absorption.

1.3 Local inflammatory response

- Symptoms: Mild redness, warmth, and inflammation may occur in the days after surgery.
- Management: Anti-inflammatory drugs (eg, chloramphenicol ointment, antibiotics) and antibiotics and, if necessary, topical medications to reduce inflammation.

1.4 Wound infection

- Symptoms: There may be redness, swelling, discharge, and fever at the wound site.
- Management: Debridement of the infected area, treatment with appropriate antibiotics, and in severe cases, surgical intervention may be required to rule out an abscess or remove infected tissue.

1.5 Slow functional recovery

- Symptoms: Patients may experience limited mobility during postoperative recovery and slower recovery of muscle and joint function.
- Treatment: Strengthen rehabilitation and physical therapy, use electrical stimulation, hot compresses, traction and other methods to help restore joint mobility, and gradually increase the amount of exercise during the rehabilitation process.

1.6 Discomfort after mild activity

- Symptoms: Patients may experience mild discomfort or joint tension during rehabilitation exercises or weight-bearing activities.
- How to do it: Adjust the intensity of the exercise, avoid excessive weight bearing and high-intensity training, gradually increase the amount of activity, and use support bands or knee protectors to assist if necessary.

2. Major Serious Adverse Events (SAEs) and how they were handled

2.1 Transplant failure or rejection

- Symptoms: Patients may experience severe pain, swelling, and loss of function at the graft site, accompanied by systemic immune responses such as fever and fatigue.
- Treatment: Immediate immunosuppressive therapy, use of anti-rejection drugs (such as cyclosporine, chlorochlorothiazine, etc.), if rejection is severe, consider re-operation or replacement of transplanted tissue.

2.2 Severe infection

- Symptoms: fever, redness and swelling, pus discharge, and symptoms of systemic infection (e.g., sepsis).
- Management: Broad-spectrum antibiotic therapy is given urgently, and appropriate drugs are selected according to the type of infection. If the infection is not controlled, further surgical debridement or drainage may be required.

2.3 Fracture or nonunion at the graft site

- Symptoms: Patients experience severe pain or deformity of the graft site, which may be accompanied by loss of function.
- Management: If a fracture or nonunion occurs, a second surgery to repair the fracture, a fracture fixator, or a bone graft may be required.

2.4 Deep vein thrombosis (DVT) or pulmonary embolism (PE).

- Symptoms:D Symptoms of VT include swelling, pain, and redness of the lower legs, and PE may manifest as shortness of breath, chest pain, and a bloody cough.
- Management: Anticoagulant drugs (eg, heparin, warfarin, etc.) and thrombolytic therapy or surgical thrombectomy if needed. Enhance the patient's mobility and avoid prolonged bed rest.

2.5 Joint dislocation or ligament injury

- Symptoms: The knee may be dislocated, limited in motion, or a ligament rupture, causing joint instability.

- Management: Depending on the circumstances, surgical reduction, ligament reconstruction, or repair may be required. Rigorous rehabilitation is carried out after surgery, and the joints are protected with braces or fixation devices.

2.6 Nerve damage

- Symptoms: Patients may experience numbness, tingling, or muscle weakness near the surgical site.
- Management: Treatment of nerve injury may include medications (eg, neurotrophic drugs), physical therapy, and rehabilitation. In severe cases, surgery is needed to repair the damaged nerve.

3. Monitoring and management

- Postoperative surveillance: Postoperative patients require regular follow-up to monitor postoperative recovery, especially for early identification of adverse events and serious adverse events.
    - Timely intervention: Once an adverse event or serious adverse event is detected, it should be evaluated and intervened promptly, and corresponding treatment measures should be taken to prevent further deterioration of complications.

5.3 Reporting Procedures

Event Identification

- Postoperative surveillance: postoperative caregivers, clinicians, or patients should be closely watched for possible AEs and SAEs.
- Defining Adverse Events: AEs are any medical events or symptoms that do not meet expectations, while SAEs are those that may pose a significant risk to the patient's health, trigger hospitalization, or require intervention.
- Classification of events: Determine whether an event is mild (AE) or severe (SAE) depending on severity and impact.

2. Event Logging

- Detailed Documentation: Each event must be documented in detail, including the time of the event, symptoms, relevant context, therapeutic intervention, and patient response.
- Symptom and management records: describe the specific symptoms, management methods, and response to adverse events, with additional imaging findings or laboratory data if necessary.
- Timely reporting: Once an AE or SAE is identified, it should be documented and reported to the hospital or clinical trial personnel immediately.

3. Reporting process

- Tier 1 Reporting:
  - The responsible health care provider or attending physician reports the incident to the hospital or healthcare facility's surveillance system, usually through an electronic medical record system (EMR) or other specialized reporting platform.
  - In the case of AEs or SAEs in a clinical trial, the report should be submitted through the trial sponsor's monitoring and data management system (e.g., Clinical Research Management System CRMS).
- Tier 2 Reporting:
  - For severe SAEs, they must be reported to regulatory agencies (e.g., Food and Drug Administration, health authorities) within a specified time (usually within 24 hours). The report includes details of the event, treatment taken, and possible consequences.
  - For AEs, reporting is made within a certain period of time (usually 7 or 30 days), depending on the regulations or protocols.

4. Incident Assessment

- Medical evaluation: Once an event has occurred, the treating physician or relevant team of specialists should conduct a medical evaluation to determine whether the event is related to the treatment plan, transplant technique, or the patient's underlying medical condition.
- Causality: Evaluate the causality of adverse events and analyze whether they are related to transplant surgery, drug treatment, or other complications.
- Severity assessment: Conduct a graded assessment of the severity of an incident to ensure a timely response to important incidents.

5. Continuous tracking and monitoring

- Patient follow-up: Patients should be followed up on an ongoing basis for reported AEs or SAEs to ensure that adverse events are adequately addressed and resolved in a timely manner.
- Regular check-ups: For patients with AEs or SAEs, the clinical team should conduct regular check-ups and evaluations to ensure the progress of recovery and cure.

6. Summary and analysis

- Periodic summaries: During clinical trials or treatments, periodic summaries of reported AEs and SAEs are conducted to understand the frequency and trends of adverse events.
- Improvement measures: According to the analysis of the reported data, the hospital and medical team should optimize the treatment process, drug use, surgical technology, etc., to reduce the occurrence of adverse events.

7. Archiving of report documents

- Reporting documentation: All reports of adverse events should be properly archived, and these documents should be kept for a certain period of time (e.g., 5 or 10 years) in accordance with medical regulations and standards for subsequent review or regulatory requirements.
- Data Confidentiality: All reports and data on adverse patient events should be kept confidential to ensure compliance with privacy regulations.

6. Medical Ethics Risk Analysis

In the clinical application of bone-patellar tendon-bone and anatomical meniscus allotransplantation, the main medical ethical risks include:

1. Informed consent: Patients may not fully understand the risks and effects of surgery. It is necessary to ensure that the patient consents voluntarily and with full knowledge.
2. Privacy protection: Patients' personal information and biological samples need to be kept strictly confidential, and measures such as de-identification are used to ensure privacy.

3. Patient safety: Surgery can be risky, and adequate monitoring must be provided before, during, and after surgery.

4. Psychological impact: Surgery may cause anxiety and other psychological burdens for patients, and psychological support should be provided.

Common reasons for exemption from informed consent include:

1. Emergency: The patient requires urgent treatment and consent cannot be obtained in a timely manner.

2. Patient unable to consent: If the patient is unconscious or unable to communicate, a representative can give consent on behalf of the patient.

3. Retrospective study: data collected cannot be obtained by the patient and requires approval by the ethics committee.

7. Signature of the investigator

Sign:

Date: 2025.05.17

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