PROTOCOL

Effect of early postoperative oral carbohydrate on postoperative recovery of the unilateral knee arthroplasty : a randomized, single-blind, parallel-controlled, multicenter study

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1. Research background

In recent years, the concept of accelerated rehabilitation surgery (enhanced recovery after surgery, ERAS) has developed vigorously, using a series of optimized evidence-based medical support with preoperative, intraoperative and postoperative programs to reduce postoperative physiological and psychological stress trauma response, so as to achieve the goal of accelerating patient rehabilitation[1]. Perioperative fasting water ban management is an important component of ERAS. Studies have found that prolonged preoperative drinking and fasting will increase the postoperative insulin resistance, cause hypertension, and increase the risk of postoperative infection, which is not conducive to the postoperative recovery of [2]. Oral carbohydrates for at least 2h before anesthesia can reduce the perioperative stress response, improve patient comfort and satisfaction, and promote the postoperative rehabilitation of [3]. The [4] of the Chinese Expert Consensus and Path Management Guide for Accelerated Rehabilitation Surgery (2018 edition) advocates the early postoperative recovery of diet. Studies have shown that the early recovery of oral eating, drinking water and early oral assisted nutrition after elective abdominal surgery can promote the recovery of intestinal motor function, help to maintain intestinal mucosa function, prevent microflora imbalance and displacement, and can reduce the incidence of postoperative infection and shorten the postoperative hospitalization time by [5]. At present, shortening the perioperative water fasting time needs to be concentrated in the preoperative stage. Although the guidelines and a small number of studies recommend the early recovery of diet after surgery, there is no clear stipulation on the recovery time of postoperative diet and drinking water, and most domestic hospitals still perform fasting for at least 6h after surgery.

Carbohydrates are perioperative good oral nutritional fluids. In recent years, studies have shown that preoperative oral carbohydrates can not only supplement the lost

water and energy, improve their thirst and hunger, but also improve the postoperative metabolism and stress changes, reduce postoperative insulin resistance, shorten the hospital stay, and accelerate the [6] recovery of patients compared with clear water. Furthermore, preoperative oral carbohydrate has been confirmed by many studies and does not increase the risk of reflux aspiration in [7]. However, most of the current clinical studies of oral carbohydrate effects on postoperative recovery focus on the preoperative oral phase, and only a few small samples have shown that postoperative oral carbohydrate improves postoperative comfort [8]. Therefore, further systematic studies on the effects of early postoperative oral carbohydrates on postoperative recovery remain lacking.

Directory of reference

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1. Study purpose and study endpoint

1.1 Study Purpose

1.1.1 Main study objective: To evaluate the effect of early postoperative oral carbohydrate on postoperative recovery of the unilateral knee arthroplasty.

1.1.2 Secondary study objectives: To evaluate the effect of early oral carbohydrate administration on the comfort and safety of patients undergoing unilateral knee arthroplasty.

1.2 Study endpoint

1.2.1 Primary study endpoints

Fasting insulin resistance index in venous blood was checked 1d after surgery;

（Fasting blood glucose (fasting plasma glucose, FPG) and fasting insulin (fasting insulin, FINS) were measured 1 day after surgery. FPG, detected by oxidase method, FINS detection by radioimmunoassay, using steady state mode assessment to calculate the steady state model insulin resistance index (homeostatic model

assessment for insulin resistance, HOME-IR): FPG (mmol/L) FINS (mU / L) / 22.5.）

1.2.2 Secondary study endpoints

1.2.2.1 Effectiveness study endpoint

1) Fasting insulin resistance index in venous blood was checked on the day of the surgery;

2) Fasting insulin resistance index in venous blood was checked 3d after surgery;

3) Fasting pre-albumin levels in venous blood on the day of surgery, 1d and 3d after surgery.

4) Fasting level of retinol-binding protein in venous blood on the day of surgery，1d and 3d after surgery;

5) The 15-item recovery quality rating scale (QoR-15);

6) NRS score of thirst and hunger at 2h, 6h and 8h after surgery;

7) Abating distension within 24h after surgery;

7) The incidence of hypoxemia and reflux aspiration within 24h after surgery(SpO_2 <91% under air inhalation was defined as hypoxemia; vomiting associated with severe coughing followed by hypoxemia and lung rales);

9) Time of anal exhaust for the first time after surgery;

10) The degree of nausea and vomiting;

11) Length of hospitalization;

12) Postoperative analgesic effect: patients consumed total sufentanil at 48 hours after surgery, number of effective pressure times of the analgesic pump, remediation of analgesia(The salvage analgesic dose was converted to morphine equivalent)；

13) Postoperative subject satisfaction score.

1.2.2.2. Safety study endpoint

1) The incidence and severity of various adverse events (AE) from the start of oral carbohydrates to the end of the trial;

2) The incidence and severity of adverse events such as nausea, vomiting and hypoxemia from the first start of drug administration to the end of the trial;

3) Number of antiemetic drugs used within 24h after the first start todrug administration;

2. Expected results

Oral carbohydrates in the early postoperative period can improve patient nutritional status, improve comfort and satisfaction without increasing the incidence of adverse events.

3. Design and method of the study

3.1.1 Screening period

Patients undergoing unilateral total knee arthroplasty of the lower limbs or monocondylar arthroplasty, screened with informed consent to enroll patients, met all enrollment criteria and did not meet any of the exclusion criteria.

3.1.2 The perioperative management protocol

Pre-operative management： All patients actively controlled blood pressure, blood glucose, correction of anaemia and hypoproteinaemia, and increased protein intake. The dietary plan was informed by the ward nurse one night before surgery, all patients fasted solid food 6 hours before surgery and 200ml of sugary drinks were taken 2-3 hours before surgery.

Intraoperative management: All patients underwent lumbar anesthesia, selected L_{3-4} or L_2-L_3 gap puncture, and the anesthesia plane was controlled below T_7. The restrictive liquid management strategy was adopted, 6ml crystalloid · kg^{-1} · h^{-1} supplemented physiological requirements, blood loss was supplemented with hydroxyethyl starch fluid, concentrated red blood cells were infused with Hb <80 g / L, and the patient blood pressure and heart rate fluctuation was less than the base value ± 20%. At 30 min before the start of the procedure, 40mg of analgesia at 5mg IV and 2mg of prophylactic antivomiting 30min before the end of the procedure.

Analgesia management:

1. Non-steroidal anti-inflammatory analgesics were given during the operation, and returned to the ward to continue on time；

2. After the operation, the adductor muscle tube block and analgesia should be performed according to the surgical incision site；

3. Sufentanil PCIA analgesia pump, formula: Sufen 150 ug + Segen 6mg + NS250ml; continuous: 3ml / h, control: 5ml, lock: 8min, limit: 35ml / h, adjust the parameters

according to the pain condition to meet the patient NRS pain score 3；

4. If the patient started PCIA treatment, the subject's NRS pain score 4 and 3 bolus did not relieve, and the investigator judged the opioid relief analgesia such as sufentanil or oxycodone until the NRS pain score 3 and recorded；

Management within the PACU:

Eligible patients were screened before surgery, and an informed consent form was signed. Patients enrolled in the experiment were randomly assigned into one of the three groups. They are early feeding group (EOF 1, EOF 2) and late feeding group (control group). Late feeding group (Group C): Group C patients observed 30min vital signs, returned to the ward to fast and drink for at least 6 h, and gradually drink and eat after anal exhaust. Early drinking water group (EOF 1): EOF 1 group received water in the resuscitation room; early drinking carbohydrate group (EOF 2): EOF 2 group received 200ml 12.5% carbohydrate (100ml containing 12.5g maltodextrin, fructose and glucose) in the resuscitation room.

To evaluate the resuscitation room of patients in the early feeding group: Steward awake score of 6 and awake level 3,5ml / kg lean weight 12.5% carbohydrate or water according to the need of consent. The process of drinking carbohydrates or water is to take 30ml orally first. After observing no abnormal swallowing, the patient was instructed to drink the remaining drinks as needed. After the patient returned to the ward, the liquid diet began to gradually excessive into the normal diet. When the patient was able to tolerate a normal diet, the intravenous fluids were stopped.

Evaluation process of drinking index：

1）Steward Score: awake: 0-no response to stimulus; 1-some response to stimulus; 2-full awake.(2) Respiratory tract patency: 0-patient's respiratory tract needs support; 1-patient's respiratory tract can maintain patency without support; 2-patient can cough according to the doctor's guidance.(3) Body mobility: 1 point-the patient has no body activity; 2 points-the unconscious activity of the patient's limb; 3 points-the patient's limb can carry out the conscious activities；

2）Grade of sobriety：according to the awake degree of the patient's consciousness: Grade 0: the patient is completely in the sleep state, No response when calling; Level

1: The patient is falling asleep, However, head and neck movement, eye opening, or limb movement occurs during breathing; Grade 2: the patient is awake, Have the same performance as level 1, At the same time can also open the mouth, stretch the tongue; Grade 3: the patient is in an awake state, Have the same performance as the level 2, At the same time, they can also clearly tell their own name, age and other information; Grade 4: The patient is awake, Have the same performance as level 3, It can also accurately identify the surrounding environment, And tell you clearly where you are.3. 3 ） The early feeding group (EOF 1 and EOF2 group) did not need to wait for peristalsis. According to the wishes of the patients, the dose was completed within 2 hours after the operation

4. Subject recruitment and protective measures

4.1 Inclusion criteria

- Age 18-79 years;
- Patients undergoing unilateral total knee arthroplasty or unicondylar joint replacement;
- Normal diet;
- ASA grade I~III;
- BMI 18-30 kg / m^2;
- No intraspinal anesthesia contraindications.

4.2 Exclusion criteria:

- Preoperative existence of gastric emptying disorders, such as gastrointestinal obstruction, gastroesophageal reflux, or previous gastrointestinal surgery;
- Patients with diabetes mellitus, severe renal dysfunction, or other severe metabolic diseases;
- History of motion sickness;
- Mental disorder, alcoholism, or a history of substance abuse;
- Patients with abnormal swallowing function;
- The operation time is greater than 3 hours;
- Maltodextrin fructose allergy or intolerance;

4.2 Standards for dropout cases: signed the informed consent form and screened the

qualified withdrawal cases in the pre-intervention, during the intervention and after the intervention follow-up process after entering the study.

4.3 Case exclusion criteria:

- Signed the informed consent, entered the study but was found not to meet the inclusion criteria during the project supervision or after the completion of the study;
- Did not sign the informed consent;
- The intervention was not performed according to the treatment standards and had poor compliance;
- Failed to accept the intervention, did not comply with or assume the corresponding responsibilities and obligations of the informed agreement.

5 Informed consent

5.1 The Informed Consent Form

The informed consent was in accordance with the ethical principles outlined in the Declaration of Helsinki. The informed consent form detailed the study protocol and process, and fully explained the risks of the study.

The informed consent form also states that the records of the individual identity must be kept confidential, but the research team and regulators can access the subject information.

5.2 Informed consent process and record

Informed consent begins before the individual consent to participate in clinical studies and continued throughout the course of the clinical study.

5.3 Confidential

Personal patient information will be given as confidential information. All patient data obtained from the patient cases will be kept as confidential. Patients will be identified by their name acronym and the numbers provided at the time of study inclusion. Patients or their families will be aware of the anonymity of the data and their right to protect their privacy. However, it is also important to understand the fact that the data will be submitted to the subject responsible unit or the government management authority, and may also be submitted to institutions such as the Ministry of Health for

inspection and evaluation. The participating physician will keep a list of patient personal data (patient data and corresponding patient names) for confirmation of the record.

6. Quality control and quality assurance

6.1 Qualification of research unit and researcher qualification

The research unit shall have the experience in drug research, the facilities and conditions of the department where the project belongs shall meet the needs of safe and effective clinical research, and the researchers shall have the professional expertise, qualifications and ability to undertake the clinical research, and shall be trained in GCP regulations.

6.2 Training of the researchers

Before the start of the study, the research leaders of each center should organize the researchers to study the program, and only the researchers who have passed the program training can participate in the study to ensure that the researchers have a consistent understanding of the protocol. For important assessment scales, relevant personnel in the participating centers need systematic training and even obtain corresponding qualification certificates.

6.3 Surveillance of clinical trials

The hospital ethics committee and institutional review board may conduct a systematic review of the clinical trial-related activities and documents, to evaluate whether the trial was conducted in accordance with the test protocol, SOP, and relevant regulations, and whether the test data are timely, true, accurate, and complete records. The audit should be performed by those who do not directly involve the clinical trial.

7. Organization and management of the research

7.1 Change of the scheme

All additional or referenced appendices are integral parts of the scheme. No one shall make any modifications or revisions to any part of the research protocol, as signed by the investigator and the principal of the project, unless these changes or revisions have been fully discussed. And through the unanimous consent of the researcher and the

subject leader.

Any agreed modifications will be recorded and will be signed by the investigator and the project leader and filed with the protocol.

7.2 Retention of the records

The investigator shall keep all the detailed original documents of the subject and record the trial process, medication status, laboratory examination data, safety data and efficacy assessment in the case report form. The recorded data shall be complete, timely and clear. The original documents and medical records should be clear, detailed and easily identified by those participating in this clinical trial.

The case report form and the original files can only be modified by the investigator. No modification to the case report form and the original file shall smear the original data off. The correct way to modify is to line the original data, and then write the modified data next to the original data, and sign the date and the name of the modification.

Test data shall be retained until 5 years after the termination of the test.

7.3 Early termination of the study

The leader of the project decides to stop or interrupt the study in advance in the case of force majeure, and should inform the doctors involved in the study in writing. Similarly, any participating unit that decides to withdraw from the study for any reason should also notify the project leader in written form.

7.4 Research, supervision and inspection

7.4.1 Research supervision

Inspectors must follow the drug clinical trial quality management specification (GCP) and standard operation procedures (SOP), visit the research unit regularly or according to the actual situation, supervise the clinical trial work and progress, check, confirm all data records and reports, correct and complete, consistent with the original data, ensure the clinical trial in accordance with the clinical trial protocol, the researchers should actively cooperate with the inspectors. The specific contents of the inspector include:

a) Ensure that the test undertaking unit has appropriate conditions, including staffing

and training, complete laboratory equipment, good operation, various inspection conditions related to the test, an estimated sufficient number of subjects, and the participants to be familiar with the requirements in the test plan;

b) Monitor the implementation of the trial program during the trial, confirm that the informed consent of all subjects is obtained before the trial, understand the enrollment rate of the subjects and the progress of the trial, and confirm that the selected subjects are qualified;

c) Confirm that the records and reports of all data are correct and complete, and that all case report forms are entered correctly and consistent with the original data. All errors or omissions have been corrected or indicated, signed and dated by the Investigator.

d) Verify that all adverse events are recorded, and that serious adverse events shall be reported and recorded within the specified time;

e) Clearly and truthfully record the failed visits, unconducted tests, and undone checks should be made, and whether the errors and omissions should be corrected;

f) The written inspection report shall be completed after each visit, which shall state the date, time, name of the inspector, the findings of the inspection, etc.

7.4.2 On-site inspection

The responsible unit may conduct an on-site inspection of the research at a clinical research institution. The audit includes the required test documents, records of the informed consent process, and the consistency of the eCRF and the original documents. But also the content and scope of the inspection can be increased according to the situation. The investigator agrees to participate at a reasonable time and in a reasonable manner.

8. Investigators' responsibilities

8.1 Participation of doctor responsibilities

The participating physicians will conduct the study following the study protocol and confirm the accuracy of the data entered. The participating physicians should be responsible for obtaining written signed informed consent for data collection from the study subjects.

8.2 Responsibility of the project leader

The project leader takes all reasonable steps and provides sufficient resources to ensure the implementation of the research, mainly involving the following aspects:

a) Ensure that the study complies with relevant national and local regulations, including ethical requirements, patient data protection regulations, etc.

b) Ensure the effectiveness of quality control and analysis of research results.

9. Share results

The intellectual property rights, trial data and research results related to this study are jointly owned by Nanjing First Hospital and the Department of Anesthesiology.

The intellectual property rights, trial data and research results related to this clinical study are owned by Nanjing First Hospital and the Anesthesiology Department.

10. Ethics principles and requirements for clinical research

Clinical research will follow the world medical congress "declaration of Helsinki" and the national health and family planning commission of the People's Republic of China "involving people biomedical research ethics review method" and other relevant provisions, the specific implementation of informed consent, the privacy protection, research free and compensation, risk control, special subject protection and research related damage compensation principles and requirements. The clinical study was performed before the ethics committee approved the trial protocol. Before each subject is enrolled in the study, the investigator has the responsibility to present the subject or / and his legal agent about the purpose, procedures of the study and possible risks, and sign a written informed consent form that their participation in the clinical study is completely voluntary, that they may refuse to participate or withdraw from the study at any time at any stage of the trial without discrimination and retaliation, and their medical treatment and interests are not affected. The informed consent form should be retained as a clinical research document for future reference to effectively protect the subjects' personal privacy and data confidentiality.