PROTOCOL

The research program of ultrasound-guided continuous gastrocnemius plane block

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1 Research background Foot and ankle surgery is a common kind of clinical surgery, mainly including ankle fracture internal fixation, bunion valgus correction and ankle skin debridement.It has been shown that foot and ankle surgery can cause moderate to severe severe pain, often producing long-term postoperative pain[1]. Often need large doses of analgesics to auxiliary treatment, intravenous although analgesia can achieve certain analgesic effect, but easy to cause adverse reactions such as vomiting, nausea, has certain limitations, ultrasound guide peripheral nerve block is a kind of analgesic method in recent years, has been the height of clinical staff recognized [2].

The nerve block commonly used for foot and ankle surgery is the sciatic nerve block at the popliteal level.Sciatic nerve block is widely used for postoperative analgesia in patients, but not without complications.A retrospective analysis of 1014 patients undergoing foot or ankle surgery for popliteal sciatic nerve block identified 5% with associated neuropathy and 0.7% with sciatic neuropathy symptoms still not resolved at the last follow-up for the suspected[3] with nerve block. The continuous sciatic nerve block catheterization technique is relatively complex, with not only the risk of catheter prolapse and leakage of[4,5], but also the risk of nerve injury. One prospective study reported 147 popliteal tube patients at 2 weeks in 41%, down to 24% at 34 weeks, and 3.4% of these patients had severe symptoms, probably also a nerve block-induced nerve [6].

The sensation of the foot and ankle joints is provided by the branches of the sciatic and femoral nerves: 1. The end of the femoral nerve is the cryptic nerve that provides sensation to the medial side of the foot. 2.The common peroneal nerve is divided into the superficial sural nerve, which provides sensation for the dorsal foot and 2-5 toes; the deep sural nerve provides sensory [3,7] for the opposite edge of 1-2 toes. 3.The sciatic nerve is divided into the tibial nerve and The common peroneal nerve .The tibial nerve provides plantar sensation through the medial plantar, lateral and calcanus nerves. 4.The sural nerve usually comes from the branches of the common peroneal nerve and the tibial nerve, and provides the lateral side of the foot, the dorsum of the foot and the lateral edge of the small toe feel like the [4,8].

Dissection revealed the common peroneal nerve beyond the lateral head of the gastrocnemius muscle, located in the depression between the biceps tendon and the lateral margin of the gastrocnemius tendon. The common peroneal nerve runs behind the small fibular head and around the fibular neck forward through the long peroneal muscle and is divided into shallow, peroneal and deep nerves. The tibial nerve is accompanied by the popliteal vessel in the popliteal fossa, passes through the deep surface of the soleus muscle with a descending posterior tibial artery, bypassing the medial malleolus, and is divided into plantar olateral and medial plantar nerves.The gastroemal nerve drops between the gastrocnemius muscles and is superficial on the far side of the calf. The common peroneal nerve crosses the back of the lateral head of the gastrocnemius muscle (in the depression between the biceps tendon and the lateral margin of the peremius tendon), behind the small head of the fibular bone and

around the neck of the perfibular muscle into the superficial sural and deep nerves.The tibial nerve is accompanied by popliteal vessels in the popliteal fossa, walking in the gastrocnemius muscle, and penetrates the gastrocnemius in the middle and upper calf into the deep surface of the soleus muscle with posterior tibial artery decline. The peroneal nerve drops along between the gastrocnemius muscles and is superficial to the subcutaneous [7] in the calf. Therefore, the local anesthetic given on the surface of the gastrocnemius muscle can theoretically block the common peroneal nerve, and between the gastrocnemius muscle and the soleus muscle, it can block the tibial nerve. Muscular space administration can avoid nerve injury, reduce the operation difficulty of sciatic nerve block, and facilitate the catheterization and analgesia of continuous common peroneal nerve and tibial nerve block.

Directory of references

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2 Study objective and study endpoint

Efficacy and safety study of ultrasound-guided gastrocnemius plane catheterization for analgesia after foot and ankle surgery-single Central, randomized, single-blind, parallel-controlled study.

2.1 Study Purpose

2.1.1 Main study objective: To evaluate the gastrocnemius plane catheterization for patients with foot and ankle surgery under elective general anesthesia efficacy of analgesia during the operative period.

2.1.2 Secondary study objective: To evaluate the plane tube emulation of gastrocnemius muscle for patients with foot and ankle surgery under elective general

anesthesia safety of analgesia during surgery.

2.2 Study endpoint

2.2.1 Primary study endpoints

PI-AUC_{48} (the area under the pain intensity-time curve within 48h after the first start of the postoperative administration)

2.2.2 Secondary study endpoints

2.2.2.1 Effectiveness study endpoint

1) Accumulated amount of remedial analgesic drugs (oxycodone, calculated as mg) used within 0-48h after the first start of postoperative drug administration;

2) Percentage of subjects who did not use remedial analgesics within 0-48h after the first start of postoperative administration;

3) Number of remedial analgesia within 0-48h after the first start of postoperative drug administration;

4) Total number of PCA compressions within 0-48h after the first start of postoperative drug administration;

5) Number of effective PCA compressions within 0-48h after the first start of postoperative drug administration;

6) Subject satisfaction score at 48h after the first start of postoperative drug administration;

2.2.2.2. Safety study endpoint

1) The incidence and severity of various adverse events (AE) from the first start of drug administration to the end of the trial;

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

3) The incidence and severity of muscle strength and paresthesia in the affected limb from the first drug administration until the end of the trial;

3. Expected results

Ultrasound-guided gastrocnemius muscle plane catheterization can be effective and safe for analgesia after foot and ankle surgery.

4. Design and method of the study

This clinical study uses a single-center, randomized, single-blind, parallel controlled trial design, divided into screening period, treatment period and follow-up periods.

4.1.1 Screening period:

Patients undergoing elective foot and ankle surgery gave informed consent to be enrolled, and subjects who met all enrollment criteria and did not meet any exclusion criteria were obtained a randomization number and drug number 1 day before the surgery or the day of the surgery in a 1:1 ratio to the trial and placebo control groups.

4.1.2 Treatment Period

Patients were randomized into two groups, the ropivacaine group and the control group.The venous access was open after home invasion and was routinely monitored ECG，NBp，SpO_2，BIS。General anesthesia was performed.

Induction of anesthesia: propofol 1mg / kg, cis atracuronium 0.2mg / kg, sufentanil 10ug, remie Tanyl at 1.5 g / kg. Anesthesia maintenance: Propofol and sevoflurane static aspiration compound BIS was maintained at 40~60, remifentanil 0.3~0.4 g /

kg/min intravenous pump, and additional cis atracurium was added according to myasasone monitoring. In the postoperative ropivacaine group, the patient took a lateral decubitus position, and underwent a gastrocnemius plane block and catheterization under ultrasound guidance to connect a disposable electron infusion pump. (Formula of 0.125% ropivacaine of 300mL, background dose of 3.0 mL/h, PCA dose of 8 ml, and locking time of 25min). The control group received intravenous oxycodone titrated according to the NRS score, and received no background dose of oxycodone PCIA pump for analgesia (single dose 1mg, locking time 5min, 4h limit 12mg). All patients were given 50mg of fluoroprirol ester intravenously.

Remedial analgesia: if PCA analgesia still can not tolerate the pain and NRS ≥4, can be given intravenously oxycodone was done 2mg, separated by over 3 min, until NRS ≤3.

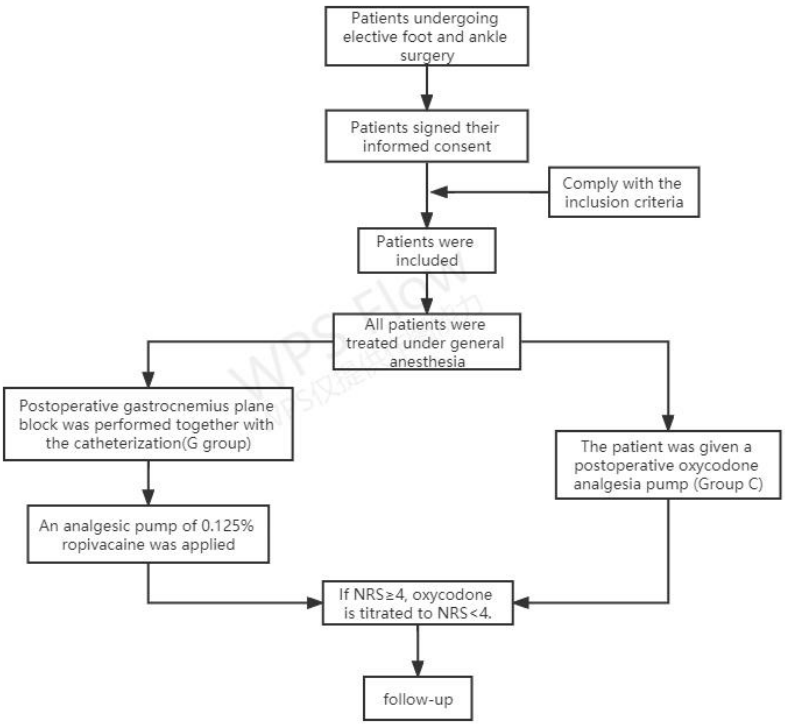
4.1.3 Follow-up period

Record: block range of 15min, 30min, 45min, 60min, 90min, 1h, 4h, 8h, 12h, 24h, 48h and NRS score during rest and exercise; time of first pressing of the analgesic pump; times of controlled analgesia (PCA); 0-4h, 0-8h, 0-16h, 0-24h, 8-16h, 16-24h, 32h, 32-40h pain intensity-time curve (AUC); dose and times of remedial analgesic administration;

Records: affected limb muscle strength and paresthesia, length of hospitalization, time of first ambulation, nausea and vomiting, neurological complications, patient satisfaction, physician and nurse satisfaction, etc.

5.0 Study the implementation process

The patient had open venous access after home invasion and was routinely monitored for ECG, NBP, SpO2, and BIS.Induction and maintenance were performed according to a uniform anesthesia protocol.Postoperatively, the block was performed by the same anesthesiologist familiar with the ultrasound-guided nerve block.Various study indicators and data were collected by the same anesthesiologist who was not aware of the grouping situation.



6. Subject recruitment and protective measures

6.1 Inclusion criteria

Patients undergoing elective foot and ankle surgery; the patient gave informed consent; age 18~65y and gender; ASAI~III; BMI 18 ~ 28 kg/m².

6.2 Exclusion criteria

puncture site infection, abnormal coagulation function, local anesthetic allergy, severe cardiopulmonary disease, liver and renal insufficiency, long-term use of sedative and analgesic drugs, communication disorders, history of chronic pain, and operation time exceeded 3h.

6.3 Exit criteria

Patients may withdraw their informed consent and withdraw from the trial at any time.

The investigator may decide on the subject to terminate the withdrawal from the study in the following circumstances.

1) Any medical condition occurring in the study may lead to the risk of continuing the study subjects;

2) The subject receives analgesic treatment other than the prescribed analgesic remedy protocol, and other subjects who cannot complete the test according to the provisions of the test protocol;

3) The researcher judges other situations that should withdraw from the trial.

7 Informed consent

7.1 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.

7.2 Informed consent process and recording

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

7.3 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.

8. Quality control and quality assurance

8.1 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.

9.2 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.

8.3 Surveillance of clinical trials

A 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 trial protocol, SOP, and relevant regulations, and whether the trial data are timely, true, accurate, and complete records.The audit should be performed by those who do not directly involve the clinical trial.

9. Organization and management of the research

9.1 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 modification will be recorded and will be signed by the investigator and the project leader
The case is filed together.
9.2 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.
9.3 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.
9.4 Research, supervision and inspection
9.4.1 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 before the test that the test undertaking unit has appropriate conditions, including staffing and training, complete laboratory equipment and good operation, various inspection conditions related to the test, and estimated sufficient quantity
All the participants were familiar with the requirements in the test protocol;
? b) Monitor the implementation of the trial protocol 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, findings of the inspection, etc.

9.4.2 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.

11. Investigators' responsibilities

10.1 Participating physician responsibilities

The participating physicians will implement 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.

10.2 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.

11. Results sharing

The intellectual property rights, trial data and research results related to this anatomical study are jointly owned by the Nanjing First Hospital and the Department of Anesthesiology, and the University and the Anatomy Teaching and Research Section of Nanjing Medical University.

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

12. Data analysis

Data collection: It was collected by the same anesthesiologist who did not know the grouping situation.

Data were calculated using SPSS 22.0 statistical software.Normally distributed measurement data are expressed as mean ± standard deviation ($x \pm s$), using one-way ANOVA and using $\chi 2$ test, $P < 0.05$ was significant.

13. Ethics principles and requirements for clinical research

Clinical research will follow the world medical congress of the declaration of Helsinki and the national health and family planning commission of the People's Republic of China involving human 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 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.