Program name: The effect of low-dose remifentanil infusion on emergence agitation and postoperative cognitive function after general anesthesia

Informed consent version number and version date: Consent 3.0/20230225

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Main researcher: Dr. Yong-Xing Yao

Participant name: Initials:

Participant address:

Participant contact number:

Dear patient:

We sincerely invite you to participate in a clinical study. This informed consent form provides you as much information as possible to help you decide whether to participate in this clinical study. Please read the following content carefully. If there are any unclear questions or terminologies, you can discuss with the physician concerned. Your participation in this study is completely voluntary. This study has been reviewed by the institution's ethics committee.

Background

Emergency agitation (EA) refers to the separation of consciousness and body movement, develops during emergence from general anesthesia, and manifests as impaired self-control, restlessness and uncontrolled movements such as turning and twisting. Severe agitation may lead to serious accidents including dramatic hemodynamic disturbance, surgical incision opening, operative site bleeding, accidental removal of various tubes and even hypoxia. Therefore, severe agitation places an extra burden on both medical staff and patients. In the past few years, studies have confused the definition of EA with emergence delirium (ED), resulting in a wide range of reported incidence rates, from 0.25% to 21.3% in adults. Recently, the definitions of EA and ED have been clarified. EA is limited to the early stage before consciousness recovery, and ED occurs after a period of wakefulness.

The mechanism of EA has not been clarified. EA is strongly associated with postoperative pain, catheter stimulation, and inhalation anesthetics. Due to the confused definition and unclear mechanism, there is currently no unified treatment for EA. According to clinical practice, it can be acknowledged that EA is still difficult to treat, especially for severe cases. The routine clinical method is to use propofol (possibly combined with opioids) to sedate the patient until recovery from consciousness. However, a single propofol injection is not sufficient for preventing EA recurrence, while long-acting opioid agents, including fentanyl, can easily accumulate and thus cause side effects such as respiratory depression after extubation. Therefore, the current methods have limited therapeutic effects in treating severe EA, even leading to prolonged recovery time after surgery.

Remifentanil is an ultrashort-acting opioid widely used for general anesthesia. It has a distinctive antinociceptive effect and extremely short half-life, and it is not affected by hepatic or renal dysfunction]. Remifentanil can produce significant antinociceptive effects while maintaining the consciousness of patients and enabling them to follow directions. Studies have shown that small doses of remifentanil infusion during extubation can prevent coughing and agitation after general anesthesia. Therefore, remifentanil may be a new option for EA treatment. However, there have been no reports on the therapeutic effect of remifentanil on severe EA and circulating cytokine levels after major abdominal surgery in adult patients.

This randomized study aims to observe the efficacy of a small dose of remifentanil for treating severe EA after general anesthesia for major abdominal surgery. Furthermore, we will also evaluate the effects of remifentanil on the comfort of extubation, cognitive recovery profile and circulating cytokine levels in the early stage after surgery. We hypothesize that remifentanil is superior to propofol and fentanyl in treating severe EA in adult patients undergoing major abdominal surgery.

Purpose

This clinical trial is to study the treatment of small-dose remifentanil infusion in patients with

severe emergence agitation after hepatobiliary and pancreatic surgery. We mainly observe the therapeutic effect of remifentanil on the recurrence rate of emergence agitation and postoperative cognitive profile, explore the clinical advantages of remifentanil in agitation after general anesthesia,and study the clinical value of remifentanil during anesthesia resuscitation.

Selection criteria: 1. Severe emergence agitation in PACU after elective general anesthesia (Ricker ≥ 6 points); 2. 18 years and 75 years; 3) ASA grades I to III.

Exclusion criteria: 1. patients who are unable to communicate normally before surgery; 2. patients with mental illness who take psychotropic drugs before surgery; 3. central nervous system diseases (such as dementia, Parkinson's disease and history of cerebral infarction); 4. allergic to opioids or opioids abuse; 5. allergic to propofol.

Procedure

Eighty cases are expected to be included in this study, and the study is expected to be completed by December 2024. Before surgery, our pre-anesthesia visit physician will introduce the study information to you. If you agree to participate in the study, our doctor will record your medical information, review your test report, assess the baseline, and determine whether you can be enrolled if EA happened. Please cooperate with the study screening, including medical history collection, physical examination, laboratory and auxiliary tests, and assessment of cognitive function and pain. If you pass the screening, you will become an "intention-to-treat" participation and sign the informed consent form.

On the day of surgery, vital signs will be monitored, and anesthesia will be managed at the discretion of the anesthesiologist. At the end of the operation, you will admit to the anesthesia care unit (PACU). When severe agitation happens to you, you will randomly divid into the remifentanil group or normal saline group. In the PACU, blood samples will be obtained through a established access without additional puncture at severe agitation, 5 min after extubation, and discharge from PACU.

During the three days after surgery, our doctor will visit you in the ward to evaluate your recovery

quality, including the postoperative cognitive profile, pain or other effect. Important postoperative examinations, drug therapy and postoperative adverse events will also be recorded.

"Randomization" means that you are randomly assigned to a intervention group to minimize bias. You have a 1/2 chance of being assigned to the study group and a 1/2 chance to the control group, which is randomly assigned by a random number table. Neither you nor your physician blinded which medication you receive, therefore, the process is unaffected by the researcher or other interference factors, which ensures that the intervention will be evaluated in an unbiased manner.

"Control" refers to the use of a "placebo" that looks much like the real trial group but does not contain any drugs.

"Double-blind" means that neither you nor your study physician know whether you are receiving remifentanil or placebo. This will ensure that everyone involved in the trial can evaluate the safety and efficacy of the intervention objectively . But in an emergent situation, your physician can discontinue the trial and know whether you are receiving remifentanil or a placebo.

In the current study, adverse events potentially related to remifentanil include apnea, bradycardia, hypotension, nausea, vomiting and pain sensitization. The most common adverse event caused by remifentanil infusion is awake apnea, with an incidence of approximately 5-10%. Another adverse effect is the withdrawal effect and hyperalgesia after the infusion is stopped. In addition, bradycardia occasionally occurs with an incidence of 1-10% during infusion. Nausea and vomiting are not common, with an incidence of 0.1-1%. Remifentanil is an ultrashort opioid with a fixed elimination half-life of 6 min. All of the adverse effects disappear several minutes after the infusion is stopped. There might be currently unpredictable risks and adverse events. However, under close surveillance and continuous monitoring, it is safe to use remifentanil for emergence agitation, and your clinical safety will be ensured during the perioperative period.

Benefits of participating in the study

If you agree to participate in the study, there is a high likelihood that you will have immediate medical benefits. A continuous small-dose infusion of remifentanil administered after severe agitation during emergence from general anesthesia may reduce the rate of recurrent agitation, achieve rapid and high-quality wakefulness, shorten the time to extubation, and reduce the length of stay in the PACU, but it may also not be beneficial. We hope that the information gained from your participation in this study will be instructive to patients with your condition in the future.

Costs associated with the study

Participation in this study will not increase your cost. Remifentanil is routinely used during the maintenance of general anesthesia, while other drugs and monitoring are routine procedures during the recovery of general anesthesia. While blood samples test is covered by grants.

Compensation

If you suffer any damage or serious adverse events result from the study during this clinical study, subsequent medical expenses will be covered by the institution. Moreover, we have purchased insurance for this study to compensate you for any damage result from the study, with a maximum limit of 500,000 RMB.

Right to refuse to participate or withdraw from the study

You can refuse to participate in this study, or have the right to withdraw without any reason at any stage of the trial. The alternative treatment is the conventional treatment for severe agitation in our center, so your medical treatments and interests will not be affected. Once you decide to participate in this study, please sign this informed consent form to indicate your consent. Before the study, you will be screened by your physician to determine if you are a suitable candidate. If you choose to participate in this study, we expect you to follow through the

whole process.

Privacy and confidentiality issues

During the study, your name, gender and other personal information will be replaced by a code number, and will be strictly confidential. Only the relevant physicians will get your information, and your privacy will be well protected. The results may be published in a journal without revealing any personal information relative to you.

If you agree to participate in this study, your medical information will be reviewed by the researchers of the study and the relevant authorities or an independent ethics committee to check whether the study is being properly performed. If you sign the informed consent form , you will agree to be reviewed by the above staff.

How to get help in the study

You can keep informed of the information and research progress related to the study. If you have any questions related to the study, please contact Dr. Yong-xing Yao at 0571-87236169. Clinical Research Ethics Committee Contact: 79 Qingchun Road, Shangcheng District, Hangzhou City, Zhejiang Province, 0571-87233418.

Informed consent signature-consent signature page

If you fully understand the content of this research and agree to participate in this study, you will sign this informed consent form in duplicate, each retained by the investigator, yourself or your client.

Clinical Research Project Name: Therapeutic effect of small-dose remifentanil infusion on severe emergence agitation after general anesthesia for major abdominal surgery in adults.

Signed by yourself or your legal representative:

Consent statement:

- I confirm that I have read and understood the informed consent for this study, and have explained to me any potential issues and solutions during the research process. Moreover, I have the opportunity to raise my own questions.
- I have made it clear that my participation in the study is voluntary, and my refusal to participate will not harm any of my interests.
- I have been informed that the physicians involved in the study and the staff in charge of the first Hospital of Zhejiang University and the Medical Ethics Committee have the authority to review the study records and data. I agree that the aforementioned staff can directly obtain my study records and understand that the above information will be treated as confidential.
- I agree to participate in this study.

Participants signed:_____ Date: _____

Participants contact details:_____

(Note: If the participant has no capacity/restricted capacity, the legal representative's signature and signing date are required.)

Guardian signature:_____ Date: _____

Guardian contact details: _____ Relationship: _____

(Note: If the participant cannot read the informed consent, an independent witness is required to prove that the investigator has informed the participant of all the contents, and the

independent witness must sign and date it.

Witness signature: _____ Date: _____

Witness contact details: _____

Investigator signature:_____ Date: _____

Investigator contact details: _____