Safety and Efficacy Evaluation of Remimazolam for Endoscopic Ultrasound-guided Fine Needle Aspiration/Biopsy

Unique protocol ID:EUS-FNA-2022-01

Date:2022-05-10

1. Research background and aim

Endoscopic ultrasound-guided fine needle aspiration/biopsy (EUS-FNA/FNB) is an important basis for the diagnosis of lesions in the upper gastrointestinal tract and adjacent organs, and plays an important role in the diagnosis of gastrointestinal tumors. Sedation is the key to a successful EUS-FNA/FNB procedure. However, intraoperative sedation in EUS-FNA/FNB is difficult and challenging. First, EUS-FNA/FNB requires a relatively long operation time and is prone to sedation-related adverse events, such as cardiovascular and cerebrovascular accidents. Second, EUS-FNA/FNB requires weakened gastrointestinal motility, thus deeper sedation is required during the operation; thirdly, the ultrasound probe used in EUS-FNA/FNB surgery is thicker than that of ordinary gastroscopes, which requires better cooperation from the patient. Therefore, the rational use of anesthesia drugs during surgery is required to ensure safety.

In current clinical studies, propofol is mostly used for anesthesia in patients undergoing EUS-FNA/FNB. In recent years, the defects of propofol for EUS sedation have gradually emerged, and its respiratory and circulatory inhibition effects have gradually caused researchers to worry. At present, propofol is still a commonly used EUS sedative drug, but with the improvement of people's requirements for sedation quality, its safety gradually cannot meet the demand. Therefore, it is the general trend to explore new EUS-FNA intraoperative sedation schemes.

Remimazolam is one of the new alternative drugs. Remimazolam is a new type of short-acting sedative-hypnotic drug, which has little inhibition on the respiratory system, less impact on hemodynamics, rapid onset of action, short half-life, rapid recovery, and no accumulation after long-term infusion. Thus, remimazolam is an effective drug for induction and maintenance of general anesthesia.

This study aims to compare the safety and efficacy of remimazolam and propofol in EUS-FNA/FNB sedation. This study is a prospective, single-blind, multicenter interventional study. We plan to enroll 264 patients undergoing EUS-FNA and divide them into two groups. The experimental group was sedated with remimazolam, and the control group was sedated with propofol; safety and efficacy parameters such as intraoperative blood pressure, pulse oxygen, heart rate and sedation success rate would be compared. We hypothesized that patients in the

experimental group would be superior in terms of safety parameters; the two would be equal in terms of sedation success.

2. Study design

This trial adopted a multicenter, prospective, single-blind, active-drug parallel-controlled design.

3. Blind, concealment and randomization

Due to the obvious differences between remimazolam and propofol, the anesthesiologists will inevitably know the grouping of patients, so this trial adopts a single-blind design. However, the drug infusion systems used by the patients are covered with black cloths to prevent the recorders, endoscopists and nurses from knowing the patient grouping information.

Randomization of patients was performed by a dedicated researcher who was not involved in the follow-up procedures. The random number table was generated in advance with the help of SPSS20.0 software, and it was divided into two groups at 1:1, corresponding to two sedation programs. The sedation regimen was determined based on the random number assigned to the patient. After the patients completed the follow-up period, the researchers who were responsible for the grouping informed them of the grouping status to protect the patients' right to know. In emergencies, the researchers and anesthesiologists in charge of the grouping have the authority to perform emergency blinding to ensure the quality of medical care.

4. Research protocol:

This study is divided into the following steps:

1. Informed consent and participant recruitment

First of all, inform the patients of the source, purpose, significance, and possible benefits and risks of participating in this study, so that patients can decide whether to participate after they have a full understanding. Patients who participated voluntarily signed the informed consent form. Eligible patients (n=264) would be selected according to the inclusion and

exclusion criteria.

2. Information collection and participant screening

Collect participant information, including name, gender, age, hospital number, enrollment date, education background, occupation, smoking status, drinking status, ASA classification, height, weight, lesion location, comorbidities (if any), medical history, physical examination results, laboratory examination results and imaging findings. Among them, physical examination results include general condition, upper limb skin, head, chest, abdomen, and necessary neurological examination results; laboratory results include blood routine, liver function, renal function, blood biochemistry, and coagulation routine. Imaging examinations are abdominal CT and other examination results that can reflect the location and size of the lesions.

3. Randomization

With the help of the random number table pre-generated by SPSS20.0 software, participants would be divided into two groups (1:1). The sedation regimen is determined according to the random number obtained by the patient's lottery. The randomization process was completed by the designated study designer. Neither the patients nor the endoscopist knew the grouping status.

4. EUS-FNA/FNB information collection and preoperative preparation

Collect operation information, including probe type, operation type, operator qualifications, operation indications, anesthesiologist qualifications, etc.

The patient fasted for at least 6 hours before the operation. Before the operation, the patient took 5ml of 2% lidocaine for topical anesthesia. Inhale oxygen for the patient (4L/min). The patient was placed in the left lateral decubitus position, connected to an ECG monitor, and venous access was established through the vein of the hand. The outpatient operating room is equipped with emergency facilities and equipment (emergency medicines, simple breathing balloons and masks, endotracheal intubation equipment and anesthesia machines).

5. Sedation induction and maintenance

1) Sedation protocol

Remimazolam group:

- Background oxycodone injection: Slowly inject oxycodone(0.05mg/kg) intravenously. Three minutes (± 1min) after the end of oxycodone injection, begin sedation induction as follows.
- Sedation induction before EUS-FNA/FNB: the initial dose of remimazolam is 0.15-0.2 mg/kg, and the intravenous injection time is about 1 minute. If the subject's MOAA/S score is 1 point or below after the initial dose, EUS-FNA/FNB can be started; if the degree of sedation is insufficient, additional remimazolam(0.05 mg/kg each time) is allowed. The injection time of additional remimazolam is not less than 15 seconds, and the time interval between each additional administration is ≥ 2 minutes.
- Maintenance of sedation: In order to maintain the MOAA/S≤1, the investigator can decide to add remimazolam 0.05mg/kg each time, and the intravenous injection time should not be less than 15 seconds, with an additional administration interval of ≥ 2 minutes.

Propofol group:

- Background oxycodone injection: Slowly inject oxycodone(0.05mg/kg) intravenously. Three minutes (± 1min) after the end of oxycodone injection , begin sedation induction as follows.
- Sedation induction before EUS-FNA/FNB: the initial dose of propofol is 1.5-2.0 mg/kg, and the intravenous injection time is about 1 minute. If the subject's MOAA/S score is 1 point or below after the initial dose, EUS-FNA/FNB can be started; if the degree of sedation is insufficient, additional propofol(0.5 mg/kg each time) is allowed. The injection time of additional propofol is not less than 15 seconds, and the time interval between each additional administration is ≥ 2 minutes.
- Maintenance of sedation: In order to maintain the MOAA/S≤1, the investigator can decide to add propofol 0.5mg/kg each time, and the intravenous injection time should not be less than 15 seconds, with an additional administration interval of ≥ 2 minutes

2) Judgment of sedation failure

After the sedation inducement, if more than 5 additional doses are injected in any 15-minute time period, it is considered as a sedation failure. The anesthesiologist should use other sedative rescue measures (such as propofol, etc.) to maintain. After the additional bolus of the sedative, if the participant is still unable to cooperate due to physical movement or other reasons, but the interval between the next additional bolus does not reach 2 minutes, the anesthesiologist can decide to give the subject other sedative rescue measures (such as propofol, etc.) .In this case, failed sedation should be judged due to the use of sedative rescue measures.

3) Treatment protocol for adverse events

The most likely adverse events in the study were respiratory depression, hypotension, and bradycardia. The corresponding treatment process is as follows: when the pulse oxygen saturation drops below 90% and does not recover spontaneously, the anesthesiologist will perform a 30-second chin lift operation; if blood oxygen saturation still cannot recover, increase the oxygen flow to 6L/min and the anesthesiologist compress the chest for assisted breathing; after 1 minute of observation, if there is still no recovery, a oxygen mask should be used; if it still cannot recover, perform mechanical ventilation or tracheal intubation. Hypotension was corrected with ephedrine (5 mg/time, intravenously) and bradycardia with atropine (0.5 mg/time, intravenously).

6. EUS-FNA/FNB operation and postoperative recovery

EUS-FNA/FNB should perform according to routine procedures. After EUS-FNA/FNB procedure, patients were monitored in the postoperative recovery room until the modified Alderte score was 9 or greater before patients were allowed to leave. Patients will fill out the Modified Brice Questionnaire before departure.

7. Follow-up of patients 1-3 days after operation

The patients were followed up 1-3 days after EUS/FNA-FNB to investigate the occurrence of adverse events and re-measure the changes of vital signs.

8. Data recording

The patient's heart rate, systolic blood pressure, diastolic blood pressure, pulse oxygen saturation and MOAA/S score would be recorded every three minutes. Record the occurrence of adverse events, specific adverse event types, treatment methods and duration. 3) Record the total dosage of propofol or remimazolam after the operation.

5. List of adverse events

Major adverse events: endotracheal intubation, permanent neurologic impairment, or death.
Other intraoperative adverse events:
Respiratory system and diaphragm:

Intraoperative cough or hiccups;

Respiratory depression: pulse oxygen saturation <90% or breathing <8 breaths/min for 1 minute or more; apnea: respiratory airflow stopped for more than 15s;

Circulatory system:

Hypotension: SBP decreased by more than 20% of the baseline SBP;

Hypertension: SBP increased by more than 20% of the baseline SBP;

Tachycardia: HR>100 bpm for 1 minute or more;

Bradycardia : HR<50bpm for 1 minute or more;

Psychiatric and nervous system:

Intraoperative awareness: The modified BRICE questionnaire determines the existence of

Delayed awakening: unable to open eyes and shake hands 30 minutes after the operation, no obvious response to pain stimuli

Skin:

Redness, induration, phlebitis, rash;

Motor system:

Body movement, injection pain, involuntary muscle movements (such as rigidity, spasticity, clonus, muscle tremors, etc.)

Postoperative adverse events:

Postoperative dizziness, headache, drowsiness, vertigo;

Postoperative weakness chills;

Postoperative agitation, postoperative cognitive dysfunction, anxiety, confusion, insomnia, nervousness, abnormal thinking, abnormal dreams;

Postoperative sore throat, nausea, vomiting, anorexia;

Bleeding, pain, infection, organ perforation, adjacent tissue organ damage, puncture needle breakage/leftover, etc.