The effectiveness and safety of propofol combined with different doses of esketamine anesthesia during loop electrosurgical excision

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Study protocol

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1. Backgroud

Loop electrosurgical excision procedure (LEEP) is an effective and widely used surgical treatment for cervical lesions like:cervical intraepithelial neoplasia (CIN),cervical erosion,cervicitis and so on [1]. The loop electrosurgical generates high frequency electric waves , When contacts with the tissue, it absorbs the high frequency electric waves and instantly generates high heat to achieve the purpose of tissue resection.Despite LEEP being a simple procedure, it causes significant pain and discomfort. It was reported that the mean VAS score during LEEP was as high as 4, even in the presence of local anesthesia [2]. Physical movement during the surgery severely impacts the surgeon's ability to perform the procedure accurately. Therefore, an effective anesthesia regimen is critical for a successful LEEP.

Propofol is common intravenous anesthetic for LEEP, with sedative and amnestic properties as well as a rapid onset of action and recovery [3]. However, propofol does not have analgesic effects, and it increases the risks of hemodynamic and respiratory depression in a dose-dependent manner. Esketamine (ESK),as a derivative of phencyclidine is an enantiomer of ketamine, with similar sedative and analgesic effects, faster clearance, and lower incidence of toxicity compared with ketamine [4].

So far,only a few studies have investigated the application of propofol combined with other analgesics in LEEP ,like fentanyl , ketamine or dezocine [5] [6].

Reference

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[6]Liu Z, Zou X, Sun X, et al. Loop electrosurgical excision procedure under propofol intravenous anesthesia combined with nano-silver gel in the treatment of cervicitis. Cell Mol Biol. 2022;68(3):96-104.

2. Objective and expected outcome

Objective: This study aims to evaluate the anesthetic effect and safety of propofol combined with different doses of ESK in LEEP.

expected outcome: Propofol combined with esketamine can effectively be used in LEEP anesthesia, with less circulatory and respiratory depression, and the postoperative recovery is faster and more stable, and the satisfaction is higher than that used alone.

3. Study design and method

This is a prospective, double-blind, randomized controlled study. The random-number table method was used to divide them into control and observation groups. The patients were divided into the propofol (2 mg/kg) +normal saline group (group P), propofol (1.5 mg/kg) + ESK (0.5 mg/kg) group (group PK1), and propofol (1.5 mg/kg) and ESK (0.25 mg/kg) group (group PK2).

Statistical analysis: Our sample size was based on the results of small sample pre-experiment. Assume the awakening time as primary outcome. Calculated by PASS software ,we will need to study 27 subjects in each group, given power of 0.90 and type I error of 0.05. Considering a dropout rate of 10%, the sample size will be 30 patients per group, thus a total of 90 patients will be randomized.

Data was processed and analyzed using SPSS 26.0. Measured data with normal distribution was presented as mean ± standard deviation ($\bar{x} \pm s$) and compared using the t-test and one-way ANOVA. Count data was expressed as frequency or percent (%) and compared using the χ^2 test or Fisher's exact test. A $p < 0.05$ was considered statistically significant.

Method of anesthesia： All patients fasted from food for 6 h and from water for 2 h prior to surgery. A peripheral venous access was established after the patient was admitted into the operating room. The heart rate (HR), SpO2 and blood pressure of the patients were monitored using 3-lead ECG, pulse oximeter and non-invasive blood pressure monitor. Patients received 5 L/min pure oxygen via oxygen mask 3 minutes minimum before anesthesia and during the surgery.

Group P was an intravenous injection of an equivalent dose of normal saline followed by 2 mg/kg of propofol. Group PK1 was an intravenous injection of 0.5 mg/kg ESK followed by 1.5 mg/kg of propofol. Group PK2 was an intravenous injection of 0.25 mg/kg ESK followed by 1.5 mg/kg of propofol. The rate of propofol induction should not exceed 40 mg/10 seconds.

Surgery was initiated when a score of <2 was observed on the modified Observer

Assessment of Alertness/Sedation scale (MOAA/S)[7](Table 1). If physical movement （movement of any part of the body such as: opening the eyes, clamping the legs, raising the hands, etc ） occurs during surgery, an additional 1 mg/kg of propofol was administered. If SpO2 drops to <95 % during surgery, the jaw thrust maneuver or face mask ventilation were performed .After surgery,patients were transferred to the recovery room to monitor HR、RR、NIBP and SPO2 ,and were discharged at a MOAA/S score of 5.

Outcome measures： The HR, respiratory rate (RR), mean arterial pressure (MAP) and SpO_2 after operating room admission and at 1 min and 5 min post-anesthesia, venous carbon dioxide (P_vCO_2) at admission and 5 min post-anesthesia, number of additional propofol usage, number of jaw thrust maneuver or face mask ventilation, postoperative awakening time (MOAA/S score >4), and incidences of postoperative vertigo, nausea, agitation and delirium were recorded for the 3 groups.

4. Risks/benefits of the study

This study aims to evaluate the effect of propofol combined with esketamine on the circulation and respiratory system, complications and postoperative recovery in LEEP surgery, and to guide the choice of anesthetic drugs for LEEP, in order to make the operation safer, faster recovery and higher comfort for patients.

5.Recruitment and protection measures

Inclusion Criteria：The patients were 20-60 years old and had a BMI of 18-30 kg/m^2 and an ASA physical status grade of I or II.

Exclusion criteria: 1) Patients who refused to participate; 2) History of hypertension,

hyperthyroidism, or neurological or mental disorder; 3) Currently taking or has taken opioids and non-steroidal anti-inflammatory drugs within 48 h before surgery; 4) Participated in other drug clinical trials within 4 weeks; 5) Allergy to ESK or propofol; 6) History of opioid or ESK addiction.

Withdrawal criteria: Patients had serious adverse reactions, complications, cardiac arrest, malignant arrhythmia and so on during the trial. The subjects withdrew their informed consent and asked to withdraw from the study. Investigators need to stop subjects for safety reasons.

6. Informed Concent Process

At the preoperative visit, patients who met the inclusion criteria were informed by the investigator about the trial protocol, how it differed from the usual protocol, and how it would not affect surgery or anesthesia, and they provided written informed consent. Patients could withdraw from the trial at any time if they wished.

7. Information about the subjects and confidentiality

The personal data of all patients in the trial are confidential. Identifying information will not be disclosed to members outside the research team unless permission is obtained from the patient. After the research is completed and the relevant papers are published, the relevant data will be archived in a timely manner as the basis for further research. To ensure that the study was conducted in accordance with the regulations, the government authorities or members of the ethics review committee were allowed to access the personal data of patients at the research sites when necessary.