Effect of Remazolam benzene-induced laryngeal mask general anesthesia on the quality of recovery after day surgery in elderly patients: a comparative study with etomidate induction

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1. Research Background

Elderly patients have reduced organ function, often with comorbidity, and the incidence of complications and mortality are significantly higher after undergoing anesthesia and surgical trauma than those in other adult patients.[1-3] At the same time, elderly patients often have problems with hemodynamic instability such as hypotension during the induction of anesthesia.[4]

Eomidate, a widely used general anesthetic, is often used for induction of general anesthesia in elderly or hemodynamically unstable patients because of its small effects on blood pressure and heart rate. However, etomidate has an inhibitory effect on adrenal function and can cause muscle tremor and stiffness. Moreover, some studies have shown that etomidate anesthesia increases postoperative nausea and vomiting (PONV), which may not be conducive to patient prognosis and reduce satisfaction.[5]

Remazolam (RT) is a new ultra-short-acting benzodiazepine drug that has been approved for clinical use since 2019. It is characterized by rapid hydrolysis into inactive carboxylate metabolites by ubiquitous tissue esterases. Compared to the classic benzodiazepine midazolam.[6-8] Also, like the other benzodiazepines, remazolam can be antagonized by the flumazenil injection. A recent study showed that remazolam is more stable hemodynamic than propofol during anesthesia.[9]

With significant advances in surgical techniques, the proportion of patients undergoing day surgery with postoperative

complications has gradually decreased. Current perioperative care that improves the recovery of surgical patients focuses more on the time to restore normal function and the subjective postoperative experience, rather than just the incidence of complications. The Quality of Recovery (QOR) score, as an objective measure of patient-centered surgery and post-anesthesia general health, is often used to assess the quality of postoperative recovery, where QoR-15 is a reliable tool for assessing early postoperative recovery [10] and has been validated for [12] in patients undergoing various surgical procedures.

If hemodynamic stabilization during the etomidate induction phase can be achieved with another anesthetic without the above associated side effects, and the quality of postoperative recovery is no worse than that in elderly patients receiving etomidate, this would provide a new option for the induction of anesthesia during daytime surgery in elderly patients. In this study, we aimed to evaluate the quality of recovery following general anesthesia with remazolam-induced laryngeal mask in elderly day surgery patients, comparing that of remazolam versus etomidate, to better guide anesthesiologists in the choice of intraoperative induced medication in elderly patients.

Effect of general anesthesia on the quality of recovery after day surgery in elderly patients: a comparative study with etomidate induction

1. Purpose Of Research

To compare the quality of postoperative recovery induced by general anesthesia with Remimazolam and etomidate in elderly patients undergoing day surgery.

2. Study Design And Methods

1. Research Design

1.1 Study Objectives

The study plans to use the Chinese version of QoR-15 score to evaluate the quality of postoperative recovery after general anesthesia in elderly day surgery patients receiving remazolam or etomidate, while observing hemodynamic changes and other adverse effects.

1.2 Study Content

This study is a randomized, double-blind parallel-controlled non-inferiority trial to enroll 112 elderly day surgery patients randomized at 1:1 to receive Remazolam or etomidate-induced general anesthesia after inclusion 1, along with three QoR-15 assessments to assess the quality of their recovery after surgery.

1.3 Primary outcome measures: quality of recovery at 24h after surgery (QoR-15 score)

Secondary study index: time of eyelash reflex disappearance after induction; SpO_2, HR, MBP, and frequency of use of vasoactive drugs during anesthesia; incidence of adverse events in PACU.

1.4 Subject selection

Selection criteria:

1) Age:> 65 years old and above;

2) The American Association of Anesthesiologists (ASA) is grades I-III;

3) The body mass index (body mass index) was 18-30 kg/m^2;

4) Voluntary provide written informed consent;

5) The patient underwent day surgery under general anesthesia with a laryngeal mask.

Exclusion criteria:

1) Cognitive dysfunction and neuropsychiatric disorders;

2) Use of benzodiazepines or opioids within 1 month;

3) Patients with contraindications or allergies to benzodiazepines, opioids, etomidates and their components;

4) Patients estimated to have a difficult airway;

5) Have adrenocortical insufficiency, porphyria, or have received chronic corticoid therapy.

2. Research methods

2.1 Study design: Randomized, controlled, parallel non-inferiority trial

Randomization: The randomization result was generated by the investigator using R software, sealed to the envelope and handed over by the patient to the anesthesia nurse before surgery, who was responsible for unpacking the randomized envelope.

Blinding: The anesthesia nurse was responsible for unpacking the randomized envelope and preparing drugs to cover the syringes (with the same appearance and volume), and blinded the anesthesiologist, postoperative visitors and patients.

2.2 Sample size estimation:

The primary outcome measure was the quality of postoperative patient recovery (QoR-15 score). According to previous studies, the minimal clinically important difference was 8. The non-inferiority bound for the mean difference between groups was set to-8. Referring to previous studies, the standard deviation (SD) of the QoR-15 scale is 14, and accounting for a 10% shedding rate, 112 achieves 90% of efficacy with a type 1 error of 0.05. We chose to include 112 subjects in this study for the analysis, with 56 subjects in each group.

3. Observation Items And Monitoring Time Point

1.1.Baseline metrics

The following data were collected during the patient screening period

Demographic data: age (yr), gender, education level, ASA grade, body mass index, diagnosis and preoperative comorbidities, and history of smoking and alcohol abuse.

Preoperative clinical data: pulse oxygen saturation (SpO_2), Non-invasive blood pressure (NIBP), heart rate and other vital signs, and electrocardiogram.

The following data will be collected during the surgical treatment period:

SpO_2, HR, systolic blood pressure, diastolic blood pressure, MBP, test time points including 5 minutes before induction of anesthesia, 1 minute after induction, 1 minute after laryngeal mask placement, and start of surgery. Where, data recorded 5 min before induction of anesthesia served as baseline.

The following data were collected during the PACU recovery period:

SpO_2, HR, systolic BP, diastolic BP, and MBP

2.2. Primary outcome measures:

Quality of patient recovery at 24h after surgery (QoR-15 score)

Patients were assessed using the Chinese version of the Recovery Quality-15 (QoR-15) scale. This is a comprehensive measure of postoperative recovery, assessing the five dimensions of recovery: physical comfort (5), physical independence (2), emotional status (4), psychological support

(2), and pain (2). Each item was rated as 11 points based on its frequency in the questionnaire (higher positive items scores, lower negative items scores). The total score ranged from 0 (worst recovery quality) to 150 (best recovery quality);

order number	contents of a project	grade
1	Smooth breathing	0~10
2	Good appetite	0~10
3	Have a good rest	0~10
4	sleep quality	0~10
5	Self-care personal hygiene	0~10
6	Talk to your family and friends normally	0~10
7	Feel the medical staff medical support	0~10
8	Participate in work or daily family activities	0~10
9	Feel comfortable and can manage your emotions by yourself	0~10
10	Overall, feeling healthy	0~10
11	Moderate pain	0~10
12	acute pain	0~10
13	N and V	0~10
14	Nervous anxiety	0~10
15	Sad depression	0~10

2.3. Secondary outcome measures:

SpO_2, HR, MBP, and frequency of vasoactive medication use during anesthesia, and incidence of adverse events in the PACU. Time to the disappearance of the lash reflex after induction.

4.Efficacy Evaluation Criteria

1. Main outcome measures:

The primary outcome measure was the quality of recovery at 24h after surgery (QoR-15 score), recording the QoR-15 score 1 day before surgery, 1 day after surgery (POD 1) and 2 days after surgery (POD 2). The POD 1 score was the primary study outcome.

2. Secondary outcome measures:

SpO_2, HR, MBP, and frequency of vasoactive medication use during anesthesia, and incidence of adverse events in the PACU. Time to the disappearance of the lash reflex after induction.

5. Statistical treatment

1. Analyze the crowd

1) Full analysis set (FAS): Subject set following the principle of intentional treatment (Intention To Treat, ITT): the data set consisting of all subjects participating in treatment and with baseline efficacy evaluation.

2) Compliance with the protocol set (PPS): refers to the completed trial and excluded the treatment population group with serious protocol violations (refers to which the study subjects violated the inclusion criteria or exclusion criteria).

3) Safety analysis set (SS): means the set of all subjects enrolled, with a study intervention, and with at least one baseline level safety evaluation.

4) Efficacy analysis will be conducted on the basis of the full analysis set and the compliant protocol set. All baseline demographic data analyses will be conducted based on the full

analysis set, and safety evaluations will be conducted on the safety set.

2. Statistical analysis method

Data management was performed by EpiData software; SPSS26.0 software was used for statistical analysis. Quantitative variables were tested for normality by using the Shapiro – Wilk test. Comparison of quantitative variables with normal distribution between groups were performed by the t-test, and quantitative data with asymmetric distribution were analyzed by the Mann Whitney U-test. Qualitative variables were compared between groups with the chi-square test or Fisher's exact test as needed. Data for the QoR-15 score are also expressed as the median difference and their 95% confidence interval (CI). Median difference is the median of all pairwise differences between the two sets of observed values, with the 95% CI estimated by Hodges-Lehmann. Data on the frequency of adverse events were reported by the proportion difference and their 95% CI. The 95% CI of proportional differences was calculated using the Wilson program. Among other parameters, such as patient demographic parameters, SpO_2, HR, MBP, and vasoactive drug application frequency, median or proportional differences and their 95% CI were calculated as described above. All analyses were assessed using two-sided tests and a P-value less than 0.05 was considered statistically significant.

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