Project Name: The 90% Effective Dose of Taiglididine for Inhibiting Laryngeal Mask Insertion Response in Elderly Patients

Research Period: September 1, 2025 to June 30, 2027

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Project Name	The 90% Effective Dose of Taiglididine for Inhibiting Laryngeal Mask Insertion Response in Elderly Patients
Research Objective	To investigate the 90% effective dose (ED90) of taiglididine for inhibiting laryngeal mask insertion response in elderly patients
Research Design	Non-randomized controlled trial with biased coin design up-down method (BCD-UDM)
Total Number of Cases	54 cases
Case Selection	Inclusion Criteria: (1) Aged 65-80 years old. (2) ASA physical status I-III. (3) BMI between 18-30 kg/m² (including critical values). (4) Mallampati class I or II, mouth opening >2.5 cm. (5) No abnormal airway or head/neck conditions. (6) No risk of reflux or aspiration (e.g., full stomach, obesity, gastrointestinal obstruction). (7) Expected surgery duration <180 min. (8) Scheduled for urological surgery requiring general anesthesia and laryngeal mask insertion. (9) Voluntary participation with signed informed consent.
	Exclusion Criteria: (1) Baseline measurements: Severe hypertension (SBP >160 mmHg or DBP >100 mmHg), heart rate <60 bpm or >100 bpm. (2) History of long-term alcohol, sedative, or analgesic use; allergy to any study drugs. (3) Severe dysfunction of vital organs (heart, lung, liver, kidney, nervous system), neuromuscular diseases, hyperthyroidism, obstructive sleep apnea syndrome. (4) History of mental disorders or cognitive impairment severe

	enough to hinder understanding or cooperation with the study. (5) Preoperative administration of sedative-hypnotics (including benzodiazepines and barbiturates). (6) Upper respiratory tract infection within 1 month before surgery. (7) Participation in other clinical studies within the past 3 months. (8)Other conditions deemed unsuitable for the trial by the investigator.
Treatment Protocol	The first patient receives an intravenous injection of 1 mg taiglididine for anesthesia induction, followed by 1-2 mg/kg propofol. When the patient's bispectral index (BIS) drops below 60, eyelash reflex disappears, and MOAA/S score is 0, intravenous rocuronium 0.6 mg/kg is given, and a laryngeal mask is inserted by a senior anesthesiologist using a unified method 1 min later. From the second patient onward, the taiglididine dose is dynamically adjusted based on the previous patient's response to laryngeal mask insertion using BCD-UDM: if the previous patient shows a positive insertion response (positive response or MOAA/S ≥2 within 2 min after induction), the next patient's dose increases by 0.1 mg; if negative, a random number (1-95) generated by computer determines the dose: doses remain unchanged when the number is 6-95 (89% probability) and decrease by 0.1 mg when the number is 1-5 (11% probability). A collaborator not involved in result evaluation provides a sealed envelope with the taiglididine dose based on the random number.
Efficacy Evaluation	Efficacy indicators (primary and secondary): 1. Primary indicator: Occurrence of laryngeal mask insertion response. 2. Secondary indicators: (1) Number of adverse events within 5 min after induction and insertion, including blood pressure elevation (SBP/DBP >20% baseline), hypotension (SBP/DBP <20% baseline or <85/50 mmHg), bradycardia (HR <50 bpm), tachycardia (HR >100 bpm), hypoxemia (SpO2 <92%), injection pain. (2) HR, SpO2, SBP, DBP, MAP, and BIS at 1 min before induction (T1), 1 min after induction (T2), 1 min after insertion (T3), and 5 min after insertion (T4); maximum values of HR,

	SpO2, SBP, DBP, MAP, BIS within 5 min after insertion (T5). (3) Successful first-time laryngeal mask insertion rate. (4) Induction time (from drug administration to MOAA/S ≤1), surgery time, recovery time (from propofol discontinuation to obeying commands to open eyes), extubation time (from surgery end to extubation), laryngeal mask insertion time (from passing teeth to capnogram appearance). (5) Incidence of adverse events within 15 min after surgery: pain, dizziness, headache, nausea/vomiting, sore throat, shivering, coughing, agitation, hoarseness and intraoperative awareness. (6) Vasoactive agent dosage, propofol rescue dosage for positive insertion response, propofol induction/maintenance dosage, muscle relaxant induction/rescue dosageSafety. indicators:Vital signs: Pulse, blood pressure, body temperature, respiratory rate, SpO2.
Statistical Methods	According to statistical requirements, at least 45 valid patients are needed to complete the trial, with an estimated total sample size of 52±2. Data analysis uses SPSS 25.0: normally distributed quantitative data are expressed as mean±SD with independent samples t-test; non-normally distributed data as M (Q1, Q3) with Mann-Whitney U test; categorical data as frequency/ratio with chi-square test. R software calculates ED90 via probit regression and 95% confidence interval via bootstrap method.

Ⅰ. Research Background

In China, the population aged 60+ accounted for 18.9% in 2021, and is expected to reach 30% by 2035. With aging, more elderly patients require surgery. Aging leads to physiological decline, comorbidities, reduced tolerance to surgery/anesthesia, and perioperative hemodynamic instability, making anesthesia selection crucial. Urological diseases are common in the elderly, often requiring short-duration surgeries with low stimulation but high requirements for recovery quality. Anesthesiologists must consider age, comorbidities, surgery duration, and blood loss to minimize physiological interference.

Laryngeal masks (LMs), widely used in short surgeries, are supraglottic airway tools between face masks and endotracheal tubes, causing less throat/trachea irritation and stable hemodynamics during insertion. Studies show LMs are superior to endotracheal intubation in elderly urological surgery, with more stable hemodynamics and fewer postoperative complications (cough, sore throat, hoarseness).

Propofol is the preferred anesthetic for LM insertion, effectively inhibiting airway reflexes and relaxing the mandible, but low doses may cause cough/laryngospasm, while high doses affect circulation/respiration, especially in the elderly. Combining propofol with opioids reduces propofol use but increases respiratory depression. Taiglididine, a G protein-biased μ-opioid receptor agonist developed by Hengrui Pharmaceuticals, selectively activates μ receptors (24× more selective than morphine). It has equivalent analgesia to morphine but fewer adverse effects (e.g., respiratory depression, nausea) due to reduced β-arrestin signaling. Taiglididine takes effect in 5 min, peaks at 10 min, has a half-life of ~6 h, and requires no dosage adjustment for renal/moderate hepatic impairment.

Currently, the dose-response relationship of taiglididine for inhibiting LM insertion response is unclear. This study evaluates its safety/efficacy and uses BCD-UDM to analyze ED90, aiming to guide clinical application.

Ⅱ. Research Objectives

1.Primary Objective:

To investigate the ED90 of taiglididine for inhibiting laryngeal mask insertion response in elderly patients.

2.Secondary Objectives:

To determine the ED90 and 95% confidence interval, perioperative adverse events, dynamic changes in vital signs during LM insertion, occurrence of intraoperative awareness, and extreme conditions.

Ⅲ. Research Design, Principles

(1) Type: Non-randomized controlled trial with BCD-UDM.

(2) Blinding: Patients, anesthesiologists, and nurses evaluating results are blinded.

(3) Sample size: At least 45 valid patients are required based on previous studies.

Ⅳ. Case Selection

1.Inclusion Criteria:

(1) Aged 65-80 years old.

(2) ASA physical status I-III.

(3) BMI between 18-30 kg/m² (including critical values).

(4) Mallampati class I or II, mouth opening >2.5 cm.

(5) No abnormal airway or head/neck conditions.

(6) No risk of reflux or aspiration (e.g., full stomach, obesity, gastrointestinal obstruction).

(7) Expected surgery duration <180 min.

(8) Scheduled for urological surgery requiring general anesthesia and laryngeal mask insertion.

(9) Voluntary participation with signed informed consent.

2.Exclusion Criteria:

(1) Baseline measurements: Severe hypertension (SBP >160 mmHg or DBP >100 mmHg), heart rate <60 bpm or >100 bpm.

(2) History of long-term alcohol, sedative, or analgesic use; allergy to any study drugs.

(3) Severe dysfunction of vital organs (heart, lung, liver, kidney, nervous system), neuromuscular diseases, hyperthyroidism, obstructive sleep apnea syndrome.

(4) History of mental disorders or cognitive impairment severe enough to hinder understanding or cooperation with the study.

(5) Preoperative administration of sedative-hypnotics (including benzodiazepines and barbiturates).

(6) Upper respiratory tract infection within 1 month before surgery.

(7) Participation in other clinical studies within the past 3 months.

(8)Other conditions deemed unsuitable for the trial by the investigator.

3.Withdrawal Criteria:

(1)Failed LM insertion after 3 attempts or insertion time >3 min.

(2)HR ≤50 bpm or MAP ≤50 mmHg during induction.

(3)Unanticipated difficult airway or severe adverse events (e.g., allergy).

(4)Adverse events/laboratory abnormalities where continued participation is deemed high-risk.

(5)Other conditions precluding continued participation.

Ⅴ. Research Methods and Technical Route

1.Study Drugs:

(1) Propofol emulsion injection (20 ml:0.2 g, H20223914, Jiangsu Yingke Biopharmaceuticals) .

(2) Taiglididine (1 ml:1 mg, H20240005, Jiangsu Hengrui Medicine) .

(3) Rocuronium (5 ml:50 mg, H20213778, Hangzhou Hongyou Pharmaceutical) .

2.Treatment Protocol:

(1) Pre-anesthesia Preparation

Patients are visited before anesthesia. Patients are routinely fasted for 8 hours and no fluids for 4 hours before surgery. There is no routine preoperative medication. After the patient enters the operating room and is placed in the supine position, non-invasive blood pressure (NIBP) of the right upper arm is continuously measured three times

within the first 10 minutes, and the average of these three measurements is determined as the baseline blood pressure. Meanwhile, routine monitoring is carried out. During the induction period, vital signs are monitored once per minute, and during the maintenance period, they are monitored once every 5 minutes, including electrocardiogram (ECG), heart rate (HR), pulse oximetry (SpO_2), and bispectral index (BIS). The baseline blood pressure and heart rate are recorded. After the nursing staff establishes a peripheral intravenous access in the upper limb, lactated Ringer's solution is infused at a rate of 2 mL/kg/h. Radial artery puncture and cannulation are performed under local anesthesia to monitor invasive blood pressure.

(2) Anesthesia Induction

After preoxygenation with a face mask (6 L/min) for 3 minutes, 1 mg of Tegaserod is injected intravenously. After 120 seconds, 1-2 mg/kg of propofol injection (> 30 seconds) is administered intravenously. When 2 ml of propofol is injected, the patient is asked if there is any injection pain. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score and corneal reflex are measured at 30-second intervals. When the patient's bispectral index (BIS) is below 60, there is no corneal reflex, and the MOAA/S score is 0, 0.6 mg/kg of rocuronium bromide is injected intravenously. After 1 minutes, a senior anesthesiologist inserts a laryngeal mask airway (LMA) according to a unified method (the LMA is selected based on the patient's weight: size 3 for 30-50 kg, size 4 for 50-70 kg, and size 5 for 70-100 kg. The tip and sides of the LMA are fully lubricated with paraffin cotton balls). Successful insertion is confirmed by bilateral chest wall movement, no air leak after LMA insertion, end-tidal carbon dioxide waveform and value, and auscultation. Another anesthesiologist, who is unaware of the drug dosage, judges and records whether there is an LMA insertion reaction. If the patient has movement during LMA insertion, twitching at the corner of the mouth, coughing, frowning, tearing, laryngospasm, BIS not decreasing to below 60, an increase in heart rate or blood pressure of more than 20% of the baseline value within 2 minutes after LMA insertion, tachycardia (heart rate >120 beats per minute), or hypertension (systolic blood pressure >180 mmHg), and one of these occurs, it is determined as a positive LMA insertion reaction; otherwise, it is negative. If the patient has an MOAA/S score of $\geqslant 2$ within 2 minutes after induction or a positive LMA insertion reaction, 0.5-1.0 mg/kg of propofol is injected as a rescue drug, and then LMA insertion is attempted again after 60 seconds. A maximum of three LMA insertions are allowed. If there are more than three LMA insertions or unexpected difficult airway occurs, tracheal intubation is required. If transient changes in blood pressure and heart rate occur during induction, no special treatment is needed; otherwise, vasopressors such as atropine or ephedrine can be chosen to maintain hemodynamic stability. All patients are given 5 mg of dexamethasone and 12.5 mg of dolasetron after induction to prevent vomiting. The number of successful first-attempt LMA insertions is recorded. LMA insertion time. The number of adverse reactions within 5 minutes after induction and LMA insertion. Heart rate (HR), SpO_2, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and BIS at 1 minute before induction (T1), 1 minute after induction (T2), 1 minute after LMA insertion (T3), and 5 minutes after LMA insertion (T4). Record the highest HR, SpO_2, SBP, DBP, MAP, and BIS at T5 (within 5 minutes after

LMA insertion). The dose of Tegaserod for the next patient is determined by a senior anesthesiologist opening an opaque envelope. The subjects, the anesthesiologist who evaluates the results, and the nurse remain blinded. This process continues until the end of the trial.

(3) Anesthesia Maintenance

During the operation, remifentanil is continuously infused at 0.1 - 0.25 μg/kg/min, propofol at 4 - 10 mg/kg/h, and 0.5% - 1% sevoflurane is inhaled to maintain the BIS value between 40 and 60. A warming air blanket is used to keep the body temperature above 36℃. If spontaneous breathing occurs during the operation, 10 mg of rocuronium bromide is given to the patient again.

(4) Intraoperative Regulation

1) Maintain blood pressure within 20% of the baseline value. If systolic blood pressure (SBP) or diastolic blood pressure (DBP) increases by more than 20% of the baseline, first adjust the depth of anesthesia and the infusion rate. If it still cannot be maintained at the target level, urapidil can be given at 0.2 - 0.5 mg/kg. If SBP/DBP decreases by more than 20% of the baseline or blood pressure is below 85/50 mmHg, first adjust the depth of anesthesia and the infusion rate. If it still cannot be maintained at the target level, norepinephrine 4 - 12 μg or ephedrine 5 - 10 mg can be given.

2) If heart rate (HR) is less than 50 beats per minute, atropine 0.5 mg is given. If HR is greater than 100 beats per minute, esmolol 10 mg is given.

3) During the operation, the inhaled oxygen concentration is adjusted to 60%, with an oxygen flow rate of 2 L/min, tidal volume of 6 - 8 ml/kg, respiratory rate of 12 - 16 breaths per minute, and an inspiration-to-expiration ratio of 1:2. The end-tidal carbon dioxide concentration is maintained between 35 - 45 mmHg by adjusting the tidal volume or respiratory rate.

(5) Anesthesia Emergence

After the operation, patients are transferred to the post-anesthesia care unit (PACU). The laryngeal mask airway (LMA) is removed after the patient's consciousness, circulation, respiration, cough and swallowing reflexes, and muscle strength are fully recovered. Patients can leave the PACU when the Steward score is $\geqslant 4$ and vital signs are stable after emergence. Record the incidence of adverse reactions such as pain, dizziness, headache, nausea and vomiting, sore throat, chills, coughing, agitation, and hoarseness within 15 minutes after surgery, as well as any recall of intraoperative events. Record induction time, surgical time, emergence time, extubation time, and LMA insertion time. Record the dosage of vasopressors, the additional dose of propofol in patients with positive LMA insertion reactions, the induction dose of propofol, the maintenance dose of propofol, the induction dose of muscle relaxant, and the additional dose of muscle relaxant.

VI. Efficacy Evaluation Criteria

1.Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale:

Grade	Description
5	Fully awake, normal response to normal voice
4	Sluggish response to normal voice
3	Response to repeated loud voice
2	Response to mild stimulation/shaking
1	Response to trapezius squeeze (voluntary/reflective withdrawal)
0	No response to painful stimulation (trapezius squeeze)

2.Steward Recovery Score:

Category	Score	Description
Alertness	2	Fully awake
	1	Responds to stimulation
	0	No response to stimulation
Airway patency	2	Coughs on command
	1	Maintains airway without support
	0	Airway requires support
Motor activity	2	Voluntary movement
	1	Involuntary movement

	0	No movement

3.Mallampati Classification:

Class I: Uvula, faucial pillars, soft palate visible.

Class II: Faucial pillars, soft palate visible.

Class III: Soft palate only visible.

Class IV: Hard palate only visible.

VII. Quality Control and Assurance

1.Strict adherence to the protocol.

2.Accurate result recording.

3.Regular calibration of monitoring equipment.

4.Rigorous data analysis by statisticians and investigators.

VIII. Data Safety Monitoring

1.Data safety monitoring plans based on risk levels.

2.Detailed recording and follow-up of adverse events, timely reporting of serious/unexpected events to the Ethics Committee and regulatory authorities.

3.Periodic review of adverse events by the principal investigator.

4.Emergency unblinding for subject safety in double-blind trials.

5.Independent data monitors for studies with risks above the minimum.

Informed Consent Form

Protocol Name: The 90% Effective Dose of Taiglididine for Inhibiting Laryngeal Mask Insertion Response in Elderly Patients

Protocol Version: V1.0, Date: March 9, 2025

Informed Consent Version: V1.0, Date: March 9, 2025

Research Institution: Lianyungang First People's Hospital

Principal Investigator: Zhao Zhibin

You are invited to participate in a clinical study. This notice provides information to help you decide whether to join. Please read it carefully and ask the investigator any questions. Participation is voluntary, and the study has been reviewed by the institution's Ethics Committee.

1. Research Objective

With the accelerated aging population, surgical needs among elderly patients are increasing. Laryngeal masks, as safe and effective airway tools, play an important role in anesthesia management for elderly patients. This study aims to determine the effective dose of taiglididine for inhibiting laryngeal mask insertion response in elderly patients, providing more reliable data support for clinical anesthesia.

2. Research Process

If you agree to participate, you will receive anesthesia induction and laryngeal mask insertion by senior anesthesiologists. During the study, we will record your insertion response, vital signs, adverse events, and relevant data during surgery and anesthesia.

3. Possible Risks and Discomforts

Participation may involve risks, including drug allergy, blood pressure fluctuations, arrhythmia, etc. While we will take all measures to reduce risks, all adverse events cannot be completely avoided. Please inform the medical staff promptly if you experience any discomfort.

4. Expected Benefits

Participation may help optimize your anesthesia plan, reduce anesthesia-related adverse events, and improve surgical comfort and safety.

5. Privacy Protection

All information about you will be kept confidential. Your medical information will be used for research by the research team. Identifiable information will not be disclosed to others without your permission. Research records will be stored in locked cabinets for researcher access only. Regulatory authorities or Ethics Committee members may review your data as required

to ensure study compliance. Your personal information will not be disclosed in study publications.

6. Compensation

In case of study-related injury, you may receive free treatment and/or corresponding compensation.

7. Rights of Subjects and Researchers

- You may choose not to participate or withdraw at any time, and your medical care will not be affected.
- The researcher may terminate your participation if you need other treatments, fail to follow the protocol, suffer study-related injury, or for other reasons.
- You have the right to know study information and progress, and will be promptly notified of new safety information related to the study.
- For questions about the study or your rights, contact Wang Yunyan at 13477980772.

8. Obligations of Subjects

- Provide truthful medical history and current health status.
- Report any discomfort during the study.
- Avoid restricted medications/foods.
- Disclose participation in other studies.

For questions about your rights and health, contact the institution's Ethics Committee at 0518-85767557, contact person: Gao Shan.

Informed Consent Signature Page

I have read this informed consent form, had the opportunity to ask questions, and all questions have been answered. I understand participation is voluntary, and I may withdraw at any time without discrimination. I will receive a signed copy of this form.

Subject Name: _____

Subject Signature: _____

Date: _____ Year _____ Month _____ Day

I have accurately informed the subject of this document, who has read it carefully and had the opportunity to ask questions.

Researcher Name: _____

Researcher Signature: _____

Date: _____ Year _____ Month _____ Day

(Note: If the subject is illiterate, a witness signature is required; if the subject is incompetent, a legal representative's signature is required.)