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Effect of remimazolam besylate versus propofol on haemodynamic profiles in patients undergoing thyroid surgery with recurrent laryngeal nerve monitoring: a protocol for a randomised controlled trial

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ABSTRACT

Introduction Thyroid surgery with intraoperative nerve monitoring under total intravenous anaesthesia often requires deeper sedation due to limitations or lack of neuromuscular blocking agents, usually resulting in haemodynamic instability. Remimazolam, a newly developed sedative, is being studied for its effect on the haemodynamic profile of patients undergoing this procedure and compared with propofol.

Methods and analysis This will be a single-centre, single-blind, randomised, controlled trial in American Society of Anesthesiologists I-III patients between the ages of 18 and 65 who require recurrent laryngeal nerve monitoring for thyroid surgery. Patients will be randomised 1:1 to either remimazolam besylate or propofol, with 142 cases in each group according to a randomised, computer-generated cohort. The primary outcome is the occurrence of hypotension from induction of anaesthesia to full recovery. Secondary outcomes include the administration of vasoactive agents, the number of hypotension or hypertension episodes, the cumulative duration of hypotension or hypertension, the dose of intraoperative rescue sedation and analgesia, the time to extubation and awakening and the incidence of adverse events.

Ethics and dissemination Ethical approval for this study was obtained from the Medical Ethics Committee of the Affiliated Cancer Hospital and Institute of Guangzhou Medical University (2023–2024). The study protocol was modified according to the reviewers' comments, and the revised version was approved by the Ethics Committee (2024 Research Ethics Amendment No. 3). On completion of the study, we will commit to ensuring that the results are made available to the public, regardless of the outcome. This will include either publication in an appropriate journal or oral presentation at academic conferences.

Trial registration number ChiCTR2300076583.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The uniqueness of this investigator-initiated trial lies in its design, which will be specifically tailored for patients with nerve monitoring who require deeper sedation due to limitations in the administration of neuromuscular blocking agents.
⇒ It is a pragmatic study that will be conducted in a real-world setting under standardised anaesthetic management. In addition, the research team has extensive experience in haemodynamic profiling and other-related assessments.
⇒ This is not a double-blind study as the different appearance of propofol and remimazolam besylate makes it impractical to blind the attending anaesthetists.
⇒ This is a single-centre trial involving only thyroid surgery, so the generalisability of the results may not be extrapolated.

INTRODUCTION

Thyroid cancer is the most common malignant tumour of the endocrine system, and the main methods of treatment include surgical resection, radiotherapy, endocrine regulation and targeted therapies.[1 2] Surgical resection is the most common method, but it carries a potential risk of damaging the recurrent laryngeal nerve (RLN), which can lead to complications such as vocal cord paralysis and difficulty speaking or swallowing.[3] The introduction of intraoperative nerve monitoring (IONM) can improve the accuracy of nerve identification and reduce the risk of nerve injury, making it a significant advancement in thyroid surgery.[4 5] Quantitative neurophysiological assessment of the RLN is based on recorded evoked potentials from the laryngeal muscles.[6] However, anaesthesia during surgery may be a potential factor that reduces or eliminates these potentials and decreases sensitivity to impending neural injury. Because action potentials are validated by muscle contraction, neuromuscular

blocking agents (NMBAs) can diminish the electromyographic (EMG) response and potentially confound the interpretation of IONM results. Therefore, it is essential to perform IONM without the administration of NMBAs or drugs with muscle relaxant properties, or drugs that prolong the effects of NMBAs. It is recommended that only a single dose of NMBA be administered during induction of general anaesthesia, and continuous administration during maintenance of anaesthesia is generally avoided.[7 8] In addition, it is not advisable to use inhaled anaesthetics to maintain anaesthesia in patients requiring IONM, as reports have shown that inhaled anaesthetics not only significantly enhance the efficacy of NMBAs, but also significantly prolong recovery time compared with total intravenous anaesthesia (TIVA).[9 10] Therefore, current routine practice in IONM is to use TIVA as the primary anaesthetic regimen and generally avoid continuous infusion of NMBAs, as this regimen has minimal impact on EMG responses.

Propofol is the most commonly used sedative due to its favourable properties such as rapid onset and predictable recovery time.[11 12] However, it has a negative impact on circulation and often requires vasopressor support, which has been identified as a significant factor contributing to adverse outcomes such as myocardial injury, acute kidney injury and death during and after surgery.[13–16] Although some literature suggests that propofol is a preferred option for maintaining a stable and consistent evoked potential signal during procedures requiring IONM, it is often necessary to administer relatively higher doses of propofol to achieve a deeper level of anaesthesia to reduce adverse events (AEs) (such as swallowing and involuntary body movements) resulting from the absence of NMBAs.[8 17] Receiving a large volume of propofol by rapid intravenous infusion increases the risk of intraoperative hypotension and often requires vasopressor support. A systematic review summarised that organ damage can occur when mean arterial pressure (MAP) falls below 80 mm Hg for ≥10 min, and this risk increases as blood pressure falls further.[15] Previous studies have shown that approximately 30% of patients undergoing gastrointestinal endoscopy with propofol sedation experience hypotension, and that higher doses and longer duration of propofol administration are associated with more sustained and significant hypotension.[18] Therefore, there is a growing desire to find alternative sedatives that can provide sufficient depth of anaesthesia with stable haemodynamics to ensure patient safety during this surgical procedure.

Remimazolam, a novel ultra-short-acting benzodiazepine, produces sedative and hypnotic effects by interacting with γ-aminobutyric acid type A receptors. Its rapid metabolism by tissue esterases to inactive products gives the advantage of faster induction and recovery, improved quality of sedation and better controllability.[19–21] Prolonged infusion or administration of large volumes does not lead to accumulation of remimazolam or its metabolite, making it an appropriate agent for the maintenance of anaesthesia compared with midazolam.[22 23] In addition, the sedative effects of remimazolam could be easily antagonised by flumazenil, a capability not offered by propofol, which improves controllability.[24] Several studies have shown that remimazolam is comparable to propofol in sedation and quality of recovery, and significantly reduces the incidence of hypotension and injection pain.[13 25 26] Case reports suggest that remimazolam may be a viable choice for anaesthesia in surgery with neurophysiological monitoring because of its minimal effect on evoked potentials.[27] Given these advantages, remimazolam appears to be more suitable for patients undergoing thyroid surgery with IONM.

Although remimazolam is comparable or superior to propofol for maintaining light to moderate sedation, there is limited evidence that it is effective for deep sedation. The aim of this study is to determine whether remimazolam combined with an opioid for TIVA is safe and effective in thyroid surgery using IONM, and whether remimazolam can achieve sedation comparable to the classical intravenous anaesthetic propofol in procedures requiring relatively deep anaesthesia. More importantly, haemodynamic stability, quality of postoperative recovery and AEs will be evaluated after the administration of remimazolam compared with propofol. This comparative analysis helps to further optimise the anaesthesia protocol for TIVA and provides a clinical reference for the prevention of haemodynamic fluctuations during surgery with IONM.

METHODS

Study setting and design

This investigator-initiated, single-centre, single-blind, randomised controlled trial will be conducted at Affiliated Cancer Hospital and Institute of Guangzhou Medical University (Guangzhou, Guangdong, China), with YY as the principal investigator (PI). Study activities are expected to start in September 2024 and be completed in September 2027. The study design follows the guidelines for standard protocol items in randomised trials. The overall schedule is outlined in table 1, and the study flow chart is shown in figure 1. The current protocol is the second version, revised according to the reviewers' comments.

Participant recruitment

Inclusion criteria

1. Aged 18–65 years old.
2. Both sexes.
3. American Society of Anesthesiologists (ASA) physical status classification I-III.
4. Body mass index (BMI)≥18 kg/m^2 and ≤30 kg/m^2.
5. Patients undergoing thyroid surgery require IONM.
6. Expected duration of surgery to be 4 hours or less.
7. Participation in the study is voluntary and requires a signed informed consent.

Table 1 Schedule of enrolment, interventions and assessments for the trial

Study period												
	Enrolment	Allocation	Postallocation									Follow-up
Time point*	1 day before surgery (T_0)	Surgery day	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}	1 day after surgery (F_1)
Enrolment													
Eligibility screen	x												
Informed consent	x												
Allocation		x											
Interventions													
Remimazolam			—	—	—	—	—	—	—	—			
Propofol			—	—	—	—	—	—	—	—			
Assessments													
Baseline variables	x	x											
Haemodynamic variables	x		x	x	x	x	x	x	x	x	x	x	
Vasoactive drugs consumption			—	—	—	—	—	—	—	—	—	—	—
The number of hypotension or hypertension episodes			—	—	—	—	—	—	—	—	—	—	—
The cumulative duration of hypotension or hypertension			—	—	—	—	—	—	—	—	—	—	—
Rescue drug consumption			—	—	—	—	—	—	—	—			
Duration of extubation and awakening										—	—	—	
Adverse event†			—	—	—	—	—	—	—	—	—	—	—

*T_0: at ward (as baseline), T_1: at intubation, T_2: 15 min after intubation, T_3: the beginning of surgery, $T_{4\text{-}7}$: 15 min, 30 min, 60 min, 90 min after the beginning of surgery, T_8: the end of surgery, T_9: at extubation, T_{10}: 10 min after extubation.
†Including hallucinations, agitation, delirium, hepatic and renal dysfunction, haematuria, nausea and vomiting, and so on.

Exclusion criteria

1. Participated in other clinical trials within the past 3 months.
2. Patients undergoing other surgery at the same time, emergency surgery and subsequent admission to the intensive care unit for postoperative care.
3. Patients with suspected allergy to remimazolam, propofol or any of the drugs used in this study (eg, remifentanil, rocuronium, sufentanil, ciprofol).
4. Severe systemic cardiovascular disease, such as congestive heart failure, frequent premature ventricular contractions, uncontrolled hypertension/hypotension.
5. Severe respiratory disease.
6. End-stage liver failure or kidney disease requiring dialysis.
7. History of dementia, mental illness or other central nervous system disorders, and current use of sedatives, or antidepressants.
8. Researcher does not believe it is appropriate to participate in this clinical trial.

Participants' consent

All patients scheduled for thyroid surgery will be screened for eligibility at the preoperative evaluation clinic on the day before surgery (or on Friday for those scheduled for surgery on the following Monday). Eligible patients will be notified by the study team coordinator. All patients will be given information about the objectives, procedures, potential benefits and risks of the study, as well as instructions on how to manage any risks, so that they can make a voluntary decision to participate. If they wish to enrol, patients or their next of kin will sign the informed consent form in triplicate (online supplemental file 1).

Randomisation and blinding

Prior to the start of the study, a randomisation code will be generated in a block size of four on the website http://www.Randomization.com and securely stored in a sealed opaque envelope by the nurse anaesthetist who will allocate patients according to the randomisation schedule. After obtaining written informed consent, the nurse

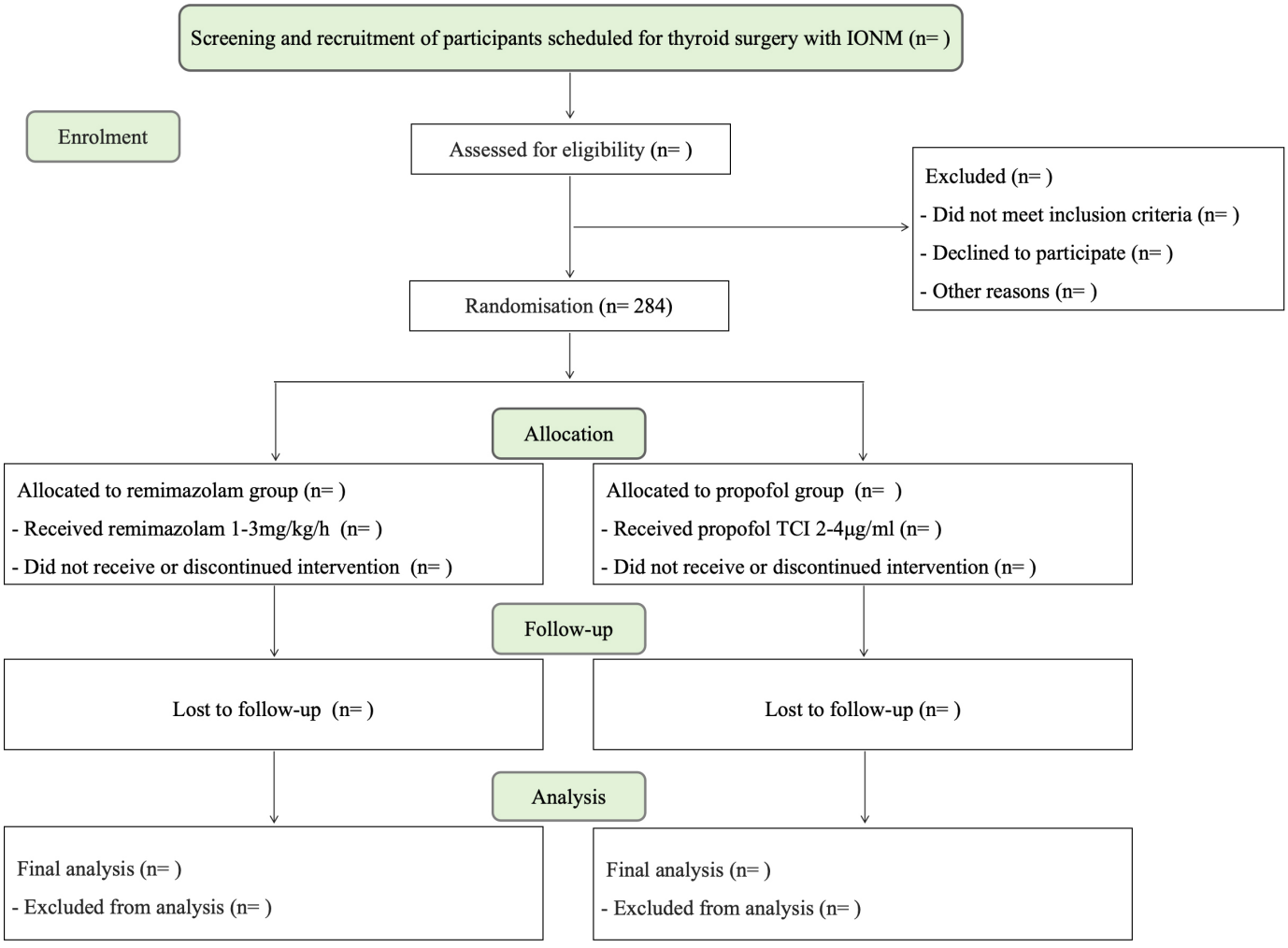

Figure 1 Study flow chart. IONM, intraoperative nerve monitoring; TCI, target-controlled infusion.

anaesthetist will assign patients to either the propofol group (P group) or the remimazolam group (R group) in a 1:1 ratio according to the randomisation schedule before entering the operating room. Study medications will be dispensed and labelled by a pharmacist. Both the nurse anaesthetist and the pharmacist will not be involved in the research or follow-up. The PI and data collecting clinicians will not be allowed to unmask the randomisation protocol until after recruitment and database closure. The syringes (50 mL) labelled 'study medication' and the infusion regimen formulated by the pharmacist according to the randomisation will be distributed to the attending anaesthetists responsible for anaesthesia management when the research team notifies the central pharmacy that a patient is about to undergo surgery. Patients, investigators responsible for data collection, and statisticians will remain blinded to the randomisation until the final analysis is completed. As the two drugs have different appearances (propofol is milky white and remimazolam besylate is transparent), the attending anaesthetists cannot be blinded. The PI will unmask the blinding in a medical emergency, including intraoperative deterioration of the patient's condition or the occurrence of a serious AE (SAE).

Standard anaesthetic management

Induction of general anaesthesia

After randomisation to either the propofol group or remimazolam group, patients will be admitted to the operating room on the day of surgery. During general anaesthesia, vital signs such as heart rate (HR), non-invasive blood pressure (BP), pulse oximetry (SpO_2), bispectral index (BIS, a processed electroencephalogram parameter) and urine output will be routinely monitored. After 5 min of preoxygenation with 100% oxygen via a face mask, ciprofol (0.2–0.4 mg/kg), sufentanil (0.2–0.4 μg/kg) and rocuronium (0.3 mg/kg) will be administered for anaesthesia induction. To minimise the potential impact on the research results, we will use the new intravenous anaesthetic ciprofol instead of the routinely used propofol for induction of anaesthesia. Ciprofol is structurally modified from propofol, which has improved efficacy such as less influence on haemodynamics, a lower incidence of respiratory depression and injection pain.[28] It was approved in 2020 for use in inducing, maintaining sedation and providing general anaesthesia.[29]

A Medtronic Nerve Integrity Monitor (NIM) Standard Reinforced EMG Endotracheal tube (internal diameter 6.0 and 7.0 mm) will be selected for both female and male

patients. Normal saline is usually recommended to lubricate the surface of the tube, while local anaesthetic gels or creams to lubricate the tube or topical anaesthetic sprays to the vocal cords are not recommended. It is advisable to administer penehyclidine hydrochloride intravenously 30 min prior to tracheal intubation to reduce the risk of excessive secretions, which is one of the major factors interfering with EMG signal acquisition. A functional IONM system relies on the proper positioning of the EMG endotracheal tube with optimal surface electrode contact with the true vocal cords. Displacement of the tube can result in false negative or reduced EMG signals. In this study, the patient's neck will be routinely placed in full extension prior to induction of anaesthesia to prevent potential displacement of the tube due to surgical repositioning. We will use a video laryngoscope to assist with tube insertion to ensure optimal placement of the surface electrode for proper contact with the vocal cords and efficient acquisition of IONM signals.[30] After tracheal intubation, the tube will be connected to the anaesthesia machine and pressure-controlled ventilation with volume-guaranteed ventilator mode will be applied for mechanical ventilation. This involves using a tidal volume of 6–8 mL/kg predicted body weight and adjusting the respiratory rate to maintain SpO2 above 98% and end-tidal carbon dioxide ($EtCO_2$) between 35 and 45 mm Hg. Then, the channel leads from the EMG endotracheal tube electrodes will be connected to the monitoring system (NIM-Response V.3.0, Medtronic). The NIM-Response stimulus settings will be as follows: time window is set to 50 ms, amplitude scale is set to 0.2 mV/division with a duration of 100 µs and a frequency of 4 Hz. The threshold for event capture will be set at 100 µV. The tube will be securely taped once it is properly placed in the trachea and the electrode integrity check is successful.

Maintenance of general anaesthesia

We will use a target-controlled infusion (TCI) of propofol or a constant-rate infusion of remimazolam to maintain sedation, aiming for a BIS value between 40 and 60. In addition, analgesia will be maintained with a TCI of remifentanil. After a single dose of rocuronium to facilitate intubation, no further doses will be administered during surgery. At the time of incision and 30 min before skin closure, all participants will receive sufentanil (0.1–0.2 µg/kg) and flurbiprofen axetil (50 mg) for hyperalgesia prophylaxis, respectively. Vasoactive drugs will be administered according to the preference of the attending anaesthetist.

Recovery from general anaesthesia

At the end of the surgery, the patient will be transferred to the post-anaesthesia care unit and the tube will be removed as soon as the patient is able to respond to verbal commands. Reversal of NMBAs will not usually be necessary after surgery, because they will be not given continuously during surgery. However, in cases of the very short duration of surgery or other specific factors identified by the anaesthetist, neostigmine (1–2 mg) and atropine (0.5–1 mg) will be used for antagonism. We will use the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, a valid tool for measuring sedation, to assess the patient's level of sedation. After study drug discontinuation, MOAA/S scores will be assessed at 5 min intervals for a minimum of 40 min until three consecutive MOAA/S scores of 5 are achieved. If the patient does not awake within 30 min after discontinuation of remimazolam, and other potential causes such as residual NMBAs have been ruled out by the attending anaesthetist, and it is believed to be due to residual remimazolam, flumazenil 0.2 mg will be administered for reversal. Additional flumazenil at a dose of 0.2 mg will be repeated as deemed appropriate based on the patient's recovery status, with documentation of the total amount of flumazenil administered.

Postoperative follow-up

Regular postoperative follow-up will be performed at least 24 hours after the end of surgery. Data collected will include postoperative complications and laboratory test results (if rechecked) compared with preoperative data to assess the safety of the study drugs and to accurately document AEs.

Study drugs' administration

Remimazolam besylate (50 mg) will be diluted with 50 mL of normal saline to achieve a concentration of 1 mg/mL; remifentanil (1 mg) will be diluted with 50 mL of normal saline to achieve a concentration of 20 µg/mL; and propofol will be administered undiluted in a volume of 50 mL. All drugs will be packaged in identical 50 mL syringes labelled with 'study medication'. After drug induction, the initial dose of propofol (TCI 2 µg/mL), remimazolam (1 mg/kg/hour) and remifentanil (TCI 2 ng/mL) will be administered before endotracheal tube insertion and the maintenance dose will be infused until skin closure. Patients in the R group will receive a constant-rate infusion of remimazolam at 1–3 mg/kg/hour, while patients in the P group will receive a Schnider model TCI of propofol at a plasma concentration (Cp) of 2–4 µg/mL, both with the goal of maintaining a BIS value between 40 and 60. Analgesic maintenance for both groups will be achieved with a TCI of remifentanil based on the Minto model with a Cp of 2–5 ng/mL. The specific study drug administration protocol is shown in table 2.

Rescue therapy for experimental group

If the BIS value cannot be maintained ≤60 during surgery even with the maximum maintenance dose of remimazolam at 3 mg/kg/h or a TCI of propofol with a Cp greater than 4 µg/mL for more than 5 min, an additional intravenous dose of ciprofol (not to exceed 0.2 mg/kg) will be administered as a rescue medication. The additional administration of ciprofol will also be used in patients with involuntary body movements and swallowing that interfere with surgical procedures. Sufentanil

Table 2 Detailed interventional protocols in the remimazolam-based TIVA group and propofol-based TIVA group

Remimazolam-based TIVA	Propofol-based TIVA
Pre-anaesthetic induction	
► Penehyclidine hydrochloride 0.5–1 mg. ► Position the head and neck properly. ► Prepare the video laryngoscope. ► Normal saline is usually recommended to lubricate the surface of the tube, while local anaesthetic gels or creams to lubricate the tube or topical anaesthetic sprays to the vocal cords are not recommended.	
Anaesthesia induction	
► Ciprofol 0.2–0.4 mg/kg	
► Sufentanil 0.2–0.4 µg/kg	
► Rocuronium 0.3 mg/kg	
Anaesthesia maintenance	
► Remimazolam besylate 1–3 mg/kg/hour	► Propofol TCI 2–4 µg/mL
► Remifentanil TCI 2–5 ng/mL	► Remifentanil TCI 2–5 µg/mL
► Sufentanil 0.1–0.2 µg/kg before and after surgery	► Sufentanil 0.1–0.2 µg/kg before and after surgery
► Flurbiprofen axetil 50 mg before and after surgery	► Flurbiprofen axetil 50 mg before and after surgery
PACU	
► Flumazenil 0.2 mg (≤2 times)	
► Neostigmine 1 mg (≤2 times)	
Rescue therapy	
► Ciprofol ≤0.2 mg/kg (≤3 times)	
► Sufentanil 0.1 µg/kg (≤3 times)	
Vasoactive drugs	
► Atropine 0.3–1 mg	
► Esmolol 20–40 mg	
► Urapidil 12.5–25 mg	
► Norepinephrine 4–8 µg (≤3 times) followed by continuous infusion with 0.01–0.2 µg/kg/min when necessary	

EMG, electromyographic; PACU, post-anaesthesia care unit; TCI, target-controlled infusion; TIVA, total intravenous anaesthesia .

will be administered as a rescue medication at a dose of 0.1 µg/kg each time, with a maximum cumulative dose of 0.3 µg/kg, if the anaesthetist deems the analgesic effect to be inadequate under certain circumstances. If ciprofol is given more than three additional times, or if the cumulative additional dose of sufentanil exceeds 0.3 µg/kg, or if there is a need to modify the anaesthetic protocol for special reasons, such as the surgeon's request to add NMBAs, this patient will be excluded.

Relevant adverse events and corresponding management

Adverse haemodynamic fluctuations will be recorded and defined as hypertension, hypotension, tachycardia or bradycardia and treated according to standard protocols as appropriate. Hypertension will be recorded when MAP is ≥30% above preoperative baseline, and hypotension will be recorded when MAP is ≥30% below preoperative baseline. Tachycardia and bradycardia will be defined as HRs≥100 beats per minute (bpm) and ≤45 bpm, respectively. Standard management of haemodynamic fluctuations is shown in figure 2 and figure 3.

Anaesthetic-induced hypotension correlates with reduced systemic vascular resistance and negative inotropic impacts on the myocardium.[31] Norepinephrine, a potent α-adrenergic receptor agonist with comparatively modest β-adrenergic activity, not only produces marked vasoconstriction, but also significantly reduces bradycardia and better maintains cardiac output, making it a superior choice to phenylephrine. Therefore, we will choose norepinephrine to treat intraoperative hypotension.

Data collection and management

Study-relevant data from enrolled patients will be collected at three different time points (preoperative, intraoperative and postoperative) and documented on paper case report forms (CRFs). The data will then be transcribed into Microsoft Excel by two trained independent investigators blinded to the research intervention. The original data, such as paper CRFs, will be stored in a secure cabinet in the anaesthesia office and will be accessible only to authorised personnel. The data, entered into Microsoft Excel, will be password-protected and securely stored on a desktop computer located in a secure office.

The following data will be collected from patient interviews, the electronic medical record system and real-time clinical observations:

Preoperative data collection

1. Basic patient demographics, including age, sex, height, weight, BMI, HR, BP.
2. Laboratory tests (eg, complete blood count and serum biochemistry), ECG, chest X-ray.
3. Cardiac function evaluation: New York Heart Association classification, metabolic equivalents, the 12-lead ECG, as well as cardiological ultrasound, coronary angiography, biomarkers (eg, cardiac troponin T and I, B-type natriuretic peptide and N-terminal proBNP), if necessary.
4. ASA classification, comorbidities, medication history, smoking and alcohol history, allergy history.

Intraoperative data collection

1. Haemodynamic parameters (HR and BP), SpO_2 and BIS value.
2. Occurrence of hypertension and hypotension (see figure 2).
3. Number of hypotension or hypertension episodes requiring intervention.
4. Cumulative duration of hypotension or hypertension.
5. Episodes of tachycardia and bradycardia (see figure 3).

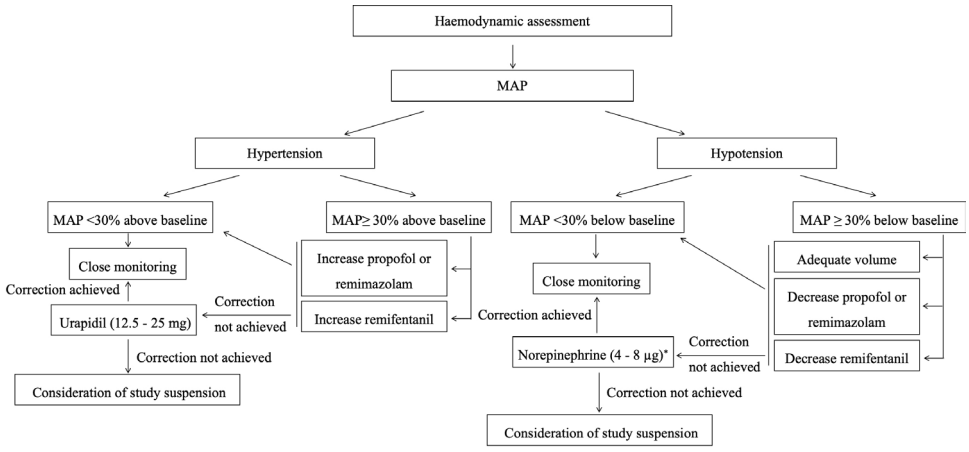

Figure 2 The definitions of hypertension/hypotension and corresponding medication rescue. *Followed by continuous infusion at 0.01–0.2 μg/kg/min as needed. MAP, mean arterial pressure.

6. Administration of vasoactive drugs, including atropine (mg), norepinephrine (μg), urapidil (mg), esmolol (mg) and others.
7. Total dose of anaesthetic agents, including remimazolam besylate (mg), propofol (mg), ciprofol (mg), remifentanil (μg), sufentanil (μg), rocuronium (mg).
8. Doses of other medicines (such as diuretics and glucocorticoids).
9. Duration of surgery and anaesthesia (min).
10. Blood loss, urine output and fluid and blood transfusion administration.
11. AEs during anaesthesia (eg, involuntary body movements, intraoperative awareness and other malignant arrhythmias).

Postoperative data collection

1. Time from end of anaesthesia to extubation and awakening (min), confirmed as the first of three consecutive MOAA/S scores of 5.
2. AEs (eg, nausea, vomiting, chills, delirium, dysphoria, anxiety, secondary sedation).
3. Flumazenil consumption (mg).
4. The dose of other medications (eg, urapidil, esmolol and others).
5. Postoperative complications.

The Data and Safety Monitoring Board (DSMB) will oversee the study process and data management and will ensure proper storage of the CRFs. The DSMB will consist of at least one experienced anaesthetist, one surgeon and one independent statistician who will be blinded to the study. On completion of the study, an independent statistician will review the data for final analysis according to the prespecified statistical plan.

Outcomes

Primary outcomes

The primary outcome is the occurrence of hypotension, defined as MAP≥30% below preoperative baseline, from induction of anaesthesia to full recovery.

Secondary outcomes

The main secondary outcome will be the administration of vasoactive agents, including the specific doses of different vasoactive agents given as single or continuous infusions and the total duration of administration,

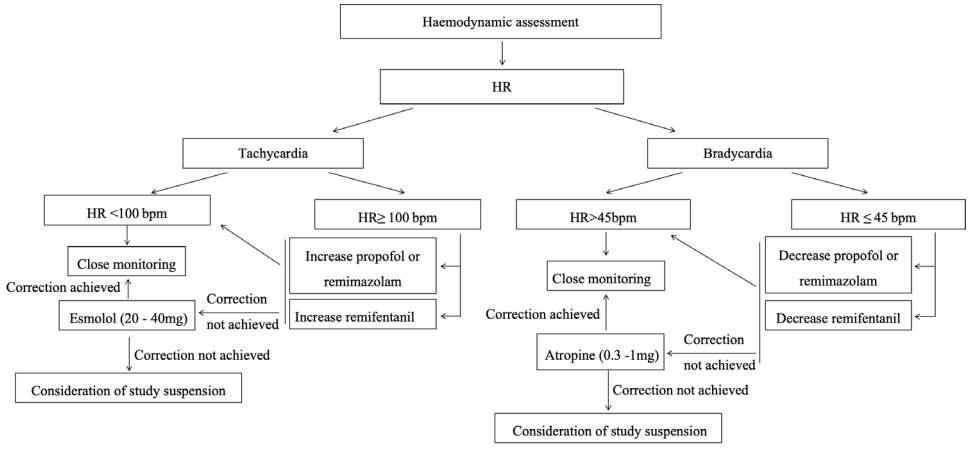

Figure 3 The definitions of tachycardia/bradycardia and corresponding medication rescue. bpm, beats per minute; HR, heart rate.

etc. Other prespecified secondary outcomes include the number of hypotension or hypertension episodes requiring intervention; the cumulative duration of hypotension or hypertension; the dosage of rescue medications (sedatives and analgesics) during surgery; the duration of extubation and awakening; incidence of AEs (such as hallucinations, agitation, delirium, hepatic and renal dysfunction, haematuria, nausea and vomiting).

Measurement of hypotension

We will record vital signs, including HR and BP, SpO2 and BIS value, on the monitor at 11 time points in each patient: at ward (T0, as baseline), at intubation (T1), 15 min after intubation (T2), the beginning of surgery (T3), 15 min (T4), 30 min (T5), 60 min (T6), 90 min (T7) after the beginning of surgery, the end of surgery (T8), at extubation (T9) and 10 min after extubation (T10). Based on the calculation of the relative threshold (MAP≥30% below preoperative baseline), we can determine if hypotension has occurred. In addition, specific regimens for the administration of vasoactive agents to maintain MAP fluctuations within 30% of baseline will be documented in detail.

Safety monitoring and adverse events

AEs refer to any unfavourable/unintended medical events experienced by patients, whether or not causally related to the study interventions. AEs will be monitored and documented in the CRF if they occur during the procedure. According to the comprehensive information in the product package inserts, potential AEs in this study include, but are not limited to, hypotension, hypertension, tachycardia, bradycardia, arrhythmia, prolongation of the QT interval on ECG and haematuria. However, because drug administration and dosing in both anaesthesia protocols are consistent with current clinical practice, we anticipate that SAEs will be rare. In the event of an SAE, the attending anaesthetist will discontinue study drug administration and will provide appropriate medical management. The PI will be responsible for collecting information on the cause, treatment and prognosis of AEs and for promptly reporting SAEs to the ethics committee.

Sample size calculation

The sample size is calculated using PASS V.15.0 for the primary outcome, the occurrence of hypotension during general anaesthesia. Based on previous studies and our recently completed data, we estimate the occurrence of hypotension to be 33% for TIVA with propofol and 18% for TIVA with remimazolam.[32 33] With 80% power and a two-sided significance level of 0.05, 258 patients (129 patients per arm) are required to detect differences. Due to a 10% dropout rate, a total of 284 patients will be enrolled in the study.

Statistical methods

The assumption of normality for continuous results will first be confirmed using the Kolmogorov-Smirnov test. The data will be presented as mean (SD), median (IQR) or frequency (proportion) according to the type and distribution of variables. For the primary outcome measure, we will use Pearson's χ^2 test or Fisher's exact test to compare the occurrence of hypotension between propofol and remimazolam patients. All other outcome measures in this study will be considered as secondary outcomes. The Mann-Whitney U test and Student's t-test will be used to compare continuous variables for secondary outcomes between propofol and remimazolam groups. Pearson's χ^2 test or Fisher's exact test will be used to compare the incidence of AEs. Effect sizes will be presented as relative risk (95% CI). For the incidence of binary dichotomous outcome variables, the mean or median difference (95% CI) for continuous variables and the CI for the median difference will be calculated using the Hodges-Lehmann calculator. When dealing with missing data using imputation methods, for continuous quantitative data, the mean or median can be used for imputation and for discrete quantitative data, the mode can be employed for imputation. The significance level for the comparison between propofol and remimazolam is set at α=0.05, with a 95% CI. Data analysis will be performed using IBM SPSS V.25.0 (IBM, Armonk, New York, USA), R statistical software V.4.4.1 (R Core Team, 2014) and GraphPad Prism V.8.0 (GraphPad Software, San Diego, California, USA).

Ethics and confidentiality

Ethical approval was obtained from the Medical Ethics Committee of the Affiliated Cancer Hospital and Institute of Guangzhou Medical University (2023–2024). The study protocol was modified according to the reviewers' suggestions, and the revised version was approved by the Medical Ethics Committee (2024 Research Ethics Amendment No. 3). The study has been registered in Chictr.org.cn and the information was updated on 27 August 2024. Individuals' personal information will be kept confidential unless authorised. In addition, each participant will receive a unique identity code, and their information will be securely protected. The CRF and Excel will be retained for at least 10 years.

Patient and public involvement

No patient or public representatives were involved in the design of this study.

Dissemination

On completion of the study, we will commit to ensuring that the results are made available to the public, regardless of the outcome. This will include either publication in an appropriate journal or oral presentation at academic meetings. Investigators who have contributed to the study for at least 4 months will be listed as coauthors, while those who have not will be acknowledged in the publication.

DISCUSSION

This is a prospective, single-centre, single-blind study to evaluate the efficacy and safety of remimazolam as an

anaesthetic for thyroid surgery with IONM. A total of 284 patients will be randomised to receive either propofol or remimazolam anaesthesia to determine whether remimazolam can achieve deep sedation with better haemodynamic stability than propofol.

IONM is a reliable method of detecting RLN injury during thyroid surgery, particularly for recurrent or invasive tumours,[34 35] but research into anaesthetic protocols for such surgery is scarce. TIVA with propofol and remifentanil is preferred to inhaled agents because of its minimal effect on neuromonitoring signals.[17] Propofol is effective for rapid sedation but can cause circulatory depression and hypotension.[36–38] Remimazolam has been reported to be more haemodynamically stable than propofol and can be rapidly reversed by flumazenil, improving the safety of its clinical use.[39 40] Research on remimazolam has mainly investigated its use in painless examinations[41–44] and induction of anaesthesia,[45 46] with limited studies in major surgery requiring deep sedation. This study will evaluate the effect of remimazolam on haemodynamics compared with propofol, with the expectation that remimazolam could replace propofol with less hypotension in thyroid surgery using IONM. The methodological strengths of the study include a positive comparison, allocation concealment, blinded assessment and appropriate sample size. The potential outcomes for remimazolam in thyroid surgery with IONM could be: it may be superior to propofol in maintaining anaesthesia with less hypotension and stable haemodynamics, suggesting that it is a better sedative for this surgery; it may complete the surgery with no significant differences or with more hypotension and adverse effects than propofol, indicating no significant clinical benefit; or it may not complete the procedure due to intraoperative consciousness, limb movement or severe haemodynamic fluctuation. This is also possible because propofol is considered to be the most effective sedative, and there is limited research on remimazolam for deep sedation.

Our study has several limitations. First, the attending anaesthetist could not be blinded due to the different appearance of remimazolam and propofol. However, this is mitigated by the separation of researchers, patients, surgeons, follow-up clinicians and statisticians. Second, the BIS has inherent limitations as it is mainly related to sedation with propofol rather than other anaesthetics. Previous studies suggest that a BIS>60 may not mean inadequate sedation under remimazolam anaesthesia, as all patients were well sedated as confirmed by other indicators (such as spectral edge frequency values and pupil diameter); there is no explicit or implicit memory formation, no intraoperative awakening or recall, no need for rescue sedation, no body movements and no severe haemodynamic fluctuations.[33 47–49] However, due to the lack of a standardised BIS setting for remimazolam sedation, we chose to maintain the BIS in the 40–60 range, as in the majority of studies. The appropriate BIS ranges for remimazolam anaesthesia require further research. Third, the study is single-centre and included only thyroid surgery, which limits its generalisability. The sample size for monitoring may be relatively small, and there may be an uneven distribution of confounders between groups. We hope that future studies will address these limitations.

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Contributors DL, YG and YY participated in conception and study design. DL, QZ and YG co-drafted the protocol manuscript. JL, AZ and WW contributed to sample size calculation and statistical advice. YG, DL and QZ developed the case report forms and Excel. YG, HH and WC participated in data acquisition and article revision. All authors refined the study protocol and approved the manuscript. YG and YY acted as the guarantors of this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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INFORMED CONSENT FORM

TITLE OF STUDY: Effect of Remimazolam Besylate versus Propofol on Haemodynamic Profiles in Patients Undergoing Thyroid Surgery with Recurrent Laryngeal Nerve Monitoring

APPLICATION UNIT: Affiliated Cancer Hospital and Institute of Guangzhou Medical University

VERSION NUMBER:V2.0

Informed Consent Form for Subjects

We are about to conduct a research study titled "Effect of Remimazolam Besylate versus Propofol on Haemodynamic Profiles in Patients Undergoing Thyroid Surgery with Recurrent Laryngeal Nerve Monitoring". You meet the enrollment criteria for this study. Therefore, we would like to invite you to participate in this study. This informed consent form will introduce to you the purpose, steps, benefits, risks, possible inconveniences or discomforts, etc. of this research. Please read it carefully and make a careful decision on whether to participate in this study. When the researcher explains and discusses the informed consent form with you, you can ask questions at any time and ask him/her to explain the parts you do not understand. You can make a decision after discussing with your family, friends, and your attending doctor.

The person in charge of this research project is Yao Yonghua from Affiliated Cancer Hospital and Institute of Guangzhou Medical University.

1. WHY IS THIS RESEARCH BEING CONDUCTED?

Surgery is the main means of treating thyroid cancer. Although the continuous progress of surgical techniques has significantly improved the quality and effect of

surgery, postoperative complications are still difficult to avoid, especially recurrent laryngeal nerve injury, which has a profound impact on the quality of life of patients. In order to reduce recurrent laryngeal nerve injury, intraoperative nerve monitoring technology emerges as the times require. IONM technology can significantly reduce nerve injury, but the successful monitoring of IONM is inseparable from the close cooperation of anesthesia technology. Choosing an appropriate anesthesia plan is crucial to ensuring the smooth progress of IONM. Although conventional anesthesia methods meet the needs of surgery to a certain extent, there are also defects that cannot be ignored. It is reported that inhaled anesthetics have an inhibitory effect on neuroelectrophysiological signals. Total intravenous anesthetics such as propofol combined with remifentanil are often used in thyroid surgery, but the possible side effects such as hypotension are worrying. The new drug remimazolam, as an ultra-short-acting benzodiazepine hypnotic, has attracted much attention due to its advantages such as cardiovascular stability. However, research on the maintenance effect of remimazolam in total intravenous anesthesia is still insufficient. This study explores the feasibility and effectiveness of remimazolam combined with remifentanil in thyroid surgery with nerve detection, and strives to determine its optimal maintenance dose through scientific methods, thus providing new ideas for anesthesia management in thyroid surgery.

2. WHO WILL BE INVITED TO PARTICIPATE IN THIS STUDY?

Inclusion criteria

1. Aged 18- 65 years old.
2. Both sexes.
3. American Society of Anaesthesiologists (ASA) physical status classification I-III.
4. Body mass index (BMI) $\geq$ 18 kg/m^2 and $\leq$ 30 kg/m^2.
5. Patients undergoing thyroid surgery require IONM.
6. Expected duration of surgery to be 4 hours or less.
7. Participation in the study is voluntary and requires a signed informed consent.

Exclusion criteria

1. Participated in other clinical trials within the past 3 months.

2. Patients undergoing other surgery at the same time, emergency surgery, and subsequent admission to the intensive care unit for postoperative care.

3. Patients with suspected allergy to remimazolam, propofol or any of the drugs used in this study (e.g. remifentanil, rocuronium, sufentanil, ciprofol, etc.).

4. Severe systemic cardiovascular disease, such as congestive heart failure, frequent premature ventricular contractions, uncontrolled hypertension/hypotension, etc.

5. Severe respiratory disease.

6. End-stage liver failure or kidney disease requiring dialysis.

7. History of dementia, mental illness, or other central nervous system disorders, and current use of sedatives, or antidepressants.

8. Researcher does not believe it is appropriate to participate in this clinical trial.

3. HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Approximately 284 people will participate in this study at our hospital.

4. WHAT DOES THIS STUDY INCLUDE?

Patients undergoing thyroid surgery who require recurrent laryngeal nerve monitoring are selected. Record the patients' preoperative vital signs and laboratory test results; intraoperative vital signs and medication use; postoperative recovery, medication use and complications. Statistical analysis is conducted after the experiment.

5. HOW LONG WILL THIS STUDY LAST?

This study will take approximately a total of 1 to 3 years. Complications will be followed up within 24 hours after surgery.

6. WHAT ARE THE RISKS OF PARTICIPATING IN THIS STUDY?

Remimazolam is a commonly used drug in clinical anesthesia and is routinely used for anesthesia induction and maintenance. The risk of this drug is not higher than the risks listed in the drug instructions. There is no special risk compared with other drugs.

Pay attention to avoid excessive drug use caused by excessive operation time.

Risk control measures: For surgeries with unexpected and prolonged operation times that will exceed the maximum dose of the drug, these surgeries will be excluded. Instead, propofol intravenous general anesthesia or inhaled anesthesia will be used for maintenance.

7. WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Considering that compared with inhaled anesthetics and propofol, remimazolam has better cardiovascular stability. The risk of intraoperative hypotension and heart rate reduction in patients may be decreased, reducing postoperative heart, brain and renal-related complications in patients and improving patient prognosis.

This study closely monitors the vital signs and complication status of patients and makes adjustments in a timely manner according to patient responses to facilitate obtaining the optimal anesthesia plan for patients undergoing this type of surgery.

8. IS IT NECESSARY TO PARTICIPATE IN AND COMPLETE THIS STUDY?

Your participation in this study is completely voluntary. If you do not wish to participate, you can refuse to do so without any negative impact on your current or future health care. Even after you have agreed to participate, you can withdraw from this study at any time without any reason, and this will also not affect your access to normal medical services. When you decide not to participate in this study anymore, we hope you will promptly inform your study doctor, who can provide advice and guidance on your health status. Once there is any information that may affect your decision on whether to continue participating in this study, we will inform you in a timely manner.

The sponsor or regulatory agency may also terminate this study during the study period. If this study is terminated prematurely, we will notify you in a timely manner, and your study doctor will provide advice on your next treatment plan according to your health status.

For subjects who withdraw midway, out of safety considerations, we have a last follow-up plan, and you have the right to refuse. If new information related to your health and rights is discovered after you withdraw, we may contact you again.

In principle, after you withdraw, the researcher will strictly keep your relevant information until it is finally destroyed, and will not continue to use or disclose this information during this period. However, in the following very few cases, the researcher will continue to use or disclose your relevant information even if you have withdrawn from the study or the study has ended. These situations include:

——Removing your information will affect the scientific nature of the research results or the evaluation of data security;

——Providing some limited information for research, teaching or other activities (this information will not include your name, ID number, or other personal information that can identify you).

When schools and government regulatory agencies need to supervise the study, they will request to view all research information, which will also include the relevant information of your participation in the study at that time.

9. ABOUT RESEARCH EXPENSES AND COMPENSATION

The cost of additional intervention drugs involved in this study is borne by our research group. Subjects participating in this study will not receive additional compensation.

10. TREATMENT OF RESEARCH-RELATED INJURIES?

The drugs used in this study are all daily medications for clinical anesthesia. The anesthesia management is mature and the expected risk of related injuries is low. In case of accidental injuries caused by performing research procedures to achieve research purposes, the project team will provide necessary medical measures and, in accordance with the relevant laws and regulations of our country, bear the corresponding medical expenses and provide corresponding economic compensation.

11. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, your participation in the study and your personal information in the study will be kept confidential. Without your permission, any information that can identify you will not be disclosed to members outside the research team. All research members and research-related parties will keep your identity confidential as required. Your file will be properly stored and only accessible to researchers. When the results of this study are published, no personal information about you will be disclosed.

12. IF I HAVE QUESTIONS OR DIFFICULTIES, WHOM SHOULD I CONTACT?

If you have any questions related to this study, please contact Gu Yu, Yonghua Yao.

During the trial, if I have complaints or intend to express relevant opinions and suggestions about the informed consent of this project, subject privacy protection, risk control or rights and interests protection, etc., I can contact the Medical Ethics Committee of Affiliated Cancer Hospital and Institute of Guangzhou Medical University. Contacts: Wang Jia, Wu Zijian. Address: Guangzhou Medical University Cancer Hospital, 78 Hengzhigang Road, Yuexiu District, Guangzhou City, Guangdong Province.

Declaration by the researcher:

“I have informed this subject of the research background, purpose, steps, risks and benefits of the comparative study on Effect of Remimazolam Besylate versus Propofol on Haemodynamic Profiles in Patients Undergoing Thyroid Surgery with Recurrent Laryngeal Nerve Monitoring. I have given him/her sufficient time to read the informed consent form, discuss with others, and answered his/her questions about the study. I have informed this subject that he/she can contact the doctor at any time when encountering problems related to the study, and contact the Medical Ethics Committee of the Affiliated Cancer Hospital and Institute of Guangzhou Medical University at any time when encountering problems related to his/her own

rights/interests, and provided contact information. I have informed this subject that he/she can withdraw from this study. I have informed this subject that he/she will receive a copy of this informed consent form, which contains my signature and his/her signature."

Signature of researcher (in block letters) Date:

Statement by the subject:

"I have been informed of the background, purpose, steps, risks and benefits of the comparative study on Effect of Remimazolam Besylate versus Propofol on Haemodynamic Profiles in Patients Undergoing Thyroid Surgery with Recurrent Laryngeal Nerve Monitoring. I have had sufficient time and opportunity to ask questions, and I am satisfied with the answers. I have also been informed of who I should contact when I have questions, want to report difficulties, concerns, suggestions for the study, or want to obtain further information or help with the study. I have read this informed consent form and agree to participate in this study. I know that I can withdraw from this study at any time during the study period without any reason. I have been informed that I will receive a copy of this informed consent form, which contains my signature and the signature of the researcher."

Signature of subject (in block letters) Date:

(When the subject's capacity or adequacy for informed consent is lacking or insufficient, add or replace with the following methods:)

Signature of legal representative (in block letters) Date:

Relationship with the subject

Signature of child subject aged 8 and above (in block letters) Date: