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: