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Informed Consent Form for Medical Research at Children's Hospital of Nanjing Medical University

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Title: Effects of Preoperative Nasal Sedation with Dexmedetomidine and Eszopiclone on Postoperative Behavioral Changes in Children with Autism Spectrum Disorder

Research institution: Department of Anesthesiology, Children's Hospital of Nanjing Medical University

Researcher: Zhang Li

Dear subject and parents (child and legal guardian):

We are conducting a study titled 'The Impact of Preoperative Nasal Sedation with Dexmedetomidine and Eszopiclone on Postoperative Behavioral Changes in Children with Autism Spectrum Disorder (ASD),' sponsored by Nanjing Children's Hospital affiliated with Nanjing Medical University, with Dr. Zhang Li as the principal investigator. Your child may meet the eligibility criteria for this study, and we hereby invite your child to participate. This informed consent form provides relevant information to assist you in deciding whether your child should join the study. Please read the following content carefully, and if you have any questions, please consult the study investigator responsible for this research.

Before deciding whether to participate in this study, please carefully read the following information, which will help you understand the study and its significance, procedures, and duration, as well as the potential benefits and risks for your child after participation. Please read this informed consent form carefully. If you have any questions, please raise them promptly, and the investigators will provide answers. If you wish, you may also discuss the matter with your relatives or friends to assist in making your decision. Below is an introduction to this study:

I. Research Background and Objectives

(1) Research Background

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder

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with clinical phenotypes encompassing various subtypes, including typical autism, pervasive developmental disorder (PDD), and Asperger syndrome. The core symptoms of ASD primarily manifest as social interaction impairments, language communication deficits, and restricted, repetitive patterns of behavior and interests. ASD is also associated with numerous non-core symptoms, including anxiety, irritability, aggression, attention deficit and hyperactivity disorder (ADHD), depression, epilepsy, gastrointestinal and immune dysfunction, metabolic abnormalities, and sleep disorders. According to the latest epidemiological survey data from the World Health Organization (WHO), the global prevalence of ASD in children exceeds 1%, with a sustained upward trend in recent years.

Non-performing postoperative behaviors (NPOBCs) are one of the significant complications in pediatric anesthesia. During the acute phase (post-anesthesia recovery period), they primarily manifest as postoperative delirium (ED), characterized by environmental disorientation and time-space cognitive disturbances. In the long-term (several weeks to months postoperatively), multidimensional behavioral abnormalities emerge, including but not limited to sleep rhythm disorders, altered eating patterns, emotional regulation disturbances (irritability/anxiety states), iatrogenic phobias (e.g., white coat phobia/nightophobia), and reduced treatment compliance, forming a composite behavioral phenotype. Epidemiological data indicate that approximately 50% of pediatric patients undergoing general anesthesia experience NPOBCs, with their occurrence showing a significant positive correlation to adverse perioperative outcomes such as prolonged hospitalization and increased medical costs. More importantly, if these behavioral changes persist without timely intervention, they may negatively impact children's emotional regulation and cognitive development, leading to decreased medical compliance and increased hospital visits, thereby causing sustained harm to their physical and mental health.

Despite the relatively low prevalence of ASD, individuals with this condition face a higher risk of postoperative non-oral intake behaviors (NPOIBs) due to their specific psychological and behavioral disorders. Therefore, exploring perioperative intervention strategies for ASD children is particularly crucial. Dexmedetomidine and eszopiclone, commonly used sedatives in pediatric anesthesia, have been

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well-established in terms of their sedative safety and efficacy. However, their impact on postoperative NPOIBs remains unclear. Existing studies are limited by insufficient sample sizes and single-arm designs, necessitating high-quality, multicenter randomized controlled clinical trials to provide more reliable evidence-based medical data.

Therefore, we designed this multicenter, prospective, randomized, controlled trial to systematically evaluate the effects of dexmedetomidine and eszopiclone nasal spray on postoperative NPOBCs in children with ASD. This study hypothesizes that dexmedetomidine and eszopiclone nasal spray can reduce the incidence of NPOBCs in ASD children after surgery. The results will provide important reference for clinicians in decision-making in related fields, while also contributing to the optimization of perioperative management strategies for children with autism spectrum disorder (ASD), improving patients' perioperative experience, enhancing postoperative recovery quality, and thereby alleviating the burden on families and society, with significant clinical and social value.

（2）purpose of research

The primary objective of our study was to compare the effects of right-metoprolol and eszopiclone nasal sprays versus saline control on NPOBCs in children with ASD. The secondary objective was to investigate the correlation between EEG characteristics during the awakening phase and changes in NPOBCs in ASD children.

II. Research Content

(1) What are the eligibility criteria for participating in the study? This includes inclusion criteria and exclusion criteria.

If your child is between 0-12 years old, has autism spectrum disorder (ASD), and is otherwise in good health, and plans to undergo general anesthesia surgery at our hospital, they meet the eligibility criteria. However, if your child meets any of the following conditions or multiple conditions, they are not suitable for participation in this study: cardiac, thoracic, or neurosurgical procedures; congenital diseases or severe hepatic or renal dysfunction; hypersensitivity to study medications;

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neuromuscular disorders, cerebral palsy, or epilepsy; other psychiatric or neurological conditions; body mass index (BMI) ≥ 30 kg/m²; severe upper respiratory tract infection prior to surgery; use of sedatives or analgesics within 48 hours before surgery; or exposure to significant life stressors (e.g., changes in family/school environment, parental divorce or death) within one month prior to surgery.

(2) How long will this study last? How many participants will be enrolled?

This study is planned to last for 3 years and will enroll 234 children. The study will be conducted at 8 centers simultaneously, including the Children's Hospital of Nanjing Medical University, Zhongda Hospital of Southeast University, Children's Hospital of Xuzhou Medical University, Wuxi Children's Hospital of Jiangnan University, Changzhou Children's Hospital of Nantong University, Pizhou Hospital of Xuzhou Medical University, Dongtai Hospital of Nantong University (Dongtai People's Hospital), and Suqian Hospital of Nanjing Drum Tower Hospital Group. Data collection will commence concurrently across all centers, with competitive recruitment and dynamic block randomization. It is estimated that each center will handle approximately 5%-50% of the cases (17-117 cases).

（3）Research process

1. research technique

1.1 Subject Grouping

If your child participates in this study, there is a 1/3 probability that they will be randomly assigned to any of the following groups: Dextromethorphan Group (Group D): Dextromethorphan 2 μg/kg, maximum dose 100 μg, diluted to 1 ml, administered via a standardized nasal spray pump. Eszopiclone Group (Group L): Eszopiclone 1 mg/kg, maximum dose 50 mg, diluted to 1 ml, administered via a standardized nasal spray pump. Saline Control Group (Group C): Saline 1 ml, administered via a standardized nasal spray pump.

1.2 randomization and blinding

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We use computers to generate a block random number table in advance, and the results are placed in opaque envelopes, which are kept confidential from all investigators, subjects, their families, and clinicians. Once your child is confirmed for enrollment, on the day of surgery, an anesthesiologist opens the envelope and determines the group assignment based on the results inside. The results are then communicated to your lead anesthesiologist, who subsequently implements the corresponding anesthesia protocol. Throughout this process, neither you nor your child, nor any of the researchers are informed.

1.3 intervention study

On the day of surgery, approximately 30 minutes prior to the procedure, the child was escorted by parents into the pediatric anesthesia preparation room. An trained investigator administered the intervention, with all preparations stored in a single nasal spray pump. The medication was administered sequentially through both nostrils of the patient.

Dextromethorphan group (Group D): Dextromethorphan 2 μg/kg, with a maximum dose of 100 μg, diluted to 1 ml, administered via a standardized nasal spray pump.

Esketamine group (Group L): Esketamine 1 mg/kg, with a maximum dose of 50 mg, diluted to 1 ml, administered via a standardized nasal spray pump.

Saline control group (Group C): 1ml of saline, administered via a standardized nasal spray pump.

Please note that preoperative administration of anxiety and fear-relieving pediatric sedation is a routine procedure in our hospital, in compliance with the guidelines and requirements of clinical practice. This technique is also widely implemented domestically. Our anesthesiologists are proficient in these anesthesia methods and will not cause additional harm to your child. All protocols are safe, comfortable, and painless for your child. If your child experiences excessive tension, they may withdraw from the study at any time.

1.4 Follow-up Time and Content

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The follow-up schedule includes preoperative inquiries regarding your child's relevant conditions and medical history, followed by postoperative visits at 3 days, 7 days, and 28 days.

There will be a telephone follow-up to ask your child about recent behavioral changes.

2 Experimental Procedures

On the day before the procedure, we will determine whether your child is eligible for enrollment based on the surgical application form. For eligible children, our researchers will provide detailed information about the study to the family members or guardians, address any concerns, and obtain their informed consent after confirming no issues. Subsequently, your child will complete the preoperative preparations as required by the surgical procedure.

Thirty minutes prior to the procedure, your child will be escorted to the anesthesia preparation room by a non-participating anesthesia nurse who will prepare the appropriate medication and hand it to the study intervention provider, who remains unaware of the administered drugs. The child will then exit the study immediately after the intervention is completed. Subsequently, continuous monitoring of the child's non-invasive blood pressure, heart rate, and pulse oximetry will be performed, with records taken every 5 minutes. Additionally, the child's sedation alertness (OAA/S) score will be assessed every 5 minutes. Prior to entering the room, if the child exhibits severe anxiety or fear, the parents will first provide verbal reassurance, along with behavioral interventions such as playing with cartoons or toys. If these measures fail to alleviate the symptoms, midazolam will be administered as an adjunctive sedative, with relevant documentation maintained.

Upon entering the operating room, we routinely monitor heart rate, pulse oximetry, and non-invasive blood pressure to maintain stable vital signs. Subsequently, the lead anesthesiologist administers anesthetic induction via intravenous injection or inhalation anesthesia through a mask to induce anesthesia in the child. An anesthesia depth monitor ensures the child remains in a sufficiently deep anesthetic state throughout the procedure until the end of surgery. After the procedure, all drug

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infusions are discontinued, and the child is transferred to the anesthesia recovery room to await recovery from anesthesia. Upon meeting the discharge criteria, the child is safely escorted to the ward, marking the conclusion of the study. All aforementioned treatments are routine and necessary, with no additional therapies or associated risks.

III. What Will Be Required to Participate in the Study

(1) Subject Screening

Prior to enrollment in this study, your child will undergo the following screening to determine eligibility: ① The physician will inquire about and document the child's medical history and perform a physical examination. ② Based on the results of relevant examinations, the eligibility criteria for inclusion will be assessed.

(2) Matters requiring cooperation from both you and your child for participation in this study

- Provide accurate information on past medical history and current condition.
- Inform the study lead physician of any health issues that arise during the study.
- Inform the study lead physician of any medications, vitamins, or traditional Chinese herbal medicines you have taken during the study.
- Do not take any medicines or treatments, including prescription medicines and over-the-counter medicines (including vitamins and herbal medicines), unless approved by your study doctor.
- Follow the physician's instructions and attend the required visits.
- Follow the guidance of your research and study physicians.
- If your child requires additional treatment during the study, please contact the study investigator in advance.
- If you have any questions, please feel free to ask.

（3）Is it possible to opt out of this study? Are there any alternative treatment options available?

Your child's participation in this study is entirely voluntary. If you and your child decide to participate, you will be

Informed consent is required and a copy will be provided. If your child participates in this study, they may withdraw at any time without affecting their regular treatment.

For your child's condition, dexmedetomidine and eszopiclone are the standard preoperative sedatives routinely used in our hospital. You may also opt to decline

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sedation or use sedatives without participating in this study. You can discuss the anesthesia plan with the lead anesthesiologist, and the decision will be made jointly by you and the lead anesthesiologist. We will not interfere with your child's treatment in any way.

(4) Medical record and biological specimen collection: This study will be conducted at the Children's Hospital affiliated with Nanjing Medical University. If you agree to participate in this study, we will collect relevant medical records of your child's diagnosis and treatment for analysis and research. We will also communicate in detail with you and your child to analyze disease-related information, including the disease course, family history, previous medical visits, and results of previous examinations.

Additionally, this study does not collect any additional biological specimens from your child. The examinations and tests required for your child are essential for routine clinical diagnosis and treatment.

If you agree to participate in this study, we will assign a number to each participant and establish a medical record file.

(6) Other matters requiring your cooperation: None

IV. Potential Benefits of Participating in the Study

Your child may benefit from this study. Such benefits include:

(1) The breakthrough achieved in this study will benefit your child's future treatment;

(2) Through this study, you will be able to enhance your knowledge related to this disease, which will facilitate your child's access to standardized treatment and promote their better recovery.

(3) Through questionnaires, you can identify disease-related risk factors and obtain professional guidance to better cooperate with physicians for diagnosis and treatment.

V. Potential Adverse Reactions and Risks Associated with Participation in the Study

This study generally does not cause harm to your child's physical, psychological, or social relationships beyond routine medical care, nor does it negatively impact the

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diagnosis or treatment of your child's condition. Participation in this study does not entail any compensation for your child, but your child's involvement will contribute to the advancement of medical scientific research.

We appreciate your and your child's contributions to medical research. The entire study process was supervised by the Ethics Committee of Children's Hospital affiliated to Nanjing Medical University. If you have any questions during the study, please consult the research physician.

VI. Your and Your Child's Rights

Throughout the entire study process, both you and your child are participating voluntarily. If you and your child decide not to participate in this study, it will not affect any other treatments your child is entitled to. If you and your child choose to participate, you will be required to sign this written informed consent form. You and your child have the right to withdraw from the study at any stage without facing discrimination or unfair treatment, and your corresponding medical care and benefits will not be affected. If you experience serious adverse events, or if your study physician determines that continuing participation is not in your best interest, they will decide to allow you to withdraw from the study. However, your withdrawal will not impact your normal medical care and benefits.

VII. Costs Related to Participation in This Study and Management of Injuries Occurred

If you agree to participate in this study, you only need to pay the standard treatment fees. This study does not involve additional treatments or medications, and you will not be required to bear any extra costs. If your health is compromised due to participation in this trial, please inform the investigator, and we will take necessary medical measures.

VIII. Confidentiality of Personal Information

If you and your child participate in this study, your participation in the study and your personal information during the study will be kept confidential. Your child's medical records (including study medical records, physical and chemical examination reports, case report forms, etc.) will be stored in the hospital in accordance with regulations. Except for the National Medical Products

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Administration (NMPA), the ethics committee, and the investigators, no other personnel will be permitted to access your child's medical records. Any public reports regarding the results of this study will not disclose your child's personal identity. We will make every effort to protect the privacy of your child's personal medical information within the permissible scope. By signing the informed consent form, you authorize the investigators of this study project to publicly disclose data (e.g., study results for publication in academic journals) while strictly maintaining the confidentiality of personal privacy. Your child's personal information (such as name, age, etc.) will be kept confidential and not disclosed.

9. Contact Information

If you experience any harm related to the study, or if you have any questions about the study or the study drug, please contact the investigator.

For inquiries regarding the rights and interests of the subjects, please contact the Medical Ethics Committee of Nanjing Children's Hospital affiliated to Nanjing Medical University at telephone number: 025-52862937.

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Informed consent signature page:

1. I have read the above introduction regarding this study and had the opportunity to discuss and raise questions with the investigators. All questions I raised were addressed.

2. I am aware of the potential benefits and risks associated with participating in this study. I confirm that my participation is voluntary and non-remunerative, and I have had sufficient time to consider this matter. I further understand that:

(1) I can consult the investigator for further information at any time;

(2) I may opt out of this study or withdraw from it at any time upon notifying the investigator, without affecting my medical benefits or entitlements.

(3) I am equally aware that if we withdraw from the study midway, particularly if my child withdraws due to medication-related reasons, informing the physician of the disease progression and completing the corresponding physical and biochemical examinations would be highly beneficial for both the child and the entire study.

(4) If any additional pharmacological interventions are required due to disease progression, I will either consult the investigator in advance or provide a truthful account to the investigator after the event.

(5) I consent to the National Medical Products Administration (NMPA), the ethics committee, and the investigators accessing my research materials;

(6) In addition to this study, there is a possibility that my child's medical records may be reviewed again in future studies. I hereby declare my consent to the use of my child's medical records for purposes other than this study.

(7) I will receive a signed and dated copy of the informed consent form.

Finally, I have decided to consent to participate in this study on behalf of my child, and agree that the data from this study may be publicly published without disclosing the personal identities of either me or my child.

Subject signature (child):_____(Subjects aged 8 years or older must sign)

Signature of the child's legal guardian:_____Relationship with the

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child:_____

contact number ： _____ date ： _____Year Month Day

I confirm that the child's legal guardian (and/or the subject themselves) have been fully informed of the details of this study, including their rights, potential benefits, and risks, and provided with a signed copy of the informed consent form.

Researcher's signature:_____ date ： _____Year Month Day

contact number ： _____