**Study Title: Exploring the Association of Perioperative Electroencephalographic Changes Following Preoperative Intranasal Dexmedetomidine or Esketamine With Negative Postoperative Behavioral Changes in Children Undergoing Day Surgery**

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

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Title: Exploring the Association of Perioperative Electroencephalographic Changes Following Preoperative Intranasal Dexmedetomidine or Esketamine With Negative Postoperative Behavioral Changes in Children Undergoing Day Surgery
Research institution: Department of Anesthesiology, Children's Hospital of Nanjing Medical University
Researcher: Sun Fei

**Dear subject and parents (child and legal guardian):**

We are conducting a study titled "Exploring the Association Between Perioperative EEG Characteristics Mediated by Preoperative Nasal Administration of Dexmedetomidine and Eszopiclone and Postoperative Behavioral Changes in Children Undergoing Day Surgery." The sponsor of this study is Nanjing Medical University Children's Hospital, with Sun Fei as the principal investigator. Your child may meet the eligibility criteria for this study, and therefore, we invite your child to participate. This informed consent form provides relevant information to assist you in deciding whether your child should participate in this 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 desired, you may also discuss the decision with your relatives or friends to assist in making an informed choice. Below is an introduction to this study:

## I. Research Background and Objectives

(1) Research Background

Postoperative behavioral changes (NPOBCs) are common perioperative complications in children, manifesting as early postoperative delirium (alterations in environmental awareness and disorientation) and sleep/diet disturbances, irritability, nightmares, anxiety, enuresis, fear of healthcare providers or darkness, and non-compliance during the postoperative period ranging from days to weeks. Day surgery procedures exhibit a higher incidence of NPOBCs due to shorter hospital observation periods and lack of specialized post-discharge care. Approximately 60% of pediatric patients exhibit significant preoperative anxiety, which is closely associated with postoperative bedwetting, sleep disorders, and dietary issues, imposing persistent burdens on both physical/mental recovery and family caregiving. Therefore, identification of high-risk factors and implementation of effective interventions are particularly critical in anesthesia management for pediatric day surgeries.

The mechanisms underlying NPOBCs remain incompletely elucidated. Animal and clinical studies suggest that general anesthetic agents can induce neuronal apoptosis, inhibit neurogenesis, impair synaptic formation and glial cell maturation in the developing brain, particularly affecting the hippocampus associated with learning and memory. Deep anesthesia-induced brainwave suppression and abnormal EEG patterns are correlated with postoperative delirium during recovery. The adverse effects of anesthetics on the developing central nervous system, along with intraoperative physiological stress, are considered critical underlying factors for postoperative neuropsychiatric abnormalities in children.

Dexmedetomidine (DEX) is a highly selective α2-adrenergic receptor agonist that exhibits synergistic sedative, anxiolytic, and analgesic effects with minimal respiratory depression. Multiple randomized controlled trials (RCTs) and meta-analyses have demonstrated that nasal administration of DEX improves preoperative sedation quality and significantly reduces the risk of postoperative delirium/agitation in pediatric patients. Electroencephalogram (EEG) studies indicate that DEX-induced sedation resembles non-rapid eye movement sleep patterns, characterized by spindle waves and slow-wave activity, closely approximating a "physiological-like" sleep state without significant interference with brain functional

connectivity or epileptiform discharges. Experimental data suggest that DEX also attenuates neuronal apoptosis and cognitive impairment induced by ketamine-based anesthetics, demonstrating potential neuroprotective effects on developing brains.

Eszopiclone (ESK), the dextrorotatory isomer of ketamine, exhibits high anesthetic potency, rapid onset of action, quick recovery, and fewer adverse psychiatric effects, leading to increased application in pediatric day surgery and outpatient procedures. Systematic reviews demonstrate that perioperative ESK significantly reduces the incidence of postoperative delirium/agitation during recovery and mitigates early adverse behaviors through effective analgesia. However, under ESK sedation, electroencephalogram (EEG) activity predominantly displays high-frequency components resembling wakefulness rather than sleep, lacking widespread slow-wave synchronization. Animal studies suggest that neonatal ketamine exposure may increase high-frequency oscillations accompanied by cognitive abnormalities, indicating potential risks to neurodevelopment. Previous in vitro and in vivo studies have found that dexamethasone (DEX) can partially counteract ketamine's adverse effects on neural stem cells and cognitive function, providing theoretical justification for combined drug administration.

Current clinical evidence regarding the impact of preoperative nasal DEX or ESK administration on long-term nonpostoperative behavioral complications (NPOBCs) in children remains limited, with most studies focusing on single surgical procedures such as tonsil/adenoidectomy and having small sample sizes. It is also unclear whether anesthesia depth-related EEG suppression can sustainably influence long-term behavioral outcomes. To address these gaps, a multicenter, randomized, double-blind clinical study will be conducted in pediatric patients undergoing day surgery to compare the effects of preoperative nasal DEX versus ESK on NPOBCs and early postoperative delirium. Combined with perioperative EEG monitoring, this study aims to explore the association between brain electrical patterns induced by different medications and NPOBCs, as well as their mediating effects. The research will evaluate the mechanisms underlying the impact of interventions on postoperative neurobehavioral outcomes, providing evidence-based insights for optimizing perioperative management in pediatric day surgery, reducing NPOBCs incidence risks, and improving postoperative rehabilitation quality.

（2）purpose of research

Primary research objective: To compare the effects of preoperative nasal spray with dexmedetomidine and eszopiclone versus saline control on NPOBCs.

Secondary research objective: To investigate the association between dexmedetomidine and eszopiclone administration and EEG characteristics as well as NPOBCs changes in awake pediatric patients.

## 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 2 and 12 years of age and plans to undergo a day surgery under general anesthesia at our hospital with otherwise good physical condition, they meet the enrollment criteria. However, participation in this study is not recommended if your child meets any of the following conditions: congenital diseases or severe hepatic/renal dysfunction; hypersensitivity to study medications; neuromuscular disorders, cerebral palsy, or epilepsy; other psychiatric or neurological conditions; body mass index (BMI) ≥ 30 kg/m$^2$; severe upper respiratory tract infection prior to surgery; use of sedatives or analgesics within 48 hours before surgery; exposure to significant life stressors (e.g., changes in family/school environment, parental divorce or death) within one month prior to surgery; or refusal of participation by family members or guardians.

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

This study is planned to last for 2 years and will enroll 342 children. The study will be conducted across four centers: Nanjing Children's Hospital, Zhongda Hospital of Southeast University, Nanjing First Hospital, and Wuxi Children's Hospital. Data collection will commence simultaneously at multiple centers, with competitive recruitment among the sites. A dynamic block randomization method will be employed, with each center expected to handle approximately 5%-50% of the cases (18-171 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: Dexmedetomidine group (Group D): Dexmedetomidine 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. Normal saline control group (Group C): Normal saline 1 ml, administered via a standardized nasal spray pump.

1.2 Randomization and blinding

We use computers to generate block random number tables in advance and place the results in opaque envelopes, which are kept confidential from all investigators, participants, their families, and clinicians. Upon confirmation of your child's 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 researchers are informed of the outcome.

1.3 intervention study

On the day of surgery, approximately 30 minutes prior to the procedure, the pediatric patient was escorted by parents into the pediatric anesthesia preparation room. Intervention was administered by a trained investigator. All preparations were stored in a centralized nasal spray pump, with medication delivered sequentially through both nostrils of the patient.

Dormetomidine group (Group D): Dormetomidine 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, maximum dose 50 mg, diluted to 1 ml, administered via a standardized nasal spray pump.

Saline control group (Group C): 1 ml of saline solution 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 clinical practice guidelines and current domestic standards. Our anesthesiologists are proficient in these anesthesia techniques and will not cause additional harm to your child. All protocols are safe, comfortable, and painless for your child. If your child experiences excessive anxiety, they may withdraw from the study at any time.

1.4 Follow-up Time and Content

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

A telephone follow-up will be conducted to inquire about recent behavioral changes in your child.

2 Experimental Procedures

On the day before surgery, we will determine whether your child is eligible for enrollment based on the surgical application form. Eligible children will receive detailed research information from our investigators, who will address any concerns raised by family members or guardians. After confirming no issues, the informed consent form for participation in the study will be signed. Subsequently, your child will complete preoperative preparations according to surgical requirements.

Thirty minutes prior to surgery, your child will be escorted into the anesthesia preparation room by you. A non-participating anesthesia nurse will prepare the appropriate medications and deliver them to the study intervention provider, who remains unaware of the administered drugs. The child will then exit the study immediately after receiving the interventions. Continuous monitoring of the child's non-invasive blood pressure, heart rate, and pulse oximetry saturation will be performed every 5 minutes, along with evaluation of the child's sedation alertness (OAA/S) score at 5-minute intervals. Prior to entering the operating room, if the child exhibits severe anxiety or fear, parents will first provide verbal reassurance, followed by behavioral interventions such as playing cartoons or toys. If symptoms persist, midazolam sedation will be administered, with relevant observations recorded.

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 agents intravenously or inhalation anesthetics via a mask to induce anesthesia in the child. An anesthesia depth monitor ensures the child remains in adequate anesthesia depth throughout the procedure until surgical completion. Postoperatively, all medication infusion is discontinued, and the child is transferred to the anesthesia recovery room to await gradual recovery from anesthesia. Upon meeting discharge criteria, the child is safely escorted to the ward, marking the conclusion of the study. All aforementioned interventions are routine and necessary, with no additional treatments or associated risks.

## III. What will be required if participating in the study

### (1) Subject Screening

Prior to enrollment in this study, your child will undergo the following screening procedures to determine eligibility: ① The physician will inquire about and document the child's medical history and perform a physical examination. ② Based on relevant diagnostic findings, 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 period.
- Inform the study lead physician of any medications, vitamins, or traditional Chinese herbal medicines you took during the study period.
- No medications or treatments, including prescription drugs and over-the-counter medicines (including vitamins and herbal medicines), should be taken unless approved by the attending physician.
- Follow the physician's instructions and attend visits as required.
- Follow the guidance of researchers and attending physicians.
- If your child requires additional treatments during the study period, please contact the study investigator in advance.
- You may ask questions at any time if there are any unclear points.

### （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 forms are required and a copy will be provided. If your child participates in this study, you may request withdrawal at any time, and such withdrawal will not affect your 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 refuse sedation or choose to 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) Collection of medical records and biological specimens: This study will be conducted at the Children's Hospital affiliated with Nanjing Medical University. If you consent to participate in this study, we will collect relevant case data from your child's medical history for analysis and research. Detailed communication will be provided to you and your child regarding disease-related information, including disease progression, family history, previous medical visits, and results of prior examinations.

In addition, this study does not collect additional biological specimens from your child. The examinations and tests conducted on your child are essential for routine clinical diagnosis and treatment.

If you agree to participate in this study, each participant will be assigned a number and a medical record file will be established.

(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 standardized treatment for your child and promote better recovery outcomes.

(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 any harm to your child's physical, psychological, or social relationships beyond routine medical diagnosis and treatment, nor will it negatively impact the diagnosis and 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 of Nanjing Medical University. If you have any questions during the study, please consult the research physician.

## VI. Your Rights and Those of Your Child

Throughout the entire participation in the study, both you and your child are voluntary. If you and your child decide not to participate in this study, it will not affect any other treatments your child is entitled to receive. 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 remain unaffected. If you experience severe adverse events, or if your study physician determines that continuing participation is not in your best interest, they will decide to allow your withdrawal from the study. However, your withdrawal will not impact your regular medical care and benefits.

## VII. Costs associated with participation in this study and management of injuries occurring during the study

If you agree to participate in this study, you only need to pay the regular 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 condition 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, both your involvement in the

research and your personal data collected 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 Administration (NMPA), the ethics committee, and the investigators, no other individuals will be permitted to access your child's medical records. Any public reports regarding the study results 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 permissible limits. By signing the informed consent form, you authorize the investigators of this study project to publicly release data materials (e.g., study results for publication in academic journals) while strictly maintaining 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 study-related harm, or if you have any questions regarding the study or the study medication, please contact the investigator.

If you have any questions related to the rights and interests of the subjects, please contact the Medical Ethics Committee of Nanjing Medical University Affiliated Children's Hospital at telephone number: 025-52862937.

## Informed consent signature page:

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

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

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

(2) I may opt out of participating in 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 examinations and biochemical tests would be highly beneficial for both the child and the entire study.

(4) If any additional pharmacological treatment is required due to disease progression, I will consult the investigator in advance or provide truthful information to the investigator after the event.

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

(6) Apart from this study, there is a possibility that my child's medical records may be reviewed again in future research 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 myself or my child.

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

Signature of the legal guardian of the child:_____Relationship with the child:_____

contact number ：_____ date ：_____Year Month Day

I confirm that the detailed information regarding this study, including its rights as well as potential benefits and risks, has been explained to the legal guardian of the child (and/or the subject themselves), and a signed copy of the informed consent form has been provided.

Researcher's signature:_____ date ：_____Year Month Day

contact number ：_____