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ORIGINAL RESEARCH

# ORAL GABAPENTIN AND LORAZEPAM AS PREMEDICATION IN PEDIATRIC ANESTHESIA: A RANDOMIZED COMPARATIVE STUDY

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**ABSTRACT**

**Background:** Preoperative anxiety in children can affect anesthetic induction, physiological stability, and postoperative outcomes. Lorazepam is a widely used benzodiazepine for anxiolysis, while gabapentin, although not commonly used in children, has shown potential anxiolytic effects.

**Methods:** This double-blind randomized controlled trial included 64 children aged 2–6 years who underwent elective procedures under general anesthesia. Subjects were randomly assigned to receive either oral gabapentin (15 mg/kg) or lorazepam (0.025 mg/kg). Preoperative anxiety was assessed using the Modified Yale Preoperative Anxiety Scale–Short Form (mYPAS-SF), while secondary outcomes included sedation, measured by the Ramsay Sedation Scale (RSS), and parental separation, assessed using the Parental Separation Anxiety Scale (PSAS).

**Results:** No significant reduction in anxiety scores was observed in either group (gabapentin: p = 0.29; lorazepam: p = 0.76). Optimal sedation occurred in 75% of lorazepam and 56.2% of gabapentin recipients. Inadequate separation and higher rescue sedation needs were more frequent in the gabapentin group. No moderate-to-severe adverse events were reported within 24 hours post-administration.

**Conclusion:** Neither drug significantly reduced preoperative anxiety scores, however, both demonstrated potential as part of pediatric premedication strategies. Gabapentin remains a promising alternative as premedication, particularly in specific clinical settings.

**Keywords:** Gabapentin; Lorazepam; Pediatric Anesthesia;Preoperative Anxiety Premedication

## INTRODUCTION

Surgical procedures are among the most significant stressors experienced by hospitalized children and their families. In pediatric patients, this stress often manifests as heightened preoperative anxiety, which may lead to adverse postoperative behavioral changes. Studies have shown that the prevalence of preoperative anxiety up to 75% among children aged 2–12 years.[1]

Younger children, particularly those aged 2–6 years, tend to experience higher levels of anxiety. Other contributing factors include developmental status, temperament, prior surgical experience, and parental anxiety levels.[2]

Children may develop preoperative anxiety due to fear of medical staff, limited cognitive understanding, separation from parents, and needle-related procedures. This emotional stress triggers physiological responses such as increased heart rate, blood pressure, and excitability, resulting from sympathetic and parasympathetic activation.[3] High levels of anxiety have been associated with

prolonged recovery times, increased postoperative pain, delayed discharge, and behavioral disturbances

including sleep problems, enuresis, and separation anxiety.[4,5]

Reducing preoperative anxiety often involves pharmacological interventions, with benzodiazepines being commonly used.[6] Oral lorazepam, a long-acting benzodiazepine, has been considered a viable option for pediatric premedication due to its sedative and anxiolytic properties. However, benzodiazepines can occasionally cause paradoxical reactions, including agitation, hallucination, and disorientation, which may distress both the patient and their caregivers.[7]

Gabapentin, a second-generation anticonvulsant structurally similar to GABA, does not directly influence GABA metabolism but has shown promise in perioperative care.[8] It has been associated with reduced preoperative anxiety in both adults and children, blunted hemodynamic response to intubation, decreased postoperative nausea and vomiting, and reduced incidence of agitation and emergence delirium in pediatric populations.[9] However, evidence comparing gabapentin to standard anxiolytics like lorazepam in pediatric anesthesia remains scarce, especially in low-resource settings.

This study aims to compare the effects of oral gabapentin and oral lorazepam as premedication in pediatric patients undergoing elective surgery under general anesthesia, with a focus on preoperative anxiety reduction as the primary outcome.

## METHODS

### Study Design

This study was designed as a prospective, randomized, double-blind controlled trial conducted from Januari-March 2025 at Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Syiah Kuala (No. 1299/EA/FK-RSUDZA/2024), and the trial was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all parents or legal guardians of the participants.

### Participants

Children aged 2–6 years scheduled for elective surgery under general anesthesia were screened for eligibility. Inclusion criteria were American Society of Anesthesiologists (ASA) physical status I or II, ability to take oral medication, and accompanied by a parent or guardian. Exclusion criteria included developmental delay, neurological or psychiatric disorders, known hypersensitivity to study drugs, recent use of sedatives or antiepileptics, and refusal to participate.

### Randomization and Blinding

Participants were assigned to either the gabapentin group (G group) or the lorazepam group (L group) in a 1:1 ratio using systematic random sampling based on the order of subject arrival. Group allocation was conducted by a research assistant using a predetermined sequence and was not involved in the administration or evaluation process. The study medications had been previously prepared by the hospital pharmacy in powdered form and individually packed in identical, opaque, and sealed envelopes labelled only with subject codes. This method ensured blinding of both the anesthesiologist and the outcome assessor throughout the study.

### Interventions

Children in the gabapentin group received oral gabapentin at a dose of 15 mg/kg body weight, while those in the lorazepam group received oral lorazepam at a dose of 0.025 mg/kg body weight. Both medications were administered at least two hours before anesthesia induction. Study drugs were prepared in powdered form by the hospital pharmacy and dispensed in identical sealed envelopes labelled according to subject codes. Intravenous cannulation was performed prior to premedication in all patients as part of the hospital's standard operating procedure, aiming to secure vascular access for potential emergency medication administration. Each child was accompanied by a parent or legal guardian up to the operating room to provide emotional support and minimize separation distress. If the child became uncooperative during monitor application or induction preparation, an additional sedative was administered at the discretion of the attending anaesthesiologist.

### Outcomes

The primary outcome was the level of preoperative anxiety, assessed using the Modified Yale Preoperative Anxiety Scale–Short Form (mYPAS-SF), which was measured at two time points: prior to the administration of premedication and at least two hours after the medication was given. Secondary outcomes included sedation level assessed using the Ramsay Sedation Scale (RSS), parental separation measured by the Parental Separation Anxiety Scale (PSAS).

### Sample Size

The required sample size for this study was calculated using a standard formula for comparative analytical research involving unpaired numerical data. The calculation was based on data from a previous study by Filho et al., assuming a moderate effect size, a significance level of 5%, and a power of 80%. The result indicated that a minimum of 26 subjects per group was required, yielding a total of 52 participants. To account for a potential dropout rate of 20%, the final target

sample size was increased to 62 participants.

**Statistical Analysis**

The distribution of preoperative anxiety scores measured by the Modified Yale Preoperative Anxiety Scale–Short Form (mYPAS-SF) was assessed for normality. Paired *t*-tests were used for within-group comparisons when data were normally distributed, while the Wilcoxon signed-rank test was applied for non-normally distributed data. Categorical variables, including sedation level based on the Ramsay Sedation Scale (RSS) and parental separation behavior assessed with the Parental Separation Anxiety Scale (PSAS), were analyzed using the Chi-square test. A two-sided *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

**Subject Characteristics**

A total of 64 pediatric patients aged 2–6 years were enrolled in the study and randomized equally into the gabapentin group and lorazepam group (each n = 32). All participants completed the study and were included in the final analysis. Baseline characteristics such as sex and BMI were comparable between groups (table 1). However, there was a statistically significant difference in age distribution, with the mean age in the lorazepam group being higher than in the gabapentin group ($p < 0.05$). This difference was taken into consideration in the interpretation of outcomes.

**Preoperative Anxiety (mYPAS-SF)**

The level of preoperative anxiety was assessed using the Modified Yale Preoperative Anxiety Scale – Short Form (mYPAS-SF) before and after administration of premedication (table 2). In the gabapentin group, the mean anxiety score decreased from 44.9 ± 15.6 to 42.8 ± 13.1. however, this reduction was not statistically significant ($p = 0.29$). In the lorazepam group, the median anxiety score declined from 33.3 (IQR 16.7) to 31.3 (IQR 22.9), also without a statistically significant difference($p = 0.76$). These findings indicate that while both premedication showed a slight reduction in anxiety levels, neither produced a statistically significant change within their respective groups.

**Sedation Level**

The sedation level was evaluated using the Ramsay Sedation Scale (RSS), where a score of 2–3 was considered to indicate acceptable sedation. In the gabapentin group, acceptable sedation was achieved in 18 children (56.2%), while 14 children (43.8%) exhibited unacceptable sedation. In the lorazepam group, 24 children (75.0%) achieved acceptable sedation, whereas 8 children (25.0%) were assessed as unacceptable sedated. Although the proportion of acceptable sedation was higher in the lorazepam group, the difference between the two groups did not reach statistical significance ($p = 0.11$).

**Parental Separation**

Difficult separation from parents, indicated by a PSAS score of ≥ 3, occurred in 78.1% of children who received gabapentin and in 62.5% of those who received lorazepam. Although this difference was not statistically significant ($p = 0.174$), the findings suggest a higher tendency toward poor separation behaviour in the gabapentin group compared to the lorazepam group, implying a potentially more favorable effect of lorazepam on preoperative separation tolerance in pediatric patients.

**Table 1. Demographic variables**

| Variables | Gabapentin | Lorazepam | p-value |
|---|---|---|---|
| Age (years) (mean ± SD) | 3.78 ± 1.39 | 4.78 ± 1.43 | 0,006* |
| BMI kg/m2 (mean ± SD) | 15.35 ± 3.80 | 14.71 ± 3.07 | 0,354 |
| Sex (n) | | | |
| Male | 15 | 21 | 0,208 |
| Female | 16 | 11 | |
| Anesthesia History (n) | | | |
| Yes | 6 | 13 | 0,055 |
| Never | 26 | 19 | |

**Table 2. Comparison mYPAS-SF score before and after premedication**

| Group | Before | After | p-value |
|---|---|---|---|
| Gabapentin (Mean ± SD) | 44,9±15,6 | 42,8±13,1 | 0,29 |
| Lorazepam (Median(IQR)) | 33,3(16,7) | 31,3(22,9) | 0,76 |

**Table 3. Comparison of sedation adequacy and parental separation between gabapentin and lorazepam groups**

| Variables | Gabapentin | Lorazepam | p-value |
|---|---|---|---|
| **Sedation** | | | |
| Acceptable sedation | 18 (56,2%) | 24 (75,0%) | 0,11 |
| Unacceptable sedation | 14 (43,8%) | 8 (25,0%) | |
| **Parental Separation** | | | |
| Acceptable separation | 7 (21,9%) | 12 (37,5%) | 0,17 |
| Difficult separation | 25 (78,1%) | 20 (62,5%) | |

## DISCUSSION

This study analysed baseline characteristics including age, body mass index (BMI), sex, and previous anesthesia history to ensure initial comparability between the gabapentin and lorazepam groups. A statistically significant difference was observed in the age variable, with the lorazepam group having a higher mean age (4.78 ± 1.43 years) compared to the gabapentin group (3.78 ± 1.39 years), p = 0.006. Body weight approached significance (p = 0.053), while no meaningful differences were found in BMI, sex distribution, or prior anesthesia exposure.

Age is a well-established predictor of preoperative anxiety in children. Children between 2 and 6 years old are particularly vulnerable to anxiety in the perioperative setting, representing a period of critical psychological development.[10] This age range includes two key phases: from 7 months to 3 years, where separation anxiety is dominant, and from 3 to 6 years, when fear of medical procedures becomes more pronounced. Children under 7 months rarely exhibit separation anxiety and are often soothed with physical comfort. However, toddlers and preschool-aged children may exhibit intense distress upon parental separation or when confronted with unfamiliar medical environments.[11]

In this study, younger children in the gabapentin group demonstrated significantly higher premedication anxiety scores than those in the lorazepam group.[2] Most children in the gabapentin group had scores above the clinical anxiety threshold, indicating moderate to severe anxiety prior to anesthesia induction. These findings support the notion that younger age is strongly correlated with higher preoperative anxiety risk. Therefore, the interpretation of anxiolytic effectiveness must consider the demographic imbalance—specifically the age difference—between the groups. This reinforces the importance of tailoring premedication strategies not only to pharmacologic efficacy but also to the child's developmental stage.

Premedication plays a pivotal role in facilitating a smooth transition to anesthesia, particularly in preschool-aged children who are highly susceptible to emotional distress in unfamiliar clinical settings. In this context, both pharmacologic and supportive non-pharmacologic interventions—such as simple

explanations, visualization tools, and mask desensitization—should be integrated to optimize patient comfort and minimize perioperative psychological trauma.

Preoperative anxiety in this study was assessed using the Modified Yale Preoperative Anxiety Scale–Short Form (mYPAS-SF). While both gabapentin and lorazepam groups showed slight reductions in anxiety scores following premedication, these changes were not statistically significant. Notably, all subjects had baseline anxiety scores above the clinical threshold (≥30), indicating a high prevalence of preoperative anxiety across the sample and suggesting limited anxiolytic efficacy from either intervention in this high-anxiety population.[12]

As shown in Table 2, both gabapentin and lorazepam groups demonstrated a reduction in anxiety scores after premedication; however, the changes were not statistically significant (gabapentin: $p = 0.29$; lorazepam: $p = 0.76$). All subjects had mYPAS-SF scores ≥30 before premedication, indicating a high baseline level of anxiety. While the gabapentin group showed a relatively consistent reduction in scores, the lorazepam group exhibited a wider post medication interquartile range despite a lower median score (from 16,7 to 22,9), suggesting greater variability in individual response. This may reflect differences in pharmacodynamic sensitivity or subtle paradoxical reactions, particularly relevant to benzodiazepine use in pediatric populations. The consistently elevated anxiety scores highlight the challenge of achieving adequate anxiolysis through pharmacological intervention alone. These findings emphasize the importance of incorporating non- pharmacological strategies alongside medication to optimize preoperative anxiety management in children.

The effectiveness of lorazepam observed in this study aligns with its pharmacological properties as a medium-acting benzodiazepine, which exerts anxiolytic effects by enhancing GABA- a receptor activity in the central nervous system.[13] With an onset time of 1.5 to 2 hours and a duration of 6 to 10 hours, lorazepam is considered suitable for pediatric use due to its lack of active metabolites.[6] However, the administration of a relatively low dose (0.025 mg/kg) in this study may have limited its maximal anxiolytic efficacy, suggesting that higher doses could be explored in future trials. A potential concern with benzodiazepine use in children is the risk of paradoxical reactions, such as agitation or restlessness, particularly in younger patients or those with neuropsychiatric susceptibility.[14] These effects are believed to be influenced by individual variability in receptor expression and neurotransmitter responses.[7] The wider interquartile range in the lorazepam group may indicate such heterogeneity in drug response, despite the absence of clinically apparent paradoxical effects during the observation period.

Gabapentin, initially developed as an anticonvulsant, has shown emerging promise as an anxiolytic in both adult and pediatric populations. Its mechanism of action does not involve direct modulation of GABA receptors; instead, it binds to the α2δ-1 subunit of presynaptic L-type calcium channels, leading to decreased release of excitatory neurotransmitters such as glutamate and substance P.[16] Downstream effects include reduced neuronal activity in limbic structures responsible for emotional regulation, as well as modulation of sympathetic tone via indirect inhibition of the *locus coeruleus*, a key brainstem region implicated in stress and arousal pathways.[17] These neurophysiological actions form the basis of gabapentin's anxiolytic potential, although its slower onset and less potent sedative profile relative to benzodiazepines may contribute to the more modest clinical outcomes observed in this study. Evidence from previous studies supports this pharmacodynamic profile. In a randomized trial comparing gabapentin at 15 mg/kg, 30 mg/kg, and placebo in pediatric surgical patients, both dosing regimens of gabapentin were associated with significantly lower mYPAS scores than placebo, indicating a dose-dependent anxiolytic effect.[18]

Several unmeasured factors may have influenced the outcomes observed in this study, particularly parental anxiety and the stress associated with intravenous (IV) cannulation. Parental anxiety has been shown to directly impact a child's emotional state, as children are highly perceptive of their parents' emotional cues—especially in high-stress situations such as surgical preparation. Excessive parental concern may unintentionally heighten a child's perception of threat, thereby amplifying their anxiety.[1,10] Furthermore, preoperative exposure to invasive procedures like IV insertion can serve as an additional stressor. Studies have demonstrated that unsedated IV placement may provoke strong emotional responses in children, increasing their risk of heightened preoperative anxiety.[1] In this study, IV cannulation was performed prior to the administration of premedication, potentially diminishing the observable anxiolytic effects of the drugs by exposing subjects to stressors before pharmacologic onset.

In pediatric anesthesia, a child's ability to achieve smooth separation from their parents and demonstrate readiness for anesthetic induction without the need for additional pharmacologic intervention is widely regarded as a key indicator of successful premedication. Among preschool- aged children, this separation phase is often the most emotionally

distressing component of the perioperative experience. It is strongly influenced not only by the pharmacological potency of the anxiolytic agent but also by the child's developmental maturity and psychological resilience. When adequate separation cannot be achieved, adjunctive sedatives—most commonly midazolam—are frequently employed to facilitate cooperation and ensure a safe and smooth induction process.

In the present study, as shown in Table 3, 78.1% of children in the gabapentin group and 62.5% in the lorazepam group experienced inadequate separation, as measured by the Parental Separation Anxiety Scale (PSAS). Although the difference was not statistically significant ($p = 0.17$), the trend suggests a potentially more favorable separation outcome associated with lorazepam. This finding, while preliminary, aligns with lorazepam's established pharmacological profile and highlights its potential utility in improving perioperative behavioral compliance.

The inability to achieve acceptable PSAS scores across both groups may be partly attributed to the conservative dosing regimens employed in this study. Lorazepam was administered at the lowest end of the recommended pediatric dosing spectrum (0.025 mg/kg), which may have limited its anxiolytic effectiveness in some children. Previous research has shown that oral midazolam at a dose of 0.5 mg/kg can reliably produce adequate separation in pediatric populations.[19] Furthermore, alternative agents such as nebulized ketamine and dexmedetomidine have demonstrated anxiolytic efficacy in similar clinical settings, though their use remains limited by regulatory approval in certain regions.[20]

Likewise, the gabapentin dose used in this study, although selected based on available pediatric data and safety considerations, may not have been sufficient to produce a clinically significant anxiolytic response. Given gabapentin's slower onset and different mechanism of action compared to benzodiazepines, its optimal anxiolytic dose and timing of administration remain subjects for future investigation. Refinement of these parameters-along with rigorous monitoring for adverse effects-may enhance its therapeutic value as a premedication agent and improve behavioral outcomes during parental separation.

In this study, the level of post medication sedation was assessed using the Ramsay Sedation Scale (RSS), a validated and widely utilized instrument for evaluating clinical sedation in perioperative care. As shown in Table 3, acceptable sedation—defined as an RSS score of 2 to 3— was achieved in 75.0% of patients in the lorazepam group compared to 56.2% in the gabapentin group. Although the difference was not statistically significant ($p = 0.11$), the results indicate a clinically relevant trend toward more consistent sedation with lorazepam. This aligns with its known pharmacological action as a benzodiazepine, enhancing GABA-A receptor activity in the central nervous system and producing a predictable sedative response within the two-hour post-administration window.[13]

In contrast, gabapentin is not a classical sedative and does not exert direct GABAergic activity. Instead, it binds to the α2δ subunit of voltage-gated calcium channels, reducing the release of excitatory neurotransmitters such as glutamate and substance P.[16] In addition to its anxiolytic and analgesic effects, gabapentin is believed to modulate noradrenergic tone through its indirect action on the locus coeruleus, a brainstem nucleus critically involved in arousal and stress responses.[17] By attenuating excitatory input within this region, gabapentin may contribute to a calming effect without inducing deep sedation.

This distinction has important clinical implications, particularly in pediatric anesthesia where airway safety is a priority. The relatively lower sedative profile of gabapentin may offer a safer pharmacological option for children at higher risk of respiratory compromise. While lorazepam may provide superior sedation efficacy, gabapentin's favorable safety margin may make it a viable alternative in clinical scenarios requiring anxiolysis without excessive sedation.

**Limitations**

This study has several limitations that warrant consideration. First, despite randomization, there was a significant difference in age distribution between the two groups, which could have influenced anxiety expression and drug response. Second, external psychosocial factors such as parental anxiety, child temperament, and prior exposure to the hospital environment were not controlled or measured, despite their well-documented impact on preoperative anxiety levels. Additionally, all patients underwent intravenous cannulation prior to drug administration, which may have acted as a procedural stressor and attenuated the anxiolytic effect of premedication, particularly in children with low distress tolerance. Finally, the assessment of adverse effects was limited to parental reports within 24 hours and did not include objective sedation-related respiratory outcomes, which may underestimate subtle or transient complications.

## CONCLUSION

Oral gabapentin and lorazepam possess potential as pharmacological strategies for managing preoperative anxiety in pediatric patients. Although no statistically significant differences were observed in anxiety scores,

lorazepam consistently showed more favourable outcomes in sedation adequacy and separation parental. These findings suggest that lorazepam may be more clinically reliable in achieving the desired anxiolytic and sedative effects in the pediatric population. Nonetheless, gabapentin remains a promising alternative, particularly in specific clinical settings. Future studies should explore the integration of pharmacologic and non-pharmacologic approaches w hile accounting for psychosocial variables to optimize perioperative anxiety management in children.

## DECLARATIONS

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**Ethics approval**

This study was approved by the Ethics Committee of The Ethics Committee of the Zainoel Abidin Hospital, in accordance with the Declaration of Helsinki and national ethical standards for research involving human subjects. The ethical clearance number is :311/ETIK-RSUDZA/2024, issued on 28th November 2024.

Written informed consent was obtained from all parents or legal guardians of participating children prior to inclusion in the study.

**Conflicts of Interest**

The authors declare that there is no conflict of interest.

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