ANESTHESIOLOGY®

# Effects of Dexmedetomidine–Remifentanil on Neurodevelopment of Children after Inhalation Anesthesia: A Randomized Clinical Trial

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## ABSTRACT

**Background:** Anesthetic exposure in young children raises concerns about neurodevelopmental safety, with preclinical evidence suggesting potential neurotoxicity of volatile anesthetics. This study aimed to assess whether the combination of dexmedetomidine and remifentanil, by reducing sevoflurane exposure, has any differential effect on neurodevelopmental outcomes in young children compared with sevoflurane alone.

**Methods:** This study was a prospective, double-blind, randomized clinical trial including children younger than 2 yr undergoing nonstaged, nonrepetitive surgeries. Participants received dexmedetomidine and remifentanil as adjuncts to sevoflurane (DEX-R group) or sevoflurane alone (control group). The study assessed their neurodevelopmental status at 28 to 30 months using the Korean Leiter International Performance Scale and the Child Behavior Checklist, as predefined secondary outcomes. The primary endpoint—full-scale IQ at 5 yr of age—will be reported after completion of long-term follow-up.

**Results:** Among 400 enrolled participants, 343 completed assessments (169 control, 176 DEX-R). There was no difference in the mean anesthesia duration between the control and DEX-R groups (77.1 min *vs.* 72.8 min; mean difference [95% CI], 4.4 [–3.8 to 12.6]; $P = 0.293$). The mean end-tidal sevoflurane concentration was significantly lower in the DEX-R group than in the control group (1.8 vol% *vs.* 2.6 vol%; mean difference [95% CI], –0.9 [–1.0 to –0.7] vol%; $P < 0.001$). The mean full-scale IQ score was 102.5 ± 11.5 in the DEX-R group and 103.6 ± 11.5 in the control group (mean difference, –1.1; 95% CI, –3.9 to 1.7; $P = 0.442$). No significant difference was observed in the Child Behavior Checklist total score between groups.

**Conclusions:** The addition of dexmedetomidine and remifentanil to sevoflurane anesthesia was not associated with significant differences in neurodevelopmental outcomes at 28 to 30 months compared to sevoflurane alone.

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Preclinical studies demonstrate that most general anesthetic agents may have negative effects on neuronal development when delivered to young animals.
- In humans, the general anesthesia spinal trial found no evidence for adverse outcomes in children exposed to 1 h of sevoflurane *versus* regional anesthesia. Some observational studies suggest weak associations between anesthesia exposure in early life and a range of neurodevelopmental outcomes. The evidence is at best weak due to the likelihood of confounding factors.

### What This Article Tells Us That Is New

- This trial randomized 400 children less than 2 yr of age to, on average, 70 min of general anesthesia under sevoflurane alone or low-dose sevoflurane with concurrent remifentanil and dexmedetomidine.
- In the 343 children who underwent assessment at approximately 30 months of age, there was no evidence of a difference in neurocognitive or behavioral outcomes.

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**Abbreviations: BIS**, Bispectral Index; **CBCL**, Child Behavior Checklist; **DEX-R**, dexmedetomidine–remifentanil; **FSIQ**, Full-Scale Intelligence Quotient; **GAS**, general anesthesia spinal; **K-DST**, Korean Developmental Screening Test for Infants and Children; **MASK**, Mayo Anesthesia Safety in Kids; **PANDA**, Pediatric Anesthesia Neurodevelopment Assessment; **TREX**, Trial Remifentanil DEXmedetomidine



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The possible neurotoxic effects of anesthetic agents during early childhood have emerged as an important issue in pediatric anesthesiology.[1] Preclinical studies since the early 2000s have demonstrated that anesthetic exposure during key periods of brain development can lead to nerve cell damage, disrupted brain connections, and lasting issues with learning and memory. A landmark study in 2003 first demonstrated neurodegeneration and lasting learning problems in young animals exposed to anesthesia.[2] These findings have driven extensive laboratory and clinical research examining the effects of anesthesia exposure on brain development and cognitive outcomes in children.

Evidence from human studies remain complex and somewhat inconclusive. Large-scale studies such as the General Anesthesia Spinal (GAS),[3,4] Pediatric Anesthesia Neurodevelopment Assessment (PANDA),[5] and Mayo Anesthesia Safety in Kids (MASK) studies[6] have suggested no significant cognitive impairment from brief anesthetic exposure. On the other hand, parental surveys have reported associations between anesthesia exposure and language delays.[5] Several meta-analyses have also associated early exposure with behavioral issues and learning delays.[7,8] However, most existing data are derived from observational studies, which are inherently prone to selection bias and confounding.[9] In this context, randomized clinical trials have been essential for clarifying potential neurotoxic effects while minimizing bias.

Despite numerous studies, the potential neurodevelopmental effects of anesthetic agents remain uncertain, underscoring the need for further investigation.[7] To address this, we conducted a prospective, double-blind randomized clinical trial comparing two anesthetic techniques in young children. To our knowledge, although randomized studies on this topic are currently in progress,[10] no results have yet been published comparing neurodevelopmental outcomes across anesthetic regimens in this context.

Dexmedetomidine, a sedative with analgesic properties, has shown minimal neurotoxic effects and may offer a safer option for young children.[11,12] Remifentanil, an ultra-short-acting opioid, provides effective analgesia without prolonged sedation when combined with other agents. While the GAS trial demonstrated no significant difference in neurodevelopmental outcomes between sevoflurane anesthesia and awake regional anesthesia in infants,[3,4] the study was conducted in a specific surgical population, namely inguinal hernia repair. Moreover, spinal anesthesia is often impractical in routine pediatric surgical settings due to technical challenges and limited procedural applicability. Consequently, reducing the exposure to volatile anesthetics such as sevoflurane by supplementing with adjuvant agents like dexmedetomidine and remifentanil presents a more feasible approach. However, to date, no study has explored the effects of combining dexmedetomidine and remifentanil during general anesthesia on neurocognitive outcomes.

The aim of this study was to compare intelligence and behavioral assessment outcomes between young children receiving sevoflurane alone *versus* balanced anesthesia with dexmedetomidine and remifentanil during single anesthetic exposure. This study was conducted in a homogeneous Korean population to provide insights supporting neurodevelopmentally safe anesthetic practices in Korea. Although the primary outcome of this trial is the Full-Scale Intelligence Quotient (FSIQ) assessed at 5 yr of age using the Wechsler Preschool and Primary Scale of Intelligence, the current report presents prespecified secondary outcomes evaluating neurodevelopmental status at 28 to 30 months of age.

## Materials and Methods

### Subjects and Study Design

This prospective, parallel-arm, double-blind, randomized controlled clinical trial was approved by the Seoul National University Hospital Institutional Review Board, Seoul, Republic of Korea (Chairperson Ok-Joo Kim) on June 1, 2020 (approval No. 2003-234-1115), and registered at https://clinicaltrials.gov (NCT04364945; April 28, 2020; principal investigator Ji-Hyun Lee) before patient enrollment. The study was conducted at Seoul National University Children's Hospital, Seoul, Republic of Korea. Before surgery, investigators evaluated patient eligibility, met with parents or guardians to explain the study protocol, and obtained written informed consent for enrollment. The consenting guardians were asked to complete the Korean Developmental Screening Test for Infants and Children (K-DST) questionnaire, and the results were reviewed; children were ultimately enrolled if the K-DST results indicated normal development, with no need for additional intervention or follow-up.

The study included patients younger than 2 yr of age undergoing general anesthesia for nonstaged and nonrepetitive procedures with American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status I or II. Surgical

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procedures included urologic, orthopedic, general, plastic, otolaryngologic, and thoracoscopic surgeries, all of which were elective and single stage. Exclusion criteria were as follows: neonates under 1 month of age; patients with history of general anesthesia or sedation; patients with adverse reactions or allergies to opioids or dexmedetomidine; and patients with significant intraoperative bleeding or shock risk, congenital heart defects, interstitial lung disease, renal or hepatic diseases, central or peripheral nervous system disorders, known genetic or chromosomal abnormalities, or developmental delay identified through K-DST results. If additional general anesthesia was required during the follow-up period, participants were withdrawn from the study.

## Randomization

Participants were randomly assigned to either the control or the DEX-R groups using a simple randomization procedure (computerized randomization: https://sealedenvelope.com/). A trained study nurse created and managed the sealed random allocation envelopes. Upon enrollment of each participant, the envelope was opened to reveal the assigned group, and the nurse prepared either dexmedetomidine and remifentanil syringes or two saline syringes. The attending anesthesiologist, participants, guardians, surgeon, and outcome assessors, including psychological examiners, were blinded to group allocation.

## Anesthesia Protocol

Peripheral intravenous access was secured before operating room entry, either in the ward or in the day surgery center. In operating rooms, standard monitoring of noninvasive blood pressure, peripheral oxygen saturation, and electrocardiography was initiated, and Bispectral Index (BIS) monitoring was commenced. Subsequently, 0.02 mg/kg atropine and 5 mg/kg thiopental sodium were administered, and facemask ventilation was provided using sevoflurane with 100% oxygen. Rocuronium (0.6 mg/kg) was then administered, after which either an endotracheal tube or a supraglottic airway device was inserted.

Anesthesia was maintained using sevoflurane in both control and DEX-R groups. For the DEX-R group, dexmedetomidine (1 μg/kg loading dose, followed by continuous infusion at 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.1 to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were administered from the induction phase. The control group received normal saline at equivalent volumes. In both groups, intravenous acetaminophen (15 mg/kg) was routinely infused at the start of surgery. Sevoflurane concentration was adjusted to maintain BIS values between 40 and 60 in both groups.

Upon completion of surgery, anesthetic administration was discontinued, and ketorolac (0.5 mg/kg) was administered intravenously. Patients were extubated or had the airway device removed once spontaneous breathing was sufficient and consciousness was regained. Patients were transferred to the recovery room for vital sign monitoring and discharged when the modified Aldrete score reached 9 or higher. All parameters, including vital signs and end-tidal sevoflurane concentrations, were automatically recorded at 1-min intervals *via* the electronic medical record system.

## Neurodevelopmental Outcome Assessment

When participants reached approximately 30 months of age, they visited the hospital for assessments using the Korean version of the Leiter International Performance Scale and the Child Behavior Checklist (CBCL). The Leiter test was administered by qualified clinical psychologists, while the CBCL was completed by each child's primary caregiver.

The Korean Leiter International Performance Scale is a standardized nonverbal intelligence assessment tool that measures performance intelligence in individuals aged 2 yr and older. This includes four core subscales—matching, associated pairs, forward memory, and sustained attention—that evaluate various cognitive abilities, including fluid reasoning, attention, visualization, and memory skills. The Korean Leiter International Performance Scale was chosen for its standardization and validated use with Korean children.[13]

The CBCL is a parent-reported questionnaire that assesses multiple areas of the behavioral and emotional functioning of a child, providing insights into social, emotional, and behavioral development from the perspective of the caregiver. In addition, the CBCL includes questions that evaluate aspects of language development, including expressive vocabulary, offering a broader perspective on the overall development of the child.

## Data Collection

In addition to perioperative data, information was collected on parental demographics (age at birth and highest educational attainment [high school diploma, bachelor's degree, master's degree, or higher]), gestational age at birth, birth weight, and self-reported socioeconomic status (classified as high, middle, or low).

## Sample Size Calculations

Based on the GAS study results,[4] the FSIQ (±SD) of study participants who underwent general anesthesia with sevoflurane for hernia repair before the age of 1 yr was 98.97 ± 19.66 on the Wechsler Preschool and Primary Scale of Intelligence test at approximately 5 yr of age. In our study, we assumed an FSIQ of 98.97 in the control group and 105 in the DEX-R group, reflecting a hypothesized neuroprotective effect of the intervention. A difference greater than 5 points was defined as the minimal clinically important difference. This estimate also accounts for the tendency of families with higher engagement and motivation to return


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for long-term follow-up, and the fact that our cohort comprised predominantly full-term infants, in contrast to the GAS study population. Assuming an SD of 20, a two-sided α of 0.05, and 80% power, a sample size of 171 participants per group was required. Allowing for an anticipated 17% attrition rate, a total enrollment target of 400 participants (200 per group) was established.

## Statistical Analysis

The primary outcome of the trial, the FSIQ score at age 5 yr, is not reported in this article. The current analyses pertain only to the prespecified secondary outcomes assessed at 28 to 30 months of age. For this report, the primary outcome measure was the K-Leiter full-scale IQ composite score at 28 to 30 months. Secondary outcomes included Brief IQ, fluid reasoning, basic visualization subscales, and CBCL T scores. CBCL scores exceeding 60 indicated clinical deficits.

Demographic data and perioperative variables were analyzed as a complete data set. Because outcome data were not available for participants who were lost to follow-up, the results of intelligence tests and CBCL were analyzed per protocol only for participants who completed the assessments. Data normality was tested using the Shapiro–Wilk test, with results expressed as the mean ± SD or the median (interquartile ranges). Group differences in primary and secondary outcomes were analyzed using independent *t* tests for normally distributed variables or Mann–Whitney U tests for nonparametric data. For categorical CBCL subdomains exceeding clinical cutoffs, chi-square tests were applied. Statistical analyses were performed using SPSS version 26.0 (IBM Inc., USA), with $P < 0.05$ considered statistically significant.

**Table 1.** Baseline Characteristics of Enrolled Patients and Parents

| Characteristic | Control Group (n = 200) | DEX-R Group (n = 200) |
|---|---|---|
| Age, months | 11.5 (5.7; range, 1.1–23.9) | 11.2 (5.7; range, 1.0–23.7) |
| Sex, male/female | 129/71 | 138/62 |
| Height, cm | 74.2 ± 8.6 | 74.0 ± 8.8 |
| Weight, kg | 9.5 ± 2.1 | 9.4 ± 2.1 |
| Body mass index, kg/m² | 17.2 ± 1.7 | 16.9 ± 2.0 |
| Gestational age, weeks | 37.8 ± 1.7 | 37.9 ± 2.1 |
| Birth weight, kg | 3.0 ± 0.6 | 3.1 ± 0.5 |
| Preterm birth, No.* | 40 (20%) | 29 (14.5%) |
| Father's age at birth, yr | 35.8 ± 5.4 | 35.8 ± 6.3 |
| Mother's age at birth, yr | 33.8 ± 4.9 | 33.6 ± 5.1 |
| Father's education | | |
| Master's degree or higher | 25 (12.5%) | 24 (12%) |
| Bachelor's degree | 154 (77.0%) | 153 (76.5%) |
| High school diploma | 21 (10.5%) | 23 (11.5%) |
| Mother's education | | |
| Master's degree or higher | 19 (9.5%) | 21 (10.5%) |
| Bachelor's degree | 156 (78.0%) | 152 (76.0%) |
| High school diploma | 25 (12.5%) | 27 (13.5%) |
| Social-economic status (H/M/L) | 10/180/10 | 10/181/9 |
| Operation | | |
| Urologic surgery | 62 (31%) | 63 (31.5%) |
| Orthopedic surgery | 48 (24%) | 45 (22.5%) |
| General surgery | 37 (18.5%) | 40 (20%) |
| Plastic surgery | 33 (16.5%) | 35 (17.5%) |
| Otolaryngologic surgery | 12 (6%) | 10 (5%) |
| Thoracoscopic surgery | 8 (4%) | 7 (3.5%) |

The data are presented as the mean ± SD or the number (percentage).
*Delivery before 37 weeks of gestation.
DEX-R, dexmedetomidine–remifentanil; H, high; L, low; M, middle.

## Results

The study enrolled 400 participants between June 2020 and March 2023, randomizing 200 to each group. Twelve children (seven in the control and five in DEX-R) withdrew due to unexpected additional surgeries. Forty-two children (23 in the control and in DEX-R) declined follow-up testing because of COVID-19–related issues or guardian circumstances. The final analysis included 169 participants from the control group and 176 from the DEX-R group who completed both K-Leiter full-scale IQ test and CBCL assessment (fig. 1). Baseline characteristics showed comparable distributions between groups (table 1). Mean ± SD age at surgery was 11.5 ± 3.2 months in the control group and 11.2 ± 3.1 months in the DEX-R group. Parental age at birth, educational level, and socioeconomic status did not significantly differ between groups. In addition, the distribution of surgical types was comparable between the two groups, with urologic and orthopedic surgeries being the most common. All participants met American Society of Anesthesiologists Phyiscal Status I criteria.

No significant differences were observed in anesthesia and surgery duration between groups (table 2). The DEX-R group demonstrated lower heart rate and systolic blood pressure compared with those in the control group, although mean blood pressure remained similar between groups. One patient in each group received vasoactive medication (ephedrine, 1 to 2 mg). The mean BIS values between the start and end of surgery were 41.3 ± 12.6 in the control group and 40.3 ± 12.2 in the DEX-R group (mean difference, 1.2 [−1.4 to 3.3]; $P = 0.414$). In contrast, the mean end-tidal sevoflurane concentration was significantly lower in the DEX-R group (1.8% ± 0.5%) compared with that in the control group (2.6% ± 0.6%; $P < 0.001$).

There were no significant differences between the DEX-R and control groups in full-scale IQ scores (102.5 ± 11.5 *vs.* 103.6 ± 11.5; mean difference, −1.1 [−3.9 to 1.7]; $P = 0.442$), Brief IQ (102.1 ± 11.5 *vs.* 102.7 ± 10.4; mean difference, −0.6 [−3.0 to 1.8]; $P = 0.613$), fluid reasoning (96.9 ± 11.3 *vs.* 98.1 ± 12.3; mean difference, −1.2 [−4.0 to 1.7]; $P = 0.421$), or basic visualization (104.5 ± 13.7 *vs.* 103.6 ± 13.1; mean difference 0.8, [−2.5 to 4.0]; $P = 0.642$; table 3).

CBCL total problem scores were also comparable between the DEX-R and control groups (46.8 ± 9.7 *vs.*


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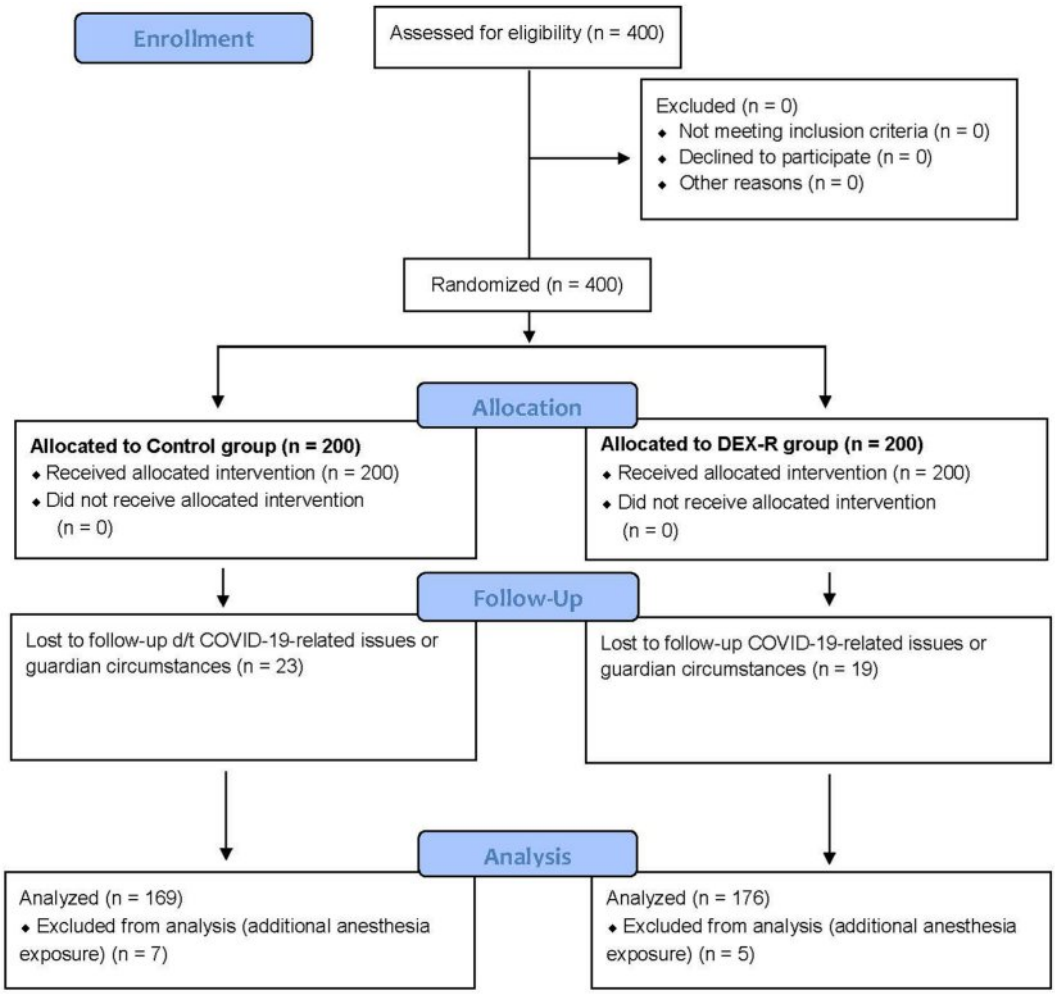


**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. DEX-R, dexmedetomidine–remifentanil; d/t, due to.

47.6 ± 10.2; mean difference, −0.9 [−3.2 to 1.5]; $P$ = 0.469), as were the internalizing (46.7 ± 9.8 *vs.* 47.3 ± 9.4; mean difference, −0.6 [−2.8 to 1.6]; $P$ = 0.602) and externalizing scores (46.5 ± 10.0 *vs.* 46.6 ± 9.6; mean difference, −0.1 [−2.3 to 2.2]; $P$ = 0.966). The proportion of children with CBCL T scores of 60 or higher did not significantly differ between groups across domains. In addition, measures of language development showed no significant differences between the two groups.

## Discussion

This randomized clinical trial found no significant differences in intelligence and behavioral assessment outcomes between the combined anesthetic protocol and standard care, although sevoflurane consumption was decreased in the DEX-R group. These results are consistent with findings from the PANDA and MASK studies, which established that a single anesthetic exposure does not significantly affect subsequent IQ and neurocognitive development.[5,6] Although the combination of dexmedetomidine and remifentanil effectively reduced sevoflurane requirements during surgery, it provided no measurable neuroprotective advantages.

We attribute the absence of demonstrable neuroprotective effects primarily to the relatively brief anesthetic exposure and single-procedure design. Previous studies, particularly the GAS trial, have indicated that short-term anesthetic exposure (under 90 min) is not associated with measurable differences in neurodevelopmental outcomes in young children.[3,4] Consistently, the mean duration of anesthesia in our study was within this range, potentially minimizing the neurotoxic effects documented in preclinical studies.

Preclinical studies have demonstrated promising results for dexmedetomidine and remifentanil in reducing neurotoxicity by attenuating oxidative stress and inflammation.[14] However, these mechanisms may not translate


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**Table 2.** Comparison of Perioperative Variables between the Control and DEX Group

| Variable | Control Group (n = 200) | DEX-R Group (n = 200) | Mean Differences (95% CI) | *P* Value |
|---|---|---|---|---|
| Intraoperative variables | | | | |
| Operation time, min | 49.4 ± 36.7 | 44.0 ± 38.1 | 5.4 (–1.8 to 12.6) | 0.141 |
| Anesthesia time, min | 77.1 ± 43.2 | 72.8 ± 44.4 | 4.4 (–3.8 to 12.6) | 0.293 |
| Dexmedetomidine dose, μg/kg | 0 | 1.9 ± 0.8 | –1.9 (–2.0 to –1.7) | < 0.001 |
| Remifentanil dose, μg/kg | 0 | 5.6 ± 4.6 | –5.6 (–6.2 to –5.0) | < 0.001 |
| Heart rate, beats/min | 151.0 ± 12.7 | 125.1 ± 13.0 | 25.9 (23.5– 28.4) | < 0.001 |
| Systolic blood pressure, mmHg | 88.1 ± 8.3 | 84.2 ± 7.6 | 4.1 (2.6 to 5.6) | < 0.001 |
| Diastolic blood pressure, mmHg | 48.1 ± 9.2 | 49.3 ± 8.8 | –1.1 (–2.8 to 0.6) | 0.191 |
| Mean blood pressure, mmHg | 60.6 ± 8.2 | 60.4 ± 8.2 | 0.2 (–1.3 to 1.7) | 0.799 |
| $Spo_2$, % | 99.9 ± 0.3 | 99.9 ± 0.3 | 0.1 (–1.0 to 0.0) | 0.058 |
| Mean BIS value | 41.3 ± 12.6 | 40.3 ± 12.2 | 1.2 (–1.4 to 3.3) | 0.414 |
| Maximum end-tidal sevoflurane concentration, vol% | 3.2 ± 0.8 | 2.2 ± 0.7 | 1.0 (0.8 to 1.1) | < 0.001 |
| Minimum end-tidal sevoflurane concentration, vol% | 2.1 ± 0.6 | 1.3 ± 0.5 | 0.7 (0.6 to 0.8) | < 0.001 |
| Mean end-tidal sevoflurane concentration, vol% | 2.6 ± 0.6 | 1.8 ± 0.5 | 0.9 (0.7 to 1.0) | < 0.001 |
| Need for vasoactive drug administration | 1 (0.5%) | 1 (0.5%) | | 1.0 |
| Postoperative variables in PACU | | | | |
| Heart rate, beats/min | 160.6 ± 28.0 | 131.2 ± 29.0 | 29.3 (23.9 to 34.7) | < 0.001 |
| Systolic blood pressure, mmHg | 104.8 ± 12.6 | 97.1 ± 10.9 | 7.8 (5.6 to 10.0) | < 0.001 |
| Diastolic blood pressure, mmHg | 71.1 ± 14.7 | 62.0 ± 12.1 | 9.2 (6.7 to 11.8) | < 0.001 |
| Mean blood pressure, mmHg | 82.2 ± 14.1 | 72.1 ± 10.8 | 10.1 (7.8 to 12.5) | < 0.001 |
| $Spo_2$, % | 99.7 ± 0.6 | 99.7 ± 0.6 | 0.0 (–0.1 to 0.1) | 0.635 |

The data are presented as the mean ± SD or the number (percentage). The DEX-R group received the dexmedetomidine and remifentanil infusion along with sevoflurane during anesthesia, while the control group received only sevoflurane.

BIS, Bispectral Index; PACU, postanesthesia care unit; $Spo_2$, oxygen saturation measured by pulse oximetry.

**Table 3.** Estimates for Mean Values of Intelligence Assessment and Child Behavior Checklist According to Groups

| | Control Group (n = 169) | DEX-R Group (n = 176) | Mean Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| Leiter full scale IQ score | 103.6 ± 11.5 | 102.5 ± 11.5 | 1.1 (–1.7 to 3.9) | 0.442 |
| Brief IQ | 102.7 ± 10.4 | 102.1 ± 11.5 | 0.6 (–1.8 to 3.0) | 0.613 |
| Fluid reasoning subset | 98.1 ± 12.3 | 96.9 ± 11.3 | 1.2 (–1.7 to 4.0) | 0.421 |
| Basic visualization subset | 103.6 ± 13.1 | 104.5 ± 13.7 | –0.8 (–4.0 to 2.5) | 0.642 |
| CBCL | | | | |
| Total problem, TS | 47.6 ± 10.2 | 46.8 ± 9.7 | 0.9 (–1.5 to 3.2) | 0.469 |
| Patients with score ≥ 60 | 17 (10.1%) | 17 (9.7%) | 0.4 (–6.4 to 7.2) | 0.955 |
| Internalizing problems, TS | 47.3 ± 9.4 | 46.7 ± 9.8 | 0.6 (–1.6 to 2.8) | 0.602 |
| Patients with score ≥ 60 | 80 (47.3%) | 93 (52.8%) | –5.5 (–16.3 to 5.4) | 0.361 |
| Externalizing problems, TS | 46.6 ± 9.6 | 46.5 ± 10.0 | 0.1 (–2.2 to 2.3) | 0.966 |
| Patients with score ≥ 60 | 16 (9.5%) | 15 (8.5%) | 1.0 (–5.5 to 7.6) | 0.892 |
| ADHD problems, TS | 53.0 ± 5.6 | 53.6 ± 5.6 | –0.7 (–2.0 to 0.6) | 0.315 |
| Patients with score ≥ 60 | 20 (11.8%) | 33 (18.8%) | –7.0 (–14.9 to 1.0) | 0.098 |
| Vocabulary, percentile | 48.1 ± 35.7 | 43.6 ± 33.7 | 4.5 (–3.6 to 12.5) | 0.269 |
| Sentence length, percentage | 65.0 ± 31.6 | 58.5 ± 31.8 | 6.5 (–1.1 to 14.2) | 0.089 |

The data are presented as the mean ± SD or the number (percentage). The DEX-R group received dexmedetomidine and remifentanil infusion along with sevoflurane during anesthesia, while the control group received only sevoflurane.

ADHD, attention deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; IQ, intelligence quotient; TS, T score.

effectively into clinical benefits during single anesthetic exposure. The ongoing TREX trial (Trial Remifentanil DEXmedetomidine) has employed a similar protocol combining dexmedetomidine and remifentanil with sevoflurane.[15] Although the dexmedetomidine dosing in our study matched that in the TREX protocol, we modified the remifentanil administration by omitting the loading dose.[16] Furthermore, unlike the TREX study, which incorporated regional anesthesia and discontinued sevoflurane, our approach maintained continuous sevoflurane administration.

While the DEX-R protocol led to a significant reduction in sevoflurane concentration compared to the control group, the extent of reduction was less than that observed in the TREX trial, which employed regional anesthesia to achieve lower concentrations (0.8 vol%).[17] However, the



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anesthetic regimen used in our study reflects broader clinical practice in which regional techniques are not routinely applicable. In this context, the study also allowed for an evaluation of the potential neuroprotective effect of dexmedetomidine under typical general anesthesia conditions.

The study population characteristics merit careful consideration. Our exclusive focus on a homogeneous Korean cohort offered methodologic advantages by minimizing genetic and cultural confounding variables. However, this design potentially limits result generalizability to other populations. Moreover, distinctive sociocultural factors in Korean society, including emphasized early childhood education and elevated parental expectations, may influence neurodevelopmental outcomes independently of anesthetic exposure.

Despite initial concerns that the combination of dexmedetomidine and remifentanil might increase the risk of intraoperative hypotension or bradycardia, hemodynamic parameters remained stable, with few cases requiring vasoactive support. This success likely stems from our protocol of prophylactic atropine administration before anesthetic induction. For comparison, the GAS study reported vasoactive drug requirements in approximately 5% of general anesthesia patients.[3] Recent TREX trial data showed reduced hypotension but increased bradycardia with dexmedetomidine–remifentanil administration.[17]

Our neurodevelopmental assessment approach using the Korean Leiter International Performance Scale IQ assessment provided distinct advantages. This nonverbal assessment tool differs from the verbally dependent Wechsler Abbreviated Scale of Intelligence used in the PANDA and MASK studies.[5,6,13] A previous study demonstrated a strong correlation between Leiter and Wechsler results ($r > 0.7$; $P < 0.001$), although Leiter testing typically yields higher scores, particularly beneficial for evaluating young children with developing language skills.[18,19]

Several important limitations warrant consideration in interpreting our results. First, children who required additional anesthesia during the follow-up period were excluded after randomization, which does not conform to the intention-to-treat principle and may have introduced selection bias. Second, the exclusive use of Korean Developmental Screening Test data may inadequately reflect baseline intelligence. Third, our reliance on basic BIS values for anesthetic depth monitoring, rather than more sophisticated measures such as density spectral array, have led to heterogeneity in anesthetic management. Although density spectral array was occasionally referenced to support anesthetic depth assessment in very young infants, it was not used systematically across all cases. Fourth, the lack of a nonanesthetized control group in the study design further limits comparative analysis. Fifth, although the end-tidal sevoflurane concentrations differed significantly between the groups, both values remained within the standard clinical range for pediatric anesthesia, which may limit the observed impact of dose variation. Sixth, while the study was powered to detect a 6-point difference in IQ scores between groups, we cannot exclude the possibility of smaller yet clinically relevant differences. Seventh, neurodevelopmental assessment at 28 to 30 months of age may lack sensitivity to detect subtle or emerging cognitive differences, which is why the prespecified primary outcome was set at 5 yr of age. Finally, due to the lack of outcome data from participants who did not complete follow-up assessments, we were unable to conduct intention-to-treat or imputation analyses. This methodologic limitation may affect the generalizability of our findings.

In conclusion, although the dexmedetomidine–remifentanil combination effectively reduced sevoflurane requirements, it was not associated with measurable short-term differences in neurodevelopmental outcomes in young children undergoing single-exposure general anesthesia. These findings support existing evidence suggesting that brief anesthetic exposure is unlikely to result in clinically significant neurodevelopmental impairment. As these results reflect predefined secondary outcomes of an ongoing randomized clinical trial, definitive conclusions regarding long-term neurodevelopmental effects will require assessment of the primary endpoint at 5 yr of age.

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## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: muslab6@snu.ac.kr or muslab@hanmail.net. Raw data available at: muslab6@snu.ac.kr or muslab@hanmail.net.

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