ANESTHESIOLOGY

# Short-term Outcomes in Infants after General Anesthesia with Low-dose Sevoflurane/ Dexmedetomidine/ Remifentanil *versus* Standard-dose Sevoflurane (the TREX Trial)

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## ABSTRACT

**Background:** The Trial Remifentanil DEXmedetomidine (TREX) trial aimed to determine whether, in children less than 2 yr old, low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia is superior to standard-dose sevoflurane anesthesia in terms of global cognitive function at 3 yr of age. The aim of the current secondary analyses was to compare incidence of intraoperative hypotension and bradycardia, postoperative pain, time to recovery, need for treatment of intraoperative hypotension and bradycardia, incidence of light anesthesia and need for treatment, need for postoperative pain medications, and morbidity and mortality outcomes at 5 days between the two arms.

**Methods:** This phase III randomized active controlled, parallel group, assessor blinded, multicenter, superiority trial was performed in 20 centers in Australia, Italy, and the United States. A total of 455 infants less than 2 yr of age expected to undergo general anesthesia for at least 2 h were enrolled. They were randomized between low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia and standard-dose sevoflurane. The short-term perioperative outcomes noted above were compared between these two groups.

**Results:** There was less hypotension (risk difference, −11.6%; 95% CI, −18.9 to −4.3%) and more bradycardia (risk difference, 18.2%; 95% CI, 8.8 to 27.7%) in the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia compared to the standard-dose sevoflurane arm. There were more patients with episodes of light anesthesia (89 *vs.* 4), and protocol abandonments (1 *vs.* 0) in the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia arm. Time from eye opening to postanesthesia care unit discharge was similar in both arms, as were morbidity and mortality. One patient in each arm suffered a life-threatening event, but neither suffered long-term sequelae.

**Conclusions:** These early postoperative results suggest that in children less than 2 yr of age receiving greater than 2 h of general anesthesia, the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia technique and the standard sevoflurane anesthesia technique are broadly clinically similar, with no clear evidence to support choosing one technique over the other.

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Concerns about anesthesia-induced developmental neurotoxicity from anesthetic agents, including propofol, sevoflurane, and ketamine, persist due to findings in animal models, but the few human studies available show conflicting results
- The Trial Remifentanil DEXmedetomidine (TREX) trial was designed to determine whether, in children less than 2 yr of age having anesthesia expected to last 2 h or longer, low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia is superior to standard-dose sevoflurane anesthesia in terms of global cognitive function, as assessed at 3 yr of age; the TREX trial is ongoing

### What This Article Tells Us That Is New

- This analysis presents and compares salient short-term perioperative outcomes from the TREX trial, including the prevalence of intraoperative hypotension, bradycardia, light anesthesia events, postoperative pain scores, time to recovery, and morbidity and mortality
- These early postoperative results suggest that in children less than 2 yr of age receiving greater than 2 h of general anesthesia, the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia technique and the standard sevoflurane anesthesia technique are broadly clinically similar, with no clear evidence to support choosing one technique over the other



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Infants undergo anesthesia for a wide range of reasons, sometimes requiring prolonged or repeated exposure to anesthesia agents. Concerns about anesthesia-induced developmental neurotoxicity from agents that enhance γ-aminobutyric acid receptor activity (*e.g.*, propofol, sevoflurane) or inhibit glutamate receptors (*e.g.*, ketamine) persist due to findings from animal models.[1] This led to the creation of the Strategies for Mitigating Anesthesia-Related neurotoxicity in Tots (SmartTots) group, a partnership between the Food and Drug Administration (Silver Spring, Maryland) of the United States and the International Anesthesia Research Society, with the goal of increasing the safety of anesthetics in children. In 2016, the Food and Drug Administration issued a safety warning stating that "repeated or lengthy use of general anesthetic or sedation drugs during surgeries or procedures in children younger than 3 yr may affect the development of children's brains" and, in 2017, approved labeling changes for anesthetic agents used in the same age group.[2,3] However, human cohort studies and one published trial showed conflicting results when comparing anesthetically exposed and nonexposed children.[4,5] Although there are some data to suggest repeated exposure may increase the risk of worse neurodevelopmental outcomes, there are minimal data available from cases involving single long exposures.[5] SmartTots have called for a trial to examine the effects of general anesthetic exposures in young children longer than 1 h in duration.

The primary aim of the Trial Remifentanil DEXmedetomidine (TREX) trial is to determine whether, in children less than 2 yr of age having anesthesia expected to last 2 h or longer, low-dose sevoflurane/dexmedetomidine/remifentanil (LD-SEVO) anesthesia is superior to standard-dose sevoflurane (STD-SEVO) anesthesia in terms of global cognitive function, as assessed by the full-scale intelligence quotient score of the Wechsler Preschool and Primary School Intelligence Scale, at 3 yr of age. A secondary aim of this trial was to compare perioperative outcomes after these two interventions. The pilot study by Szmuk *et al.*[6] suggested feasibility of the LD-SEVO arm protocol with an 87.5% success rate, and the low-dose sevoflurane component added to increase the practical utility of the technique to a wider number of surgeries. These data are important given that if one technique was found to be superior in terms of neurodevelopment, this would have to be balanced against outcomes in terms of feasibility and the clinical acceptability of the two techniques. It is also plausible that regardless of the neurodevelopmental outcome, one technique may have better perioperative outcomes, which might drive a change of practice. The objectives of this analysis are

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to present and compare the salient short-term perioperative outcomes, with the primary neurodevelopmental outcome to be presented in a subsequent article when the data are available. The perioperative outcomes include the incidence of intraoperative hypotension, bradycardia, and light anesthesia events, postoperative pain scores, time to recovery, and morbidity and mortality outcomes at 5 days postoperatively.

## Materials and Methods

This phase III randomized active controlled, parallel group, assessor blinded, multicenter, superiority trial was performed in Australia (seven centers), Italy (eight centers), and the United States (five centers) between August 2017 and April 2023 (table S1, Supplemental Digital Content 1, https://links.lww.com/ALN/D688, all enrolling centers). Ethics approval was obtained from the Royal Children's Hospital Human Research Ethics Committee in Australia on May 17, 2017 (approval number HREC/17/RCHM/57), and Italy on February 3, 2020 (Comitato Etico Regionale Liguria number 365/2019.) Participating centers in the United States individually obtained ethics approval from their respective institutional review boards. The study protocol was registered at ClinicalTrials.gov (number NCT03089905, principal investigator: Andrew J. Davidson, date of registration: March 24, 2017, https://clinicaltrials.gov/ct2/show/NCT03089905; accessed October 4, 2024) and EudraCT (number 2017-002803-81, principal investigator: Andrew J. Davidson, date of registration: August 2, 2021, https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002803-81/IT; accessed October 4, 2024).

### Recruitment

Eligible patients were identified from operating room schedules or in the preadmission clinics at participating sites. Written informed consent was obtained from a parent or legal guardian before recruitment into the trial. The study population included 450 infants of both sexes with a chronological age of less than 2 yr and expected duration of anesthesia of at least 2 h (and/or total operating room scheduled for at least 2.5 h). Exclusion criteria included known neurologic, chromosomal, or congenital anomaly that is likely to be associated with poor neurobehavioral outcome, existing diagnosis of behavioral or neurodevelopmental disability, prematurity (defined as less than 36 weeks gestational age at birth), birth weight less than 2 kg, congenital cardiac disease requiring surgery, intracranial neurosurgery and intracranial craniofacial surgery, previous cumulative exposure to general anesthesia of greater than 2 h, planned future cumulative exposure to anesthesia greater than 2 h before the age of 3 yr, any specific contraindication to any aspect of the protocol, previous adverse reaction to any anesthetic, circumstances likely to make long-term follow-up impossible, living in a household where the primary language spoken at home is not a language in which we can administer the Wechsler Preschool and Primary School Intelligence Scale, and planned postoperative sedation with any agent except opioids (*e.g.*, benzodiazepines, dexmedetomidine, ketamine, barbiturates, propofol, clonidine, chloral hydrate, and other nonopioid sedatives), including planned sedation for postoperative ventilation.

### Study Procedures

Once eligibility and consent had been confirmed, patients were randomized in a 1:1 ratio to either LD-SEVO or STD-SEVO, using block randomization with variable block sizes, stratified by site and age at the time of exposure. Random allocation occurred *via* an online central randomization service within Research Electronic Data Capture. Given the nature of the interventions, the trial was not blinded, but the neuropsychologist performing the assessment was blinded to group allocation. Parents were not informed of group allocation but were told if they asked. Patients in both arms were treated by anesthesiologists who were part of the research team, familiar with the study protocol, and instructed on specific definitions and rescue treatments for hypotension, bradycardia, and light anesthesia. Figure 1 shows the detailed steps of the perioperative management in the two intervention arms. Supplemental Digital Content 2 (https://links.lww.com/ALN/D689) details the rescue protocols for hypotension, bradycardia, and light anesthesia events.

### Data Collection

Demographic data were collected for all participants on age, birth weight, singleton or multiple gestation birth, weight at the time of surgery, sex, gestational age at birth, surgical history, indication for surgery, primary language spoken at home, maternal education, maternal age, family structure, rurality, birth order, and number of siblings. Clinical data were also collected, namely vital signs (systolic blood pressure, mean arterial pressure [MAP], heart rate, and oxygen saturation) recorded preanesthesia, every 3 min intraoperatively, and every 5 min for at least the first 60 min after surgery; pain and sedation scores recorded every 5 min postoperatively for at least 60 min; doses or infusion rates and timing of all medications administered; end tidal concentrations of volatile anesthetics intraoperatively; any hypotension, bradycardia, or light anesthesia event requiring intervention; type of airway device; timepoints of induction, surgery start and end, removal of airway, arrival in postanesthesia care unit (PACU), eye opening, and discharge from PACU; surgical procedure; and details of any peri- and intraoperative anesthetic complications. The families of enrolled patients were then contacted at 24 h and 5 days postanesthesia to inquire about any major events.

### Outcomes

The outcomes of interest in this analysis (which were detailed in the initial trial registration) include incidence of intraoperative hypotension (defined as MAP less than

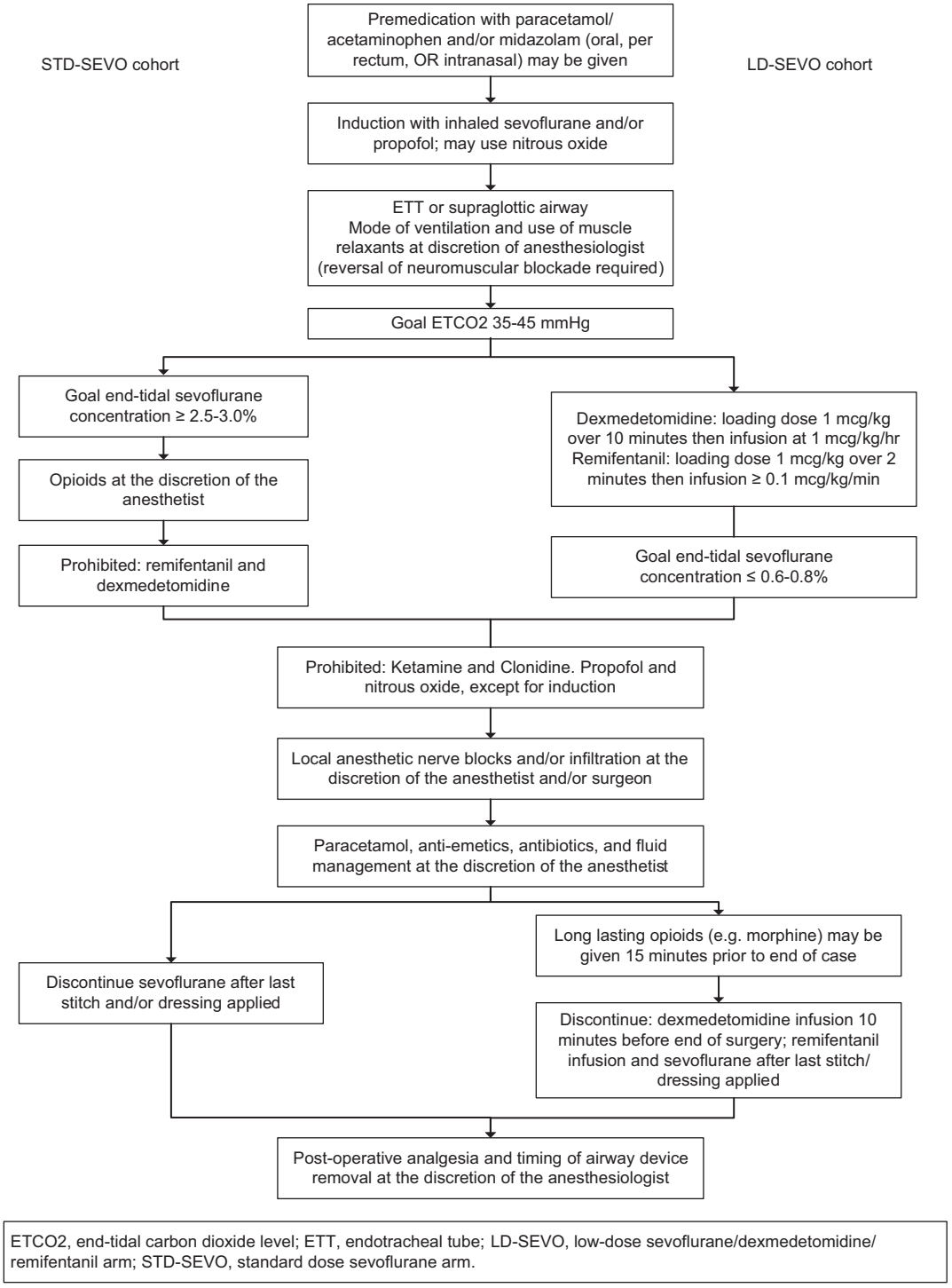


**Fig. 1.** Protocol flowchart. $ETCO_2$, end-tidal carbon dioxide level; ETT, endotracheal tube; LD-SEVO, low-dose sevoflurane/dexmedetomidine/ remifentanil arm; STD-SEVO, standard-dose sevoflurane arm.

35 mmHg in children weighing less than 5 kg and MAP less than 40 mmHg in children weighing more than 5 kg),[7] incidence of intraoperative bradycardia (defined as heart rate of less than 90 beats/min for more than 1 min), postoperative pain assessed at 60 min after surgery (recorded as range, median, and mean of Face, Legs, Activity, Cry, Consolability [FLACC] scale scores), and time to recovery (defined as end of surgery to time of

eye opening and time of eye opening to discharge from PACU). The intraoperative period was defined as the time from induction of anesthesia until removal of airway.

Additional outcomes (which were not in the initial trial registration) included need for pharmacologic treatment of intraoperative hypotension (with intravenous fluids and/or vasoactive agents) and bradycardia (with atropine or glycopyrrolate), incidence of light anesthesia (defined as movement with or without hypertension or confirmed hypertension with two consecutive measurements, where hypertension is defined as MAP greater than 70 mmHg in children weighing less than 5 kg and MAP greater than 75 mmHg in children weighing more than 5 kg) and need for pharmacologic treatment (by increasing the rate of remifentanil infusion and/or inhaled sevoflurane concentration), need for postoperative pain medications during the first 60 min of PACU stay, and morbidity and mortality outcomes at 5 days postoperatively, including postoperative readmission, prolonged hospitalization (more than 5 days), serious morbidity (resulting in persistent or significant disability), occurrence of life-threatening events, and death. Episodes of light anesthesia were not recorded for 115 of 221 patients (52%) randomized to the STD-SEVO arm because this outcome was not consistently collected over time and across sites in the STD-SEVO arm, until it was recognized that it was a poor decision not to include these data. Subsequently, data on episodes of light anesthesia were collected for both arms. The prespecified Statistical Analysis Plan for this analysis can be found at https://clinicaltrials.gov/study/NCT03089905#moreinformation (accessed October 4, 2024).

In addition to the prespecified analysis, *post hoc* analyses are also presented on the lowest intraoperative MAP, average heart rate intraoperatively and in the first postoperative hour, lowest median intraoperative heart rate, propofol bolus administration during maintenance of anesthesia, time from end of surgery to removal of airway, time from end of surgery to departure from the operating room, duration of PACU stay, and discharge within 24 h.

### Statistical Analysis

The sample size was based on the primary outcome of the trial: neurodevelopmental outcome measured using the Weschler composite cognitive score at 3 yr of age. In a healthy population, the Wechsler composite cognitive score has a mean of 100 and a SD of 15. Any difference larger than one third of a SD (5 points) is regarded as being minimally clinically important. For our study, 190 children in each arm were required to have a 90% power to detect a difference of 5 points based on a two-sided test with $\alpha = 0.05$. The recruitment target of 450 children was set to allow for 15% loss to follow up. A similar trial by our group had a retention rate at 2 yr greater than 85%.[8] This is also consistent with other similar studies.

All analyses were performed using the modified intention-to-treat population. This consisted of all participants who were randomized according to the arm in which they were randomized to, irrespective of the intervention received, excluding participants who did not have surgery done (cancellation). The intercurrent event of not having surgery is unrelated to the intervention received; hence, these exclusions are not expected to bias the results. A treatment policy strategy was employed to address all other intercurrent events; that is, their occurrence is ignored in the analysis.

The results are presented as differences in medians or risk difference and its 95% CI. For binary outcomes, the risk difference was estimated using a generalized linear model, which employed a Gaussian distribution (to avert convergence difficulties with low prevalence outcomes) and an identity link with a random effect to account for the clustering by site, and a fixed effect for the stratification factor of age at exposure (less than 12 months and greater than 12 months.) The continuous outcomes were skewed, and hence, treatment effects are presented as differences in medians estimated using quantile regression with a random effect to allow for the clustering by site and a fixed effect for the stratification factor of age at exposure. The data were analyzed using Stata/SE version 18.0 (StataCorp, USA).

## Results

Between August 9, 2017, and April 21, 2023, 455 children were enrolled from 20 centers in Australia, Italy, and the United States (supplemental table 1, https://links.lww.com/ALN/D688). After excluding 2 patients due to surgery cancellations, 5 who met exclusion criteria, 10 who withdrew from the trial before surgery, and 10 who were misrandomized, 428 children were included in the analysis: 207 randomized to the LD-SEVO arm and 221 randomized to the STD-SEVO arm. These exclusions were not considered part of the population of interest, and their exclusion or withdrawal was not related to randomization (fig. 2). Table 1 reveals that both arms were well matched in terms of demographic data, and table 2 details the surgical procedures in each arm. There was also a good separation of treatment; for the LD-SEVO arm, the median end-tidal sevoflurane concentration was 0.8% (interquartile range, 0.6 to 1.0) compared to 2.5% (interquartile range, 2.3 to 2.7) for the STD-SEVO arm.

There was less hypotension (risk difference, −11.6%; 95% CI, −18.9 to −4.3%) and more bradycardia (risk difference, 18.2%; 95% CI, 8.8 to 27.7%) in the LD-SEVO compared to the STD-SEVO arm. Unfortunately, data on rescue treatment administered were missing for 13 of 78 episodes of hypotension (17%, 3 of 25 in the LD-SEVO arm and 10 of 53 in the STD-SEVO arm) and 42 of 62 episodes of bradycardia (68%, 34 of 50 in the LD-SEVO arm and 8 of 12 in the STD-SEVO arm). Recorded interventions for hypotension included administration of intravenous fluids and vasoactive agents. Interventions for bradycardia, including atropine or glycopyrrolate, were recorded for eight patients (twice in one patient) in the LD-SEVO arm; one bradycardic episode was surgery-induced. No patient in the STD-SEVO arm

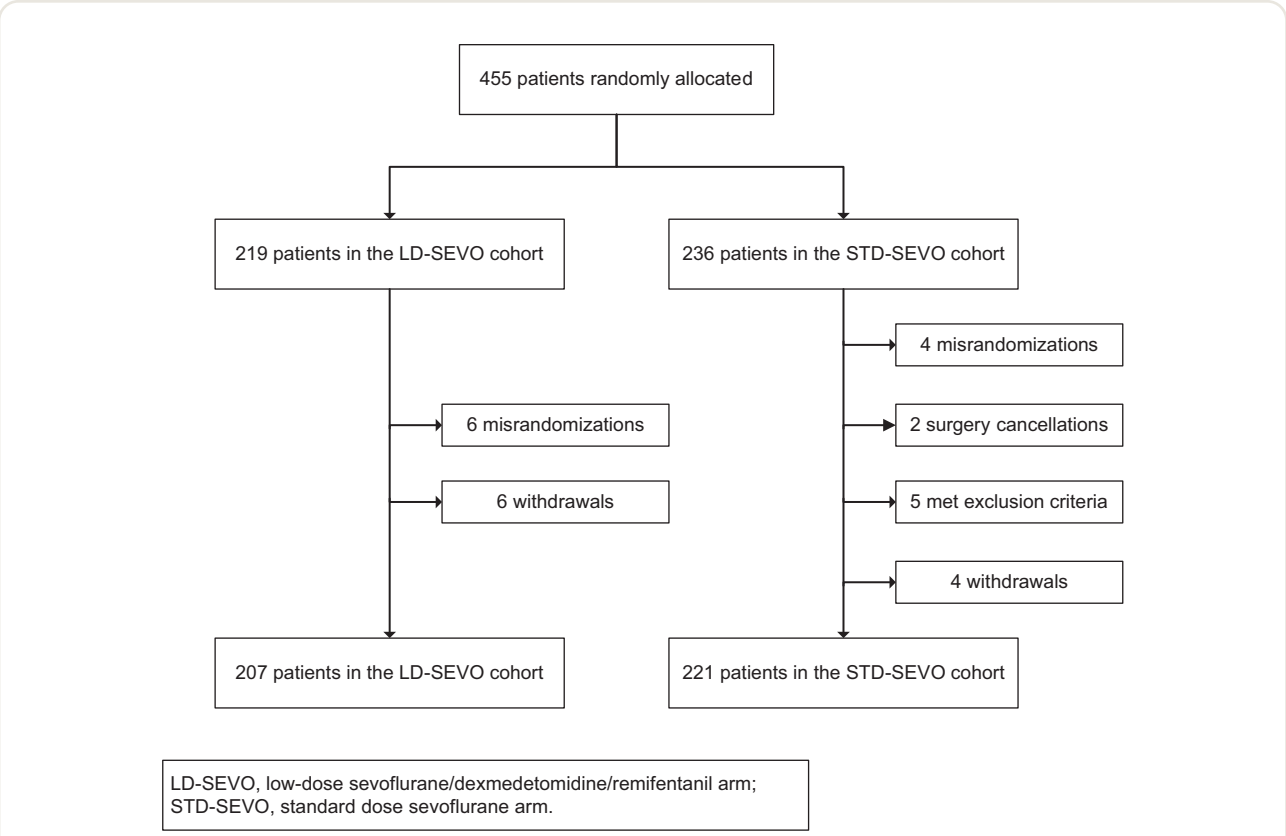


**Fig. 2.** Enrollment flowchart. LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; STD-SEVO, standard-dose sevoflurane arm.

received treatment for bradycardia. There were 89 of 207 patients (43%) in the LD-SEVO arm and 4 of 106 patients (4%) in the STD-SEVO arm with episodes of light anesthesia (risk difference, 39.8%; 95% CI, 31.1 to 48.5%; table 3). The protocol was abandoned in 1 of 428 patients (0.2%), in the LD-SEVO arm, when a prohibited medication was administered to treat substantial patient movement. FLACC scale scores were lower for the LD-SEVO compared to the STD-SEVO arm (median difference, −0.52; 95% CI, −0.87 to −0.17). A similar number of children required intervention for pain in the PACU in the two arms (table 4). After surgery, patients in the LD-SEVO arm had a shorter time to eye opening and to departure from the operating room than those in the STD-SEVO arm, but the times from end of surgery to removal of airway and from eye opening to PACU discharge were similar in both arms (table 4).

There was a similar incidence of postoperative readmission, prolonged hospitalization, and serious morbidity by postoperative day 5 in the two arms. One child from the LD-SEVO group suffered an intraoperative life-threatening event: severe bradycardia without desaturation upon removal of supraglottic airway (7 min after drug discontinuation) and progressed to asystole requiring treatment with cardiopulmonary resuscitation and epinephrine. The child was intubated and transferred to the intensive care unit postoperatively. One child from the STD-SEVO group suffered a postoperative life-threatening event: in the postoperative ward, the patient was found to be significantly bradycardic with a heart rate of less than 80 beats/min and hypothermic with a temperature of 33°C. Possible etiology included sensitivity to morphine and clonidine administered postoperatively, and treatment consisted of an active warming device and intravenous fluid resuscitation. Both patients recovered with no long-term sequelae. Both events were treated as serious adverse events and reported accordingly. There were no reported deaths in either arm (table 5).

## Discussion

Analysis of the short-term outcomes of the TREX trial reveals that the intraoperative hemodynamic profiles were similar in children less than 2 yr of age receiving greater than 2 h of general anesthesia randomized to STD-SEVO *versus* LD-SEVO. There was less bradycardia but more hypotension in the STD-SEVO arm. Assessment and clinical interpretation of hypotension is problematic because there is no established definition for hypotension in infants and no standardized guidelines regarding the diagnosis of hypotension in anesthetized children. Although intraoperative blood pressure measurements are considered an indirect measure of organ perfusion under general anesthesia, there may not be any association between hypotension

**Table 1.** Baseline Characteristics and Clinical Data

| Characteristics and Clinical Data | LD-SEVO (n = 207) | STD-SEVO (n = 221) |
|---|---|---|
| Sex, male, n (%) | 141 (68%) | 154 (70%) |
| Age, yr, mean (SD) | 0.9 (0.5) | 0.9 (0.5) |
| Weight, kg, mean (SD) | 9.1 (2.2) | 9.2 (2.3) |
| Gestational age at birth, weeks, mean (SD) | 39.0 (1.3) | 38.9 (1.3) |
| 36–37 weeks, n (%) | 25 (12%) | 31 (14%) |
| 38–40 weeks, n (%) | 163 (79%) | 172 (78%) |
| 41–43 weeks, n (%) | 19 (9%) | 18 (8%) |
| Type of airway device, n (%) | | |
| Endotracheal tube | 190 (92%) | 205 (93%) |
| Supraglottic airway | 17 (8%) | 16 (7%) |
| Duration of anesthetic, h, median (interquartile range) | 2.8 (2.2–3.7) | 2.8 (2.1–3.4) |
| Premedication, n (%) | | |
| None | 149 (72%) | 157 (71%) |
| Acetaminophen only | 1 (0.5%) | 6 (3%) |
| Midazolam only | 53 (26%) | 56 (25%) |
| Acetaminophen and midazolam | 4 (2%) | 2 (1%) |
| Neuromuscular blocking agent administered, n (%) | 160 (77%) | 157 (71%) |
| Lowest intraoperative MAP, mmHg, median (interquartile range) | 36 (35–38) | 35 (32–37) |
| Average intraoperative heart rate, beats/min (SD) | 109 (11.6) | 125 (12.4) |
| Lowest intraoperative heart rate, beats/min, median (interquartile range) | 80 (75–84) | 84 (76–93) |
| Average heart rate after 1 h in PACU, beats per minute (SD) | 117 (17.8) | 140 (58.9) |

LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; MAP, mean arterial pressure; PACU, postanesthesia care unit; STD-SEVO, standard-dose sevoflurane arm.

**Table 2.** List of Surgical Procedures

| Surgical Specialty | Standardized Procedure Name | LD-SEVO (n = 207) | STD-SEVO (n = 221) |
|---|---|---|---|
| Ear, nose, and throat | Cochlear implants | 2 | 1 |
| General surgery | Major abdominal surgery | 15 | 19 |
| | Orchiopexy/hernia repair | 4 | 0 |
| | Other | 1 | 1 |
| | Thoracic surgery | 10 | 13 |
| Neurosurgery | Craniofacial surgery | 1 | 1 |
| | Cranioplasty | 0 | 1 |
| | Spinal surgery | 3 | 3 |
| Ophthalmology | Eye surgery | 0 | 1 |
| Orthopedic surgery | Hand or foot surgery | 2 | 1 |
| | Hip surgery | 7 | 2 |
| | Other | 0 | 1 |
| Plastic surgery | Cleft lip ± palate repair | 15 | 20 |
| | Craniofacial surgery | 1 | 1 |
| | Cranioplasty | 4 | 4 |
| | Hand or foot surgery | 12 | 10 |
| | Other | 4 | 5 |
| Urology | Hypospadias repair | 56 | 50 |
| | Major urology surgery | 8 | 8 |
| | Orchiopexy/hernia repair | 2 | 6 |
| | Other | 1 | 1 |
| | Ureteric surgery | 59 | 72 |

LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; STD-SEVO, standard-dose sevoflurane arm.

and poor neurocognitive outcomes later in life.[9] In 2016, de Graaff *et al.*[7] developed multiple age- and sex-specific percentile charts of reference ranges for noninvasive blood pressure measurements in children under general anesthesia. The nomograms of de Graaff *et al.*[7] for the weight–MAP relationship were used to define hypotension, where the average MAP under anesthesia for infants weighing 5 kg was 40 mmHg. Hypotension was defined as 1 SD below this, which was 35 mmHg.[7] For infants greater than 5 kg in weight, a threshold of 40 mmHg was selected based on the same data set and process. This is supported by work on cerebral blood flow and oxygenation by Rhondali *et al.*[10] These data were utilized in developing our definitions of hypotension for the TREX trial. Furthermore, the NECTARINE trial highlights the clinical significance of hypotension (mean MAP of 32.7 mmHg [SD, 6.5]) as the most common etiology of cardiovascular instability that triggered intervention in infants up to 60 weeks postmenstrual age.[11] Our results suggest that despite the increased incidence of relative hypotension in the STD-SEVO arm compared to the LD-SEVO arm, the degree of hypotension reported was not clinically significant in either arm.

Bradycardia is a concern in infants and toddlers undergoing general anesthesia because of their limited ability to increase stroke volume and subsequent concern of a resulting decrease in cardiac output. Of 16 properly documented reported episodes of bradycardia in the current trial, only 9 (56%) received atropine or glycopyrrolate. Unfortunately, we cannot comment on the clinical importance of these bradycardic episodes given the lack of data.

In the TREX protocol, there was more light anesthesia in the LD-SEVO than the STD-SEVO arm. However, there were low rates of protocol abandonment in both arms (1 of 428 [0.2%] patients overall, in the LD-SEVO arm),

**Table 3.** Intraoperative Anesthetic Events and Subsequent Rescue Treatment Administered

| Anesthetic Event and Rescue Treatment | LD-SEVO (n = 207) | STD-SEVO (n = 221) | Risk difference, % (95% CI) | *P* Value |
|---|---|---|---|---|
| Hypotension, n (%) | 25 (12%) | 53 (24%) | −11.6 (−18.9 to −4.3) | 0.002 |
| Hypotension (episodes documented properly) | 22 | 43 | | |
| Treated with intravenous fluids, yes, n (%) | 10 of 22 (46%) | 32 of 43 (74%) | | |
| Treated with vasoactive agents, yes, n (%) | 3 of 22 (14%) | 7 of 43 (16%) | | |
| Bradycardia, n (%) | 50 (24%) | 12 (5%) | 18.2 (8.8 to 27.7) | < 0.001 |
| Bradycardia (episodes documented properly) | 16 | 4 | | |
| Treated with atropine or glycopyrrolate, yes, n (%) | 9 of 16 (56%) | 0 | | |
| Light anesthesia: hypertension and/or movement, n (%) | 89 of 207 (43%) | 4 of 106 (4%)* | 39.8 (31.1 to 48.5) | < 0.001 |
| Remifentanil infusion increased, yes, n (%) | 71 of 89 (80%) | 0 | | |
| Sevoflurane concentration increased, yes, n (%) | 30 of 89 (34%) | 1 of 4 (25%) | | |
| Propofol bolus administered during maintenance of anesthesia, yes, n (%) | 8 of 89 (9%) | 0 | | |

*The data was not collected for the first 115 in the STD-SEVO arm.

LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; STD-SEVO, standard-dose sevoflurane arm.

**Table 4.** Recovery Outcomes

| Outcome | LD-SEVO | STD-SEVO | Median Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| FLACC average scores, median (interquartile range) | 0.3 (0.0 to 1.2; n = 203) | 0.8 (0.0 to 2.1; n = 211) | −0.52 (−0.87 to −0.17) | 0.004 |
| Analgesic agents administered, yes, n (%) | 67 (33%; n = 204) | 83 (38%; n = 220) | RD: −4.8 (−14.3 to 4.8) | 0.33 |
| Time from end of surgery to eye opening, min, median (interquartile range) | 16 (9 to 34; n = 202) | 25 (15 to 39; n = 219) | −8.0 (−13.4 to −2.6) | 0.004 |
| Time from end of surgery to departure from the operating room, minutes, median (interquartile range) | 14 (10 to 20; n = 206) | 16 (11 to 23; n = 221) | −2.0 (−3.6 to −0.4) | 0.012 |
| Time from eye opening to PACU discharge, median (interquartile range) | 59 (28 to 84; n = 196) | 55 (29 to 81; n = 213) | 1.0 (−8.5 to 10.5) | 0.84 |
| Time from end of surgery to removal of airway device, minutes, median (interquartile range) | 8 (5 to 12; n = 205) | 10 (6 to 16; n = 221) | −2.0 (−4.2 to 0.2) | 0.08 |
| Duration of PACU stay, min, median (interquartile range) | 60 (35 to 86; n = 202) | 61 (41 to 86; n = 215) | 0.0 (−8.1 to 8.1) | 1.0 |
| Discharge within 24 h, yes, n (%) | 82 (40%; n = 206) | 74 (34%; n = 220) | RD: 6.2 (−3.9 to 16.3) | 0.23 |

FLACC, Face, Legs, Activity, Cry, Consolability scale; LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; PACU, postanesthesia care unit; RD, risk difference; STD-SEVO, standard-dose sevoflurane arm.

highlighting that the higher incidence of light anesthesia episodes in the LD-SEVO arm did not require a complete change in anesthesia management, and the clinical signs suggesting light anesthesia responded well to the described increases in suggested drug dosing. It should also be kept in mind that the LD-SEVO technique is a newer one, and practitioners describe a learning curve related to its use in this study, which is part of all modifications to standard techniques in clinical anesthesia. The level of sevoflurane in the LD-SEVO arm was 0.8%, which in this patient population is approximately 0.33 minimum alveolar concentration (MAC).[12,13] The estimated MAC amnesia for volatile anesthetics is 0.3 MAC,[14,15] so theoretically at least this dose is sufficient to provide amnesia. Dexmedetomidine premedication also lowers MAC, with a study in young adults undergoing gynecologic surgery finding that MAC of sevoflurane was decreased by 50% with the addition of dexmedetomidine.[16] Analysis of pharmacokinetics of dexmedetomidine in the Italian cohort of enrolled patients in the TREX trial showed that the target plasma concentration of dexmedetomidine in infants appeared similar to that required for sedated adult patients.[17]

There is a concern that the administration of dexmedetomidine during a general anesthetic leads to delayed emergence and prolonged recovery in children.[17–19] Our results reveal that the LD-SEVO arm had a faster emergence time (time from end of surgery to eye opening and time from end of surgery to departure from the operating room) compared to the STD-SEVO arm. These findings are consistent with the conclusion of Le *et al.*[20] that dexmedetomidine does not delay extubation. The decision on timing for removal of the airway device was left to the discretion of the anesthesiologist, which may affect the recovery times listed in table 4. Furthermore, the duration of PACU stay was similar in both arms, which is consistent with several other studies.[21,22] However, it is well recognized that PACU length of stay does

**Table 5.** Incidence of Adverse Events and Serious Adverse Events

| Event | LD-SEVO (n = 207) | STD-SEVO (n = 221) | Risk Difference, % (95% CI) | *P* Value |
|---|---|---|---|---|
| Postoperative readmission | 10 (6%; n = 181) | 6 (3%; n = 197) | 2.4 (–0.4 to 5.3) | 0.09 |
| Prolonged hospitalization | 24 (12%; n = 205) | 21 (10%; n = 218) | 2.0 (–3.2 to 7.2) | 0.46 |
| Serious morbidity | 3 (1%) | 2 (1%) | 0.5 (–1.2 to 2.2) | 0.53 |
| Life-threatening events | 1 (0.5%) | 1 (0.5%) | | |
| Death | 0 | 0 | | |

LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; STD-SEVO, standard-dose sevoflurane arm.

not correlate well with readiness for discharge to ward, due to protocols, ward bed availability or other logistical reasons.

Last, regional anesthesia was allowed in both arms, and the timing of administration was left to the discretion of the anesthesiologist. Both arms had exceptionally low FLACC scores, demonstrating an adequate level of postoperative analgesia for all children enrolled in the trial. Although there was some evidence for higher FLACC scores in the STD-SEVO arm, this is not a clinically relevant difference, given the already low values and the small numeric difference in the FLACC scores. The findings from the current trial will have direct clinical implications once the primary outcomes for the TREX study become available but in the interim reinforce that the two techniques are broadly clinically similar, with no clear evidence to support choosing one technique over the other.

This analysis of the short-term outcomes of the TREX trial had several limitations. First, the power calculation was based on the primary outcome of the trial (neurodevelopment at 3 yr), not these short-term outcomes. Second, we are unable to exactly quantify the number of "light anesthetic" episodes in the STD-SEVO arm because they were not recorded in greater than 50% of patients in this arm. Although we realize that the lack of data on light anesthesia events in the STD-SEVO arm is not ideal, we do not expect the missingness of the data to be related to the outcome itself. Thus, we feel that it is important to present these data but note that it should be interpreted with caution. Third, although we report on the available data for the episodes of bradycardia, this outcome should also be interpreted with caution, given the large amount of missing data. Fourth, this article only addresses the anesthetic outcome measures and does not examine LD-SEVO *versus* STD-SEVO in terms of surgical suitability. It is also possible that patient movement during a critical period of a procedure could have deleterious effects on surgical outcomes. The low level of protocol abandonment in the LD-SEVO arm suggests that clinically this was not a problem. Fifth, this study did not address the possibility of postoperative hyperalgesia secondary to remifentanil infusion. There was less opioid rescue in the immediate postoperative period in the LD-SEVO arm, but the overall narcotic dosing during the patient's hospitalization was not measured. Sixth, we did not collect any data after the patients were discharged from the PACU and therefore cannot comment on adverse events that may have occurred later in the postoperative course. Finally, there is no accurate monitor for intraoperative awareness for children less than 1 yr of age. It is possible that there was a greater incidence of unrecognized intraoperative awareness in the LD-SEVO arm, although the additive effects of dexmedetomidine with sevoflurane should have ensured amnesia.

## Conclusions

These early postoperative results suggest that in children less than 2 yr of age receiving greater than 2 h of general anesthesia, the LD-SEVO anesthesia technique and the standard sevoflurane anesthesia technique are broadly clinically similar, with no clear evidence to support choosing one technique over the other.

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## Competing Interests

Dr. Andropoulos has been Medical Officer of SmartTots (San Francisco, California); he was not involved in funding decisions for the TREX Trial from the SmartTots organization. The other authors declare no competing interests.

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## Supplemental Digital Content

Supplemental Table 1. List of enrolling centers, https://links.lww.com/ALN/D688
Supplemental Table 2. Titration of agents and rescue treatments, https://links.lww.com/ALN/D689

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