Short-term outcomes in infants following general anesthesia with low-dose sevoflurane/dexmedetomidine/remifentanil versus standard dose sevoflurane (The TREX trial)

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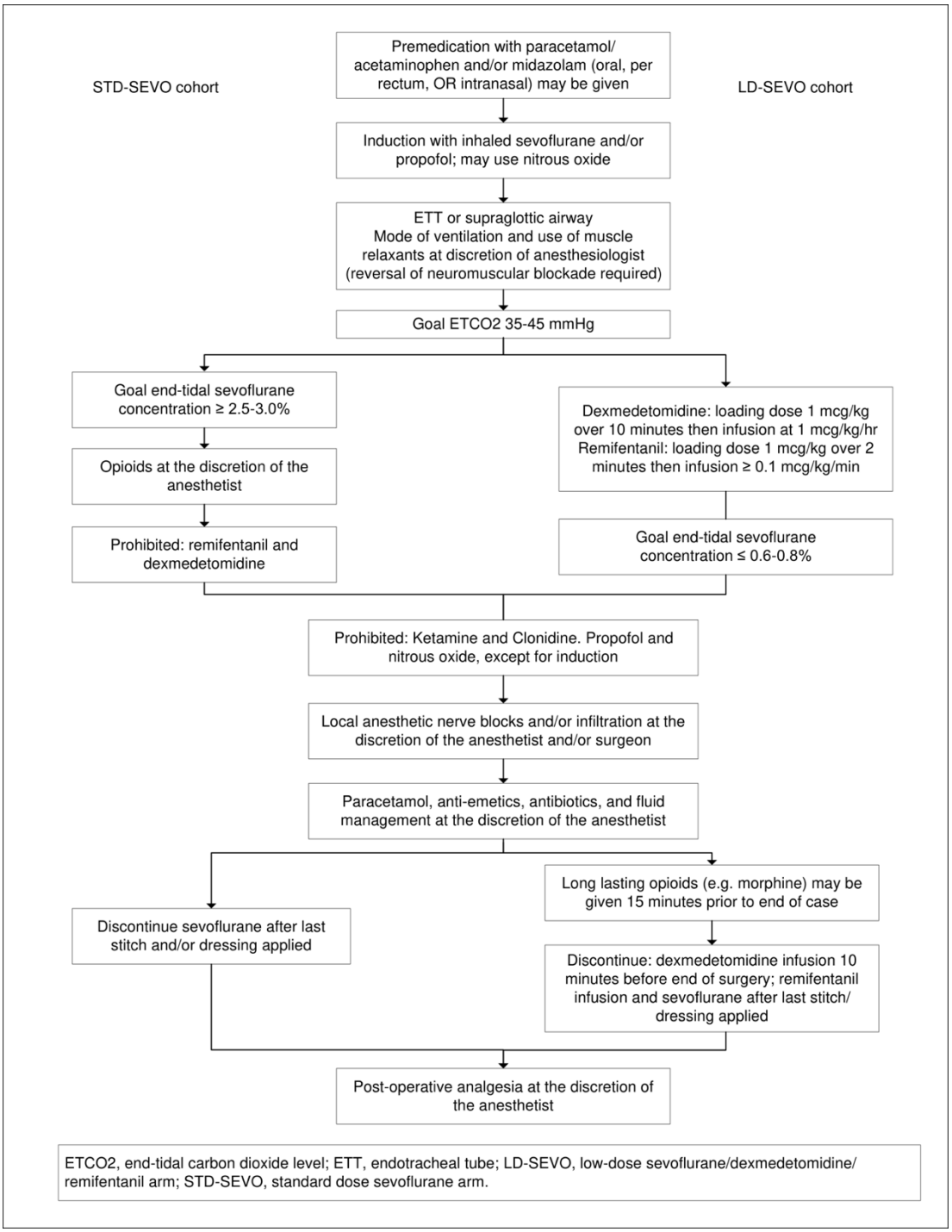
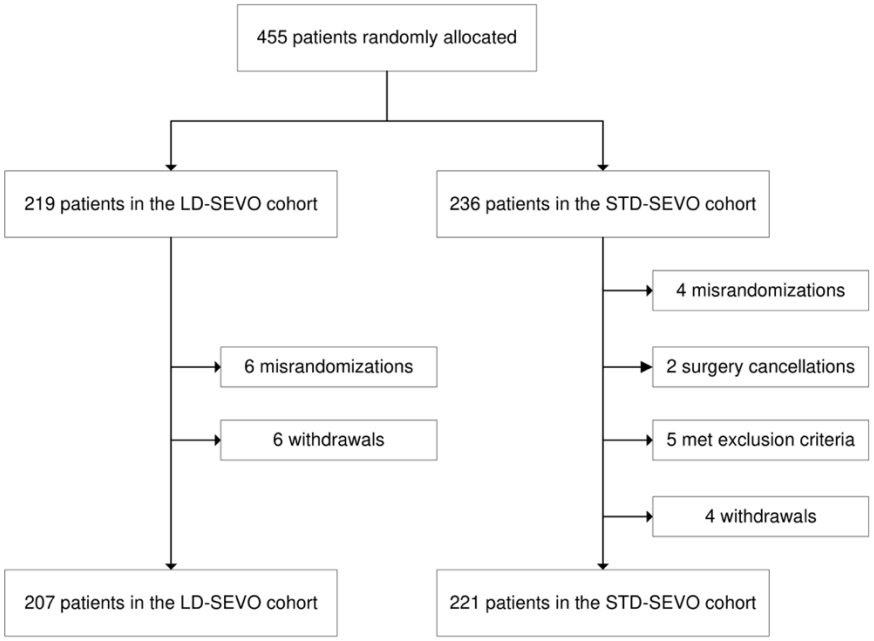
Introduction: Infants undergo anesthesia for a wide range of reasons, sometimes requiring prolonged or repeated exposure to anesthesia agents. Concerns about anesthesia-induced developmental neurotoxicity persist due to findings from animal models1. While there are some data to suggest repeated exposure may increase the risk of worse neurodevelopmental outcomes, there is minimal data available from cases involving single long exposures2. The TREX (Trial Remifentanil DEXmedetomidine) trial aimed to determine if, in children < 2 years old, low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia (LD-SEVO) is superior to standard dose sevoflurane (STD-SEVO) anesthesia in terms of global cognitive function at 3 years of age. (Figure 1) The aim of the present 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. Four hundred and fifty five infants < 2 years of age expected to undergo general anesthesia for at least 2 hours were enrolled. 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. The short-term perioperative outcomes noted above were compared between these two groups. Intraoperative hypotension was defined as mean arterial pressure < 35mmHg in children weighing < 5 kilograms and MAP < 40mmHg in children weighing > 5 kilograms, and intraoperative bradycardia as heart rate < 90 beats per minute for > 1 minute. Postoperative pain was assessed at 60 minutes after surgery (recorded as range, median, and mean of Face, Legs, Activity, Cry, Consolability (FLACC) scale scores). Time to recovery was defined as end of surgery to time of eye opening and time of eye opening to discharge from PACU). An episode of light anesthesia was defined as movement with or without hypertension or confirmed hypertension with 2 consecutive measurements. The intraoperative period lasted from induction of anesthesia until removal of airway. Morbidity and mortality outcomes included postoperative readmission, prolonged hospitalization (> 5 days), serious morbidity (resulting in persistent or significant disability), occurrence of life-threatening events, and death. All analysis were performed using the modified intention to treat population. Results are presented as a difference in medians or risk difference and its 95% confidence interval (CI).

Results: Between August 9, 2017, and April 21, 2023, 455 children were enrolled from 20 centers in Australia, Italy, and the United States. After excluding 2 patients due to surgery cancellations, 5 who met exclusion criteria, 10 who withdrew from the trial prior to surgery, and 10 who were misrandomized, 428 children were included in the analysis: 207 randomized to the LD-SEVO arm and 221 to the STD-SEVO arm. (Figure 2) 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. There were more patients with episodes of light anesthesia (89 vs. 4), and protocol abandonments (3 vs. 0) in the LD-SEVO arm. (Table 1) 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). (Table 2) Time from eye-opening to Post Anesthesia Care Unit discharge was similar in both arms (Table 2), as were morbidity and mortality (Table 3). One patient in each arm suffered a life-threatening event but neither suffered long-term sequelae.

Conclusions: Although there was less bradycardia but more hypotension in the STD-SEVO arm, there was no evidence of a clinically significant difference in the intraoperative hemodynamic profiles between the two arms. These early postoperative results suggest that the low-dose sevoflurane/dexmedetomidine/remifentanil anesthesia technique is clinically appropriate with similar hemodynamic and analgesia profiles compared to the standard sevoflurane anesthesia technique.





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

Table 1. Intraoperative anaesthetic events and subsequent rescue treatment administered.

	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 (%)	10/22 (46%)	32/43 (74%)		
Treated with vasoactive agents, yes, n (%)	3/22 (14%)	7/43 (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 (%)	9/16 (56%)	0		
Light anesthesia: hypertension and/or movement, n (%)	89/207 (43%)	4/106 (4%)*	39.8 (31.1 to 48.5)	<0.001
Remifentanil infusion increased, yes, n (%)	71/89 (80%)	0		
Sevoflurane concentration increased, yes, n (%)	30/89 (34%)	1/4 (25%)		
Propofol bolus administered during maintenance of anesthesia, yes, n (%)	8/89 (9%)	0		

* Data was not collected for the first 115 in the STD-SEVO arm.
CI, confidence interval; LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; STD-SEVO, standard dose sevoflurane arm.

Table 2. Recovery outcomes.

	LD-SEVO	STD-SEVO	Median difference (95% CI)	p-value
FLACC average scores, median (IQR)	0.3 (0.0, 1.2) (n = 203)	0.8 (0.0, 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, minutes, median (IQR)	16 (9, 34) (n = 202)	25 (15, 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 (IQR)	14 (10, 20) (n = 206)	16 (11, 23) (n = 221)	-2.0 (-3.6 to -0.4)	0.012
Time from eye-opening to PACU discharge, median (IQR)	59 (28, 84) (n = 196)	55 (29, 81) (n = 213)	1.0 (-8.5 to 10.5)	0.84
Time from end of surgery to removal of airway device, minutes, median (IQR)	8 (5, 12) (n = 205)	10 (6, 16) (n = 221)	-2.0 (-4.2 to 0.2)	0.08
Duration of PACU stay, minutes, median (IQR)	60 (35, 86) (n = 202)	61 (41, 86) (n = 215)	0.0 (-8.1 to 8.1)	1.0
Discharge within 24 hours, yes, n (%)	82 (40%) (n = 206)	74 (34%) (n = 220)	RD: 6.2 (-3.9 to 16.3)	0.23

CI, confidence interval; FLACC, Median Face, Legs, Activity, Cry, Consolability scale; IQR, interquartile range; LD-SEVO, low-dose sevoflurane/dexmedetomidine/remifentanil arm; PACU, post-anesthesia care unit; RD, risk difference; STD-SEVO, standard dose sevoflurane arm.

Table 3. Incidence of adverse events and serious adverse events.

	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)	0.60
Life-threatening events	1 (0.5%)	1 (0.5%)		
Death	0	0		

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