

Combined Esketamine and Dexmedetomidine Decreases the Risk of Postoperative Delirium in Neurosurgical Pediatrics: A Randomized Controlled Trial

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Purpose: Present study was designed to investigate whether combined esketamine and dexmedetomidine could decrease the risk of postoperative delirium in neurosurgical pediatric.

Patients and Methods: In this prospective randomized controlled study, pediatrics (aged 2–16 years) who were scheduled for selective neurosurgery were enrolled. Patients were randomized to receive combined esketamine (0.5 mg/kg) and dexmedetomidine (0.5 µg/kg) or normal saline as placebo at anesthesia induction. Primary outcome was the incidence of delirium within postoperative the first five days which was assessed twice daily using the Cornell Assessment of Pediatric Delirium (CAPD). CAPD ≥ 10 at any assessment point was considered as delirium. Secondary outcomes included the incidence of emergence delirium, non-delirium complications within postoperative 30 days, postoperative length of in-hospital stay, and medical cost during hospitalization. The change of systematic inflammation was reflected by Neutrophil-to-Lymphocyte Ratio.

Results: From July 2021 to March 2023, 270 patients were screened, and 190 patients were randomized. Median age of enrolled patients was similar between two groups (63.0 [43.3, 111.3] vs 70.0 [46.3, 114.8] months, $P = 0.883$). Patients in esketamine-dex group suffered lower incidence of postoperative delirium than control group (intention-to-treat analysis: 22.8% [21/92] vs 38.0% [35/92], RR = 0.600, 95% CI 0.380–0.948, $P = 0.025$; per-protocol analysis: 22.0% [20/91] vs 38.2% [34/89], RR = 0.575, 95% CI 0.360–0.919, $P = 0.018$). The incidence of emergence delirium was lower in esketamine-dex group than control group (20.7% [19/92] vs 50.0% [46/92], RR = 0.413, 95% CI 0.263–0.648, $P < 0.001$). Patients in esketamine-dex group had lower medical cost ($P < 0.001$), and there was no statistical significance in the incidence of non-delirium complications within postoperative 30 days and postoperative length of in-hospital stay. The neutrophil-to-lymphocyte ratios at postoperative first and third day were comparable between two groups. Safety outcomes such as bradycardia and hypotension were comparable between groups.

Conclusion: Combined esketamine and dexmedetomidine could decrease the risk postoperative delirium and emergence delirium in pediatrics after neurosurgery.

Keywords: pediatric, neurosurgery, esketamine, dexmedetomidine, delirium

Introduction

Postoperative delirium (POD) is a common complication in surgical pediatrics which is usually manifested as acute change of mental status, inattention, and deficits in awareness and cognition.¹ The incidence of POD varies from 10% to 66% depending on the type of surgery and severity of diseases.^{2,3} In one cohort study of 170 pediatric patients, the incidence of POD was about 43.5% in those undergoing neurosurgery.³ POD is associated with adverse outcomes such as

prolonged length of stay, higher medical cost, decreased quality of life, and increased risk of mortality.^{4,5} Prevention of POD may improve the outcomes of pediatric patients.

Occurrence of POD in pediatrics is multifactorial.⁶ Participating factors include comorbidities such as developmental delay and neurodisease.^{7–9} Predisposing factors include anxiety, pain intensity, and surgery-induced inflammatory response.^{6,10–12} In clinical studies, esketamine (an N-Methyl-D-Aspartate receptor antagonist) and dexmedetomidine (a selective alpha-2 receptor agonist) can significantly alleviate perioperative anxiety and pain intensity.^{13–18} Meanwhile, both of them can inhibit surgery-induced inflammatory response which is detrimental to the function of neurons in basic research.^{19,20}

A single bolus of esketamine or dexmedetomidine has been validated as safe methods to reduce the risk of emergence delirium in pediatrics receiving general anesthesia.^{13,21} Compared with single use of the two drugs, recent evidences showed that the combination of esketamine and dexmedetomidine (esketamine-dex) was more efficient in reducing anxiety, improving pain management, and decreasing the incidence of emergence agitation.^{22–24} Pediatrics undergoing neurosurgery were characterized by abnormal brain development and impaired cognitive function. They are at high risk of POD. Esketamine and dexmedetomidine had been independently used for sedation in neurosurgery or related procedures such as MRI.^{25,26} However, there is insufficient data to support the effect of esketamine-dex on postoperative delirium in pediatrics undergoing neurosurgery.⁹

The present study was designed to investigate whether the administration of esketamine in combination with dexmedetomidine (esketamine-dex) could reduce the risk of postoperative delirium (POD) in pediatric patients undergoing neurosurgery.

Materials and Methods

Ethics

This prospective randomized controlled study was approved by Institution Review Board of Peking University First Hospital (No. 2020–06-20, Date: June 20, 2020) and was registered at Chinese Clinical Trial Registry (ChiCTR2100048713, Date: July 13, 2021, Website: <https://www.chictr.org.cn/showproj.html?proj=130166>). All procedures were conducted in accordance with the ethical standards of the *Declaration of Helsinki* (1964) and its later amendments. Written informed consent was obtained from legal representatives of all enrolled pediatrics. First patient was enrolled on July 19, 2021. The study was conducted in Peking University First Hospital.

Participants Recruitment

Patients (aged 2–16 years old) who were scheduled for selective neurosurgery were enrolled if the expected surgery duration was longer than 1 hour.

Patients were excluded if they met with any one of the following criteria: (1) refused to participate; (2) could not complete delirium assessment because of neurodisease; (3) severe cognitive impairment that impeded delirium assessment; (4) vision or hearing impairment that impeded delirium assessment; and (5) American Society of Anesthesiologist Classification IV or above.

Randomization, Group Allocation, and Blind Method

Randomization was computerized by SAS 9.2 (SAS Institute, Cary, NC) with a ratio of 1:1 and block size of 4. Random numbers were enveloped with opaque bags in sequence. Allocation of random numbers and preparation of study drugs were administrated by an independent researcher who did not take part in intervention administration and postoperative follow-up.

All study drugs were colorless and prepared into 20-mL syringe of the same brand. To avoid potential bias, randomization and group allocation were blinded to responsible anesthesiologists, researchers in charge of postoperative follow-up and data collection, patients, and other related health-care providers.

Blind method was kept until the end of study. In emergency cases such as occurrence of serious adverse events, group allocation could be unmasked in necessity.

Study Protocol

Pediatrics arrived at the operating room with an intravenous access. All patients received standard monitoring including electrocardiography, cuff blood pressure, and peripheral arterial oxygenation (SpO₂). End-tidal carbon dioxide and body temperature were monitored during anesthesia.

In esketamine-dex group, combined esketamine (0.5 mg/kg) and dexmedetomidine (0.5 µg/kg) was titrated within 20 minutes by electrical pump at anesthesia induction. The above single dosage of dexmedetomidine or esketamine had been validated to reduce the risk of emergence agitation in literatures.^{13,21} And the safety of above dosages was also validated in pediatrics. For patients in control group, they received an identical volume of normal saline as placebo.

Meanwhile, anesthesia induction was sequentially conducted with sufentanil (0.1–0.3 µg/kg) and propofol (3–5 mg/kg). Depth of anesthesia was maintained by continuous infusion of propofol (4–12 mg/kg/h) and remifentanyl (0.05–0.3 µg/kg/min). In patients who received sevoflurane, the minimum alveolar concentration was maintained at 0.8–1.0 with fresh gas flow at 2 L/min. Cis-atracurium was intermittently injected for muscle relaxant. The aim of anesthesia was to maintain: (1) fluctuation of blood pressure and heart rate within 20% baseline reference; (2) end-tidal carbon dioxide at 35–45 mmHg; and (3) nasopharyngeal temperature at 36–37°C.

Patients were transferred to PACU after extubation or to intensive care unit (ICU) with/without intubation. Postoperative pain intensity was assessed by the face, legs, activity, cry and consolability (FLACC) scale. The aim of postoperative analgesia was to keep FLACC ≤ 3. Analgesics was provided with sufentanil (0.05–0.1 µg/kg per se) in PACU or flurbiprofen (1 mg/kg, twice daily) in general ward if necessary.

Outcomes

Primary Outcome

The primary outcome was the incidence of POD within postoperative first five days. POD was assessed twice daily (7 am–9 am and 6 pm–8 pm, respectively) using the Chinese version Cornell Assessment of Pediatric Delirium (CAPD).²⁷ CAPD ≥ 10 at any assessment point was considered as POD.²⁷

The Chinese version CAPD has been validated with sensitivity of 96.7% and specificity of 93.1%.²⁷ At the beginning of the study, all researchers received a 3-hour training on CAPD which included the following contents: (1) an instruction lecture of CAPD; (2) a video learning including 10 assessment examples; and (3) actual assessment practice. Under supervision of psychiatrists, each researcher completed at least 5 positive cases and 5 negative cases assessments. The training session was stopped when the diagnostic agreement between researchers and psychiatrists reached to 100%. The training session was repeated at 6–9 months.

Secondary Outcomes

Emergence delirium was assessed using CAPD in the post-anesthesia care unit (PACU), and it was established if CAPD ≥ 10. Postoperative non-delirium complications were defined as the new onset adverse events which were detrimental to patient's safety and needed medical treatment (ie, Clavien-Dindo classification of surgical complications grade 2 and above).²⁸ The definitions of complications were provided in [Supplemental File 1](#). Postoperative complications mainly included intracranial infection, epidural effusion, seizures, pneumonia, upper respiratory tract infection, urinary tract infection, sepsis, and unintended bleeding. The duration of POD, length of postoperative in-hospital stay and medical cost during hospitalization were recorded. The change of systematic inflammation was reflected by neutrophil-to-lymphocyte ratio (NLR) at postoperative first and third days.²⁹

Data Collection

Eligible patients were visited at one day before surgery. With written informed consents, baseline characteristics such as age, sex, body mass index, and comorbidities were collected.

Intraoperative data were collected including surgery type, type of anesthesia and dosage of anesthetics, fluid input and output, use of allogenic blood transfusion, and anesthesia and surgery time. AUC of sevoflurane was calculated with the concentration of sevoflurane multiple by the duration (hour). The concentration of sevoflurane was recorded at 15 minutes interval.

Drug-related adverse events within postoperative 2 hours were collected including bradycardia, tachycardia, hypotension, hypertension, and hallucination.

Postoperative data included emergence delirium, duration of stay in post-anesthesia care unit (PACU), use of supplemental analgesics and anti-seizure drugs, pain intensity within postoperative first 5 days. Delirium within postoperative first 5 days, medical cost during hospitalization, postoperative length of in-hospital stay, non-delirium complications within postoperative 30 days were collected.

Statistical Analyses

Our observational study showed that the incidence of POD was about 13.5% in pediatrics after selective surgery, but it might reach up to 40% in those undergoing neurosurgery.³ Previous studies showed that the combination of esketamine and dexmedetomidine could decrease the risk of emergence delirium by 70% in pediatrics undergoing adenotonsillectomy.²⁴ Considering the difference in study population, we assumed that the risk of POD might be 50% lower in esketamine-dex group than control group. When significance level at 0.05 and power at 0.8, 91 patients in each arm were needed to detect the assumed difference between two groups. Considering a loss to follow-up rate of 5%, we planned to enroll 95 patients in each arm.

The histogram was used to test the normality of continuous data. Normal data were presented as mean± standard deviation (SD) and compared by independent sample *t* test, whereas data without normality were presented as median (Q1, Q3) and compared by Wilcoxon sum rank test. Categorical data were presented as number (percentage) and compared by Chi-square test or Fisher's exact test.

Analysis of primary outcome was administrated in intention-to-treat and per protocol population, respectively. The incidence of POD was presented as number (percentage). The difference between two groups was analyzed by Chi-square test with relative risk and 95% confidence interval (CI). Kaplan-Meier analysis with Log rank test was used to illustrate the cumulative risk of POD between two groups; the difference between two groups was analyzed with Cox regression proportional hazards model and the result was presented as hazard ratio and 95% CI. Categorical outcomes were analyzed with the same method including the incidence of emergence delirium and the incidence of postoperative non-delirium complications. The postoperative length of in-hospital stay and medical cost were analyzed using independent sample Wilcoxon sum rank test. The median difference with 95% CI between two groups was calculated with Hodges-Lehmann estimate. Missing data was not replaced.

Two-sided $P < 0.05$ was considered as statistical significance. Statistical analysis was conducted by SPSS 26.0 software (SPSS, Inc., Chicago, IL).

Results

Participants Population and Baseline Variables

From July 19, 2021, to March 29, 2023, 270 patients were screened, and 190 patients were randomized, [Figure 1](#). Three patients in each group were excluded because of surgery cancellation. Ninety-two patients in each group were analyzed in intention-to-treat analysis. One patient in esketamine-dex group and 3 patients in control group were excluded from per-protocol analysis because of unplanned administration of dexmedetomidine. No death case happened within postoperative 30 days.

Median age was 63.0 (43.3, 111.3) months in esketamine-dex group which was similar with 70.0 (46.3, 114.8) months in control group ($P = 0.883$), [Table 1](#). Other variables were well balanced between two groups such as sex, history of pre-term birth, and comorbidities.

Less patients in esketamine-dex group received sevoflurane in comparison with control group (87.0% [80/92] vs 96.7% [89/92], $P = 0.028$), [Table 2](#). There was no statistical significance in other variables such as type of surgery, duration of surgery and anesthesia, and postoperative pain intensity.

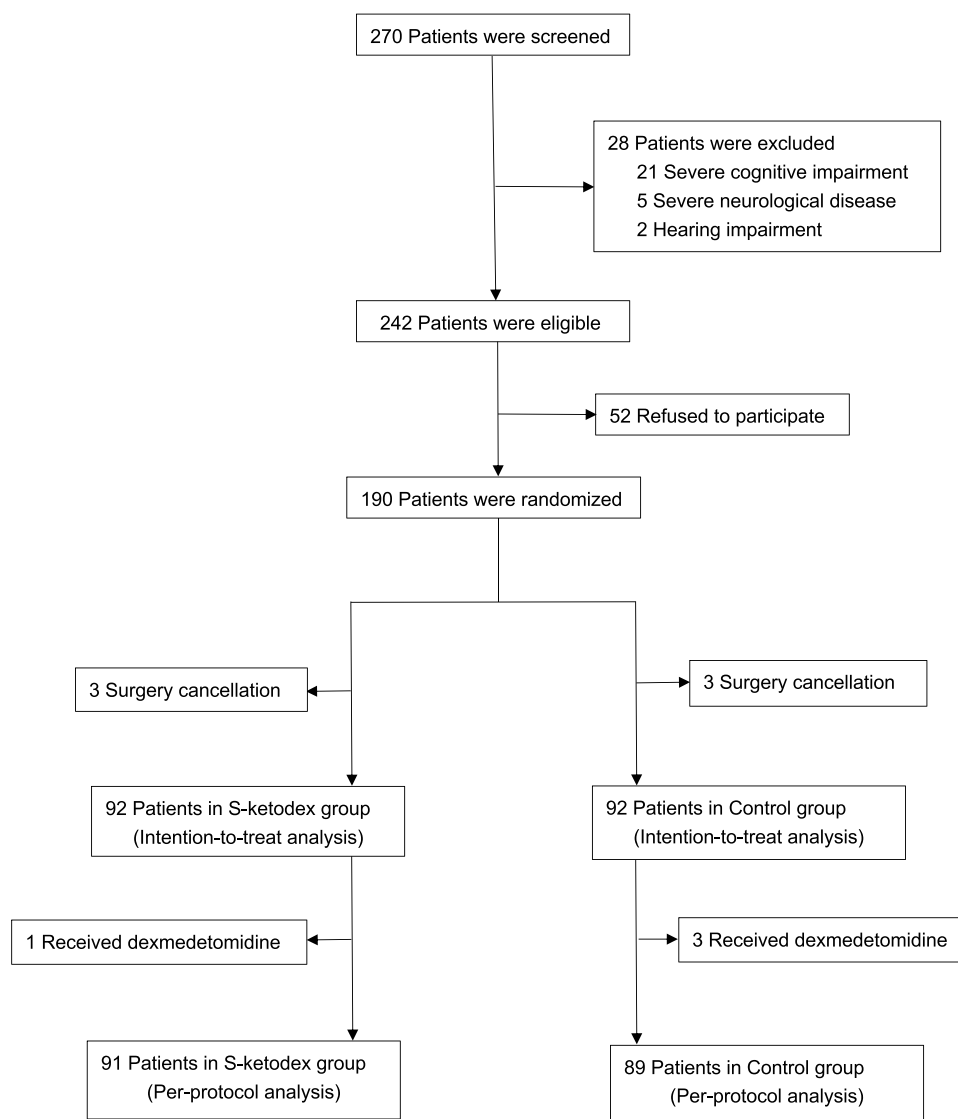


Figure 1 Flow chart of the study.

Primary Outcome

The incidence of POD in esketamine-dex group was significantly lower than control group (22.8% [21/92] vs 38.0% [35/92], RR = 0.600, 95% CI 0.380–0.948, P = 0.025; number needed-to-treat 6.6, 95% CI 3.5–47.5), [Table 3](#) and [Figure 2A](#)

Table 1 Baseline Variables

Variables	Esketamine-dex Group (n = 92)	Control Group (n = 92)	P value
Age (months)	63.0 (43.3, 111.3)	70.0 (46.3, 114.8)	0.883
Male	48 (52.2%)	51 (55.4%)	0.657
Height (cm)	120.5±23.4	120.4±24.5	0.968
Weight (kg)	21.0 (16.3, 32.8)	22.0 (16.0, 31.4)	0.768
Pre-term birth	5 (5.4%)	6 (6.5%)	0.756

(Continued)

Table 1 (Continued).

Variables	Esketamine-dex Group (n = 92)	Control Group (n = 92)	P value
Birth asphyxia	3 (3.3%)	6 (6.5%)	0.497
Neurological disorders			0.425
Epilepsy	84 (91.3%)	79 (85.9%)	
Tumor	3 (3.3%)	7 (7.6%)	
Hydrocephalus	4 (4.3%)	5 (5.4%)	
Hemorrhage	1 (1.1%)	1 (1.1%)	
Antiepileptic drugs	84 (91.3%)	80 (87.0%)	0.343
Congenital heart disease ^a	1 (1.1%)	1 (1.1%)	>0.999
History of upper respiratory infection ^b	3 (3.3%)	2 (2.2%)	>0.999
History of general anesthesia	28 (30.4%)	34 (37.0%)	0.349
ASA physical status			0.837
I	1 (1.1%)	1 (1.1%)	
II	86 (93.5%)	84 (91.3%)	
III	5 (5.4%)	7 (7.6%)	
Preoperative delirium	0 (0.0%)	0 (0.0%)	NA
Neutrophil-to-lymphocyte ratio ^c	0.72 (0.50, 1.21)	0.80 (0.51, 1.31)	0.268

Notes: Data are presented as mean \pm standard deviation, n (%) or median (interquartile range). ^aIncluding atrial septal defect and ventricular septal defect. ^bHistory of upper respiratory infection within preoperative one month. ^cHigher neutrophil-to-lymphocyte ratio indicated heavier systematic inflammation.

Abbreviations: ASA, American Society of Anesthesiologist; NA, not available.

Table 2 Perioperative Variables

Variables	Esketamine-dex Group (n = 92)	Control Group (n = 92)	P value
Surgery type			0.425
Epilepsy surgery	84 (91.3%)	79 (85.9%)	
Tumor resection	3 (3.3%)	7 (7.6%)	
Ventriculoperitoneal shunt	5 (5.4%)	6 (6.5%)	
Intraoperative data			
Propofol (mg)	500.0 (401.5, 752.5)	500.0 (355.0, 604.0)	0.883
Morphine milligram equivalents (mg) ^a	59.9 (34.0, 88.1)	70.4 (53.0, 96.6)	0.883
Remifentanyl (μ g)	566.0 (306.0, 824.0)	652.0 (490.0, 896.0)	0.658
Sufentanyl (μ g)	5.0 (4.0, 9.3)	4.5 (3.4, 8.0)	0.657
Use of midazolam	6 (6.5%)	10 (10.9%)	0.295
Use of etomidate	1 (1.1%)	2 (2.2%)	>0.999
Use of sevoflurane	80 (87.0%)	89 (96.7%)	0.028
AUC of Sevoflurane (%*h) ^b	2.0 (0.9, 3.0)	2.4 (1.1, 3.6)	0.041
Use of 5-HT ₃ receptor antagonists ^c	45 (48.9%)	43 (46.7%)	0.768
Use of glucocorticoids ^d			0.161
None	3 (3.3%)	3 (3.3%)	
Dexamethasone	69 (75.0%)	65 (70.7%)	
Methylprednisolone	20 (21.7%)	19 (20.7%)	
Both	0 (0%)	5 (5.4%)	
Intraoperative fluid			
Crystalloid, mL	600.0 (400.0, 875.0)	720.0 (500.0, 1100.0)	0.101
Use of colloid	1 (1.1%)	1 (1.1%)	>0.999

(Continued)

Table 2 (Continued).

Variables	Esketamine-dex Group (n = 92)	Control Group (n = 92)	P value
Intraoperative blood transfusion			
Use of packed red blood cells	53 (57.6%)	55 (59.8%)	0.765
Use of fresh frozen plasma%	7 (7.6%)	6 (6.5%)	0.774
Estimated blood loss (mL)	150.0 (100.0, 200.0)	150.0 (100.0, 200.0)	0.358
Urine output, mL	400.0 (200.0, 600.0)	300.0 (150.0, 600.0)	0.461
Anesthesia time (h)	4.3±1.0	4.5±1.0	0.223
Surgery time (h)	2.9±0.9	3.0±0.9	0.177
Postoperative data			
Duration of stay in PACU (min) (n = 88)	22.5 (16.3, 32.8)	24.0 (20.0, 30.0)	0.827
ICU admission after surgery	4 (4.3%)	4 (4.3%)	>0.999
With endotracheal intubation	2 (2.2%)	2 (2.2%)	>0.999
Supplemental analgesics			
Opioids ^e	5 (5.4%)	5 (5.4%)	>0.999
NSAIDs ^f	54 (58.7%)	58 (63.0%)	0.546
Anti-seizure drugs			
Phenobarbital	7 (7.6%)	11 (12.0%)	0.321
Benzodiazepines	21 (22.8%)	22 (23.9%)	0.862
Use of 5-HT ₃ receptor antagonists	78 (84.8%)	77 (83.7%)	0.840
Use of glucocorticoids ^d	81 (85.3%)	84 (88.4%)	0.520
Postoperative pain intensity (score) ^g			
Day 1 am	1 (0, 2)	1 (1, 2)	0.767
FLACC≥ 4	5 (5.4%)	7 (7.6%)	0.550
Day 1 pm	1 (0, 2)	1 (0, 2)	0.879
FLACC≥ 4	3 (3.3%)	6 (6.5%)	0.497
Day 2 am	1 (0, 1)	1 (0, 1)	1.000
FLACC≥ 4	1 (1.1%)	4 (4.3%)	0.368
Day 2 pm	1 (0, 1)	1 (0, 2)	0.863
FLACC≥ 4	0 (0%)	2 (2.2%)	0.497
Day 3 am	1 (0, 1)	0 (0, 1)	0.506
FLACC≥ 4	0 (0%)	1 (1.1%)	>0.999
Day 3 pm	0 (0, 1)	0 (0, 1)	0.280
FLACC≥ 4	0 (0%)	0 (0%)	>0.999
Day 4 am	0 (0, 1)	0 (0, 1)	0.711
FLACC≥ 4	1 (1.1%)	0 (0%)	0.497
Day 4 pm	0 (0, 1)	0 (0, 1)	0.868
FLACC≥ 4	1 (1.1%)	1 (1.1%)	>0.999
Day 5 am	0 (0, 1)	0 (0, 0)	0.392
FLACC≥ 4	0 (0%)	1 (1.1%)	>0.999
Day 5 pm	0 (0, 0)	0 (0, 0)	1.000
FLACC≥ 4	0 (0%)	0 (0%)	>0.999

Notes: Data are presented as mean± standard deviation, n (%) or median (interquartile range). P-value less than 0.05 is marked in bold font. ^aMorphine milligram equivalents were calculated using the following formulation: morphine (i.v.) 10mg = remifentanyl (i.v.) 100 µg = sufentanil (i.v.) 10 µg. ^bAUC of sevoflurane was calculated with the concentration of sevoflurane multiple by the duration (hour). The concentration of sevoflurane was recorded at 15 minutes interval. ^cIncluding ondansetron (0.1mg/kg) or tolansetron (0.1mg/kg). ^dDexamethasone 0.1mg/kg or methylprednisolone 1mg/kg or hydrocortisone 1 mg/Kg. ^eIncluding fentanyl 5–10 µg/Kg or oxycodone 0.1mg/kg. ^fFlurbiprofen 1 mg/Kg. ^gPain intensity was assessed twice daily using the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale (11-score, 0 for no pain and 10 for worst pain). The highest pain score at each day was provided. FLACC≥ 4 was considered as moderate-to-severe pain.

Abbreviations: AUC, area under curve; 5-HT₃, 5-hydroxytryptamine₃; ICU, intensive care unit; NSAIDs, non-steroid anti-inflammatory drugs; FLACC, the Faces, Legs, Activity, Cry, and Consolability scale.

Table 3 Efficacy Outcomes

Variables	Esketamine-dex Group (n = 92)	Control Group (n = 92)	Estimated Effect Size (95% CI)	P value
Primary endpoint				
Incidence of postoperative delirium within the first 5 days ^a				
Intention-to-treat analysis	21 (22.8%)	35 (38.0%)	RR = 0.600 (0.380, 0.948)	0.025
Per-protocol analysis	20 (22.0) (n = 91)	34 (38.2) (n = 89)	RR = 0.575 (0.360, 0.919)	0.018
Secondary endpoints				
Incidence of emergence delirium ^b	19 (20.7%)	46 (50.0%)	RR = 0.413 (0.263, 0.648)	<0.001
Duration of postoperative delirium	0 (0, 0)	0 (0, 1)	MD = 0 (0, 0)	0.055
Non-delirium complications within postoperative 30 days ^c	52 (56.5%)	48 (52.2%)	RR = 1.083 (0.831, 1.413)	0.554
Postoperative length of in-hospital stay (days)	10.0 (8.0, 14.0)	11 (9.3, 14.8)	MD = 1 (0, 2)	0.072
Medical cost during hospitalization (thousand-Yuan)	79.0 (73.3, 91.6)	88.4 (76.5, 114.5)	MD = -9.1 (-14.7, -3.7)	0.001
Neutrophil/lymphocyte ratio				
Postoperative day 1	5.7 (3.9, 8.6) (n = 91)	6.7 (3.7, 10.5) (n = 91)	MD = 0.492 (-0.597, 1.698)	0.138
Postoperative day 3	3.1 (2.4, 4.5) (n = 66)	3.6 (2.4, 4.7) (n = 62)	MD = 0.135 (-0.425, 0.679)	0.377

Notes: Data are presented as n (%) or median (interquartile range). Numbers in brackets indicate patient with missing data. P-value less than 0.05 is marked in bold font. ^aDelirium was assessed twice daily (0700–0900 and 18:00–20:00, respectively) using the Chinese version Cornell Assessment of Pediatric Delirium (CAPD). Patients with CAPD ≥ 10 at any assessment point was considered as POD. ^bEmergence delirium was assessed with the same method of postoperative delirium. ^cThe incidence of non-delirium complications was listed in [Supplemental file 1](#). Generally, Postoperative non-delirium complications were defined as the new onset adverse events which were detrimental to patient's safety and needed medical treatment (ie, Clavien-Dindo classification of surgical complications grade 2 and above).

Abbreviations: RR, relative risk, MD, median difference.

(Kaplan-Meier analysis), and [Figure 2B](#) (daily prevalence of POD). This result was consistent in per-protocol analysis (22.0% [20/91] vs 38.2% [34/89], RR = 0.575, 95% CI 0.360–0.919, P = 0.018).

Secondary Outcomes

In comparison with control group, patients in esketamine-dex group suffered lower incidence of emergence delirium (20.7% [19/92] vs 50.0% [46/92], RR = 0.413, 95% CI 0.263–0.648, P < 0.001) and had lower medical cost (thousand-Yuan, 79.0 [73.3, 91.6] vs 88.4 [76.5, 114.5], MD = -9.1 (-14.7, -3.7), P = 0.001), besides, the duration of POD in esketamine-dex group was comparable with the control group (0 [0,0] vs 0[0,1], MD = 0 [0,0], P = 0.055) in ITT analysis, [Table 3](#). There was no statistical significance in the incidence of postoperative non-delirium complications (P = 0.554) and postoperative length of in-hospital stay (P = 0.072). The NLRs at postoperative first and third days were comparable between two groups (all P values > 0.05).

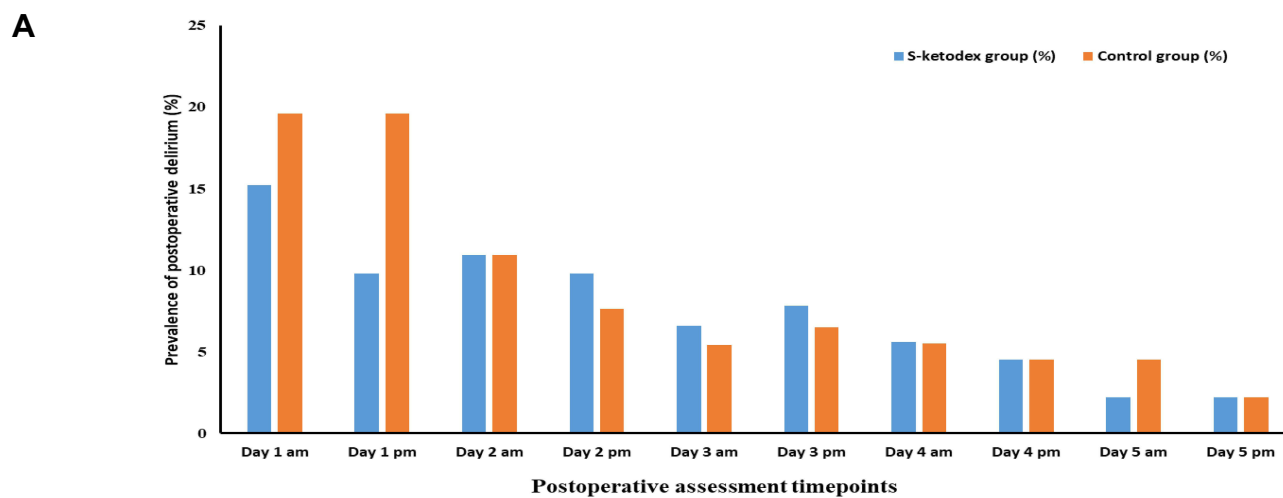
Safety Outcomes

The incidence of drug-related adverse events was comparable between two groups including bradycardia, tachycardia, hypotension, hypertension, and hallucination, [Table 4](#).

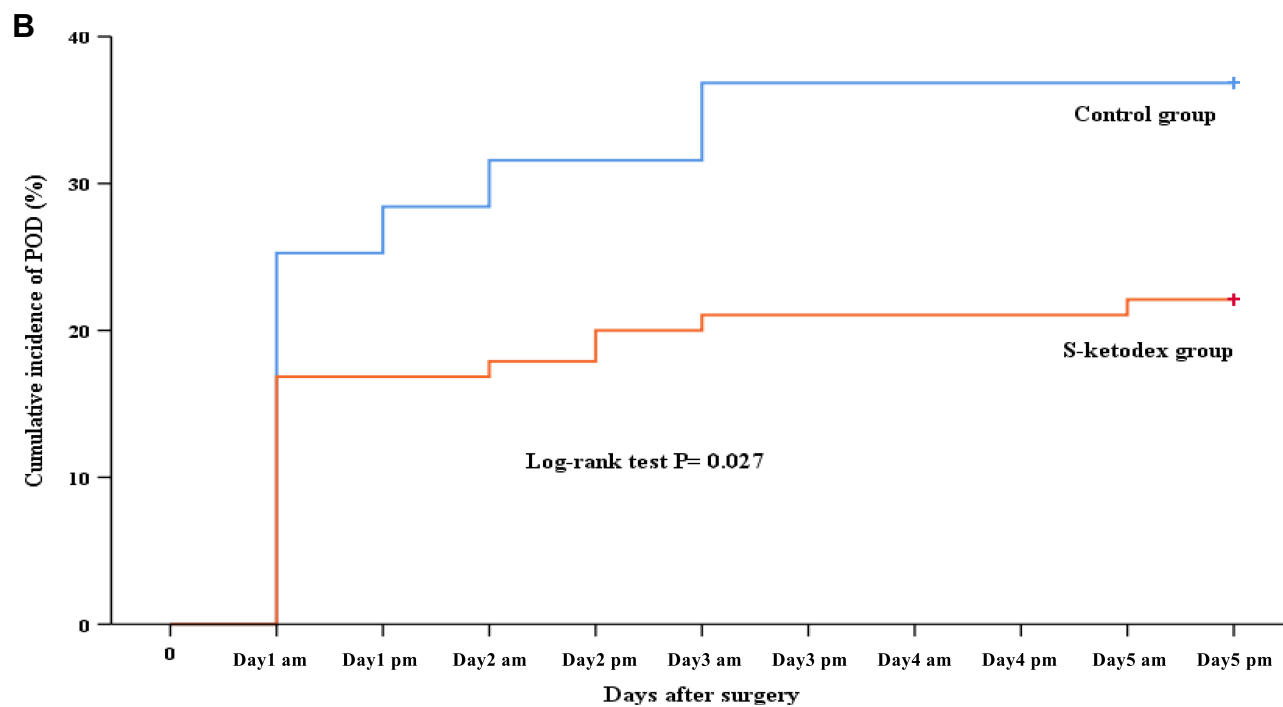
Discussion

The present study found that the combination of esketamine and dexmedetomidine could significantly reduce the incidence of postoperative delirium (POD) and emergence delirium in pediatric patients undergoing neurosurgery. This result provided practical of POD prevention and may benefit patients such as reduction the length of in-hospital stay and lower medical cost.

There is insufficient data to describe the prevalence of delirium in neurosurgical pediatrics.⁹ In a cohort study of 50 pediatrics, 24% of the enrolled patients were diagnosed as developmental delay.³⁰ Overall incidence of delirium was about 28% in these patients. This study also validated the diagnostic performance of CAPD in patients with neurodisease. In present study, POD and emergence delirium were assessed by the Chinese version CAPD.²⁷ Pediatrics were visited twice daily for POD assessment which had been proposed as the optimal strategy to screen most delirious cases.³¹ The



P	0.437	0.061	>0.999	0.601	0.742	0.742	>0.999	>0.999	0.682	>0.999
Sketodex group (%)	15.2	9.8	10.9	9.8	6.6	7.8	5.6	4.5	2.2	2.2
Number at risk (n)	92	92	92	92	91	90	90	89	89	89
Control group (%)	19.6	19.6	10.9	7.6	5.4	6.5	5.5	4.5	4.5	2.2
Number at risk (n)	92	92	92	92	92	92	91	89	89	90
RR (95% CI)	0.949 (0.831-1.084)	0.892 (0.790-1.006)	1.000 (0.904-1.106)	1.024 (0.937-1.120)	1.012 (0.941-1.089)	1.014 (0.935-1.099)	1.001 (0.933-1.074)	1.000 (0.938-1.066)	0.977 (0.925-1.032)	1.000 (0.957-1.046)



Number at risk (n)	92	71	68	65	65	60	60	60	60	60
Control group	92	71	68	65	65	60	60	60	60	60
S-ketodex group	92	79	79	78	76	75	75	75	74	73

Figure 2 (A) The cumulative incidence of postoperative delirium was lower in patients who received S-ketamine and dexmedetomidine than control group (Log rank test $P = 0.027$, Cox hazard risk model: Hazard ratio 0.574, 95% CI 0.334–0.986, $P = 0.044$). **(B)** The prevalence of postoperative delirium at each assessment timepoint between two groups.

Table 4 Adverse Events

	Esketamine-dex Group (n = 92)	Control Group (n = 92)	P value
Intraoperative bradycardia with treatment ^a	18 (19.6%)	23 (25.0%)	0.378
Tachycardia ^b	0 (0.0%)	0 (0.0%)	NA
Hypotension ^c	20 (21.7%)	20 (21.7%)	>0.999
Hypertension ^d	0 (0.0%)	1 (1.1%)	>0.999
Hallucination ^e	0 (0.0%)	0 (0.0%)	NA

Notes: Data were presented as n (%). ^aHeart rate \leq 60 beats/min or \leq 80% baseline reference. ^bHeart rate $>$ 80% baseline reference. ^cBlood pressure \leq 80% baseline reference. ^dBlood pressure \geq 120% baseline reference. ^eIncluding nightmare, visual and auditory hallucination.

incidence of POD in neurosurgical pediatrics was about 38% in control group which was higher than those undergoing non-neurosurgery.³ This might be attributed to disease-related neurodevelopmental delay in these patients.⁷⁻⁹

Our study found that the combination of esketamine and dexmedetomidine could significantly prevent POD and emergence delirium in neurosurgical pediatrics. A single use of esketamine or dexmedetomidine had been investigated to reduce the incidence of emergence agitation in children.^{13,21} In adult patients, either esketamine or dexmedetomidine as adjuvant to general anesthesia might decrease the risk of POD in elder patients after selective major surgery.^{32,33} But there was insufficient data to explain the combined effect of esketamine and dexmedetomidine on POD in neurosurgical pediatrics. Two randomized trials reported that premedication with intranasal esketamine and dexmedetomidine could lower the severity of preoperative anxiety and reduce the risk of emergence agitation in children undergoing dental and general surgery, but delirium was not observed in the two studies.^{22,23} To be noted, one study of them reported that compared with the single use, combined use of esketamine and dexmedetomidine can significantly improve the cooperation of children with inhalation anesthesia masks, and the incidence of emergence agitation and the pediatric anesthesia emergence delirium score were much lower.²³

The protective effect of esketamine-dex on POD may be attributed to its potential to reduce the requirement for general anesthetics. In this study, we observed that a smaller number of patients in the esketamine-dex group received sevoflurane, and the area under the curve (AUC) of sevoflurane concentration was significantly lower in this group compared to the control group. Previous studies had reported that cumulative dosage of sevoflurane was associated with an increased risk of delirium.³⁴ Surgery-related inflammation response was considered as a major contributor to delirium.³⁵ Present study employed NLR to reflect the acute change of systematic inflammation. Several studies reported that NLR was a good predictor of emergence delirium in children and POD in adult patients.^{36,37} However, our study did not detect a significant difference in NLR on the first and third postoperative days. Considering that mere NLR was used as inflammation indicator and there was missing data of NLR, our result is insufficient to support the neuroprotective effects of esketamine and dexmedetomidine against inflammatory response, warranting further investigation. There might be other mechanisms. For example, basic research showed that the combination of ketamine and dexmedetomidine could facilitate glymphatic cerebrospinal fluid influx which was important to clearance of brain metabolite.³⁸

The incidence of postoperative complications was similar between two groups. We noticed that most complications were occurrence of seizure. Both esketamine and dexmedetomidine were used for seizure control in clinical settings.^{39,40} However, we did not find the difference in occurrence of seizure symptoms between two groups. This might be attributed to the short duration of a single dose.

It's worth noting that the occurrence of adverse events such as bradycardia and hypotension were also comparable between two groups. These data inferred that combination of esketamine and dexmedetomidine was safe in pediatrics.

Patients in the esketamine-dex group exhibited lower medical costs, which may be attributed to a reduced incidence of postoperative delirium and a marginally shorter duration of hospital stay following surgery.

Our study had some limitations. First, a combination of esketamine and dexmedetomidine was administered during anesthesia induction. Further studies may be warranted to investigate whether postoperative administration of these two agents could reduce the risk of POD such as continuous infusion for 3 days in terms of patient-controlled analgesia. For

instance, postoperative infusion of low-dose esketamine combined with dexmedetomidine has been associated with reduced pain intensity and improved sleep quality in adult surgical patients.⁴¹ Both pain intensity and sleep disturbance were identified as risk factors for delirium. Second, the long-term neurodevelopmental outcomes of these children were not assessed in our study. However, considering that a single dose of esketamine-dexmedetomidine likely exerts effects limited to several hours, its influence on long-term neurodevelopment may be minimal. Third, we utilized the neutrophil-to-lymphocyte ratio (NLR) as a marker to reflect acute changes in the systemic inflammatory response. Regrettably, approximately one-third of the blood samples scheduled for collection on postoperative day 3 were missing. Indeed, obtaining blood samples in pediatric populations remains a significant ethical challenge. Fourth, this was a single center study, and the generalizability of result was limited in pediatrics undergoing neurosurgical procedures.

Conclusion

Combined esketamine and dexmedetomidine could significantly decrease the risk of POD and emergence delirium in pediatrics after neurosurgery. This might also benefit patient's clinical outcome such as lower medical cost.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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