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Original Article

Ketamine versus sevoflurane for pediatric intracranial tumor surgery: impact on perioperative stability and postoperative recovery

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Abstract: This study compared the clinical efficacy of ketamine and sevoflurane in anesthetic management for pediatric intracranial tumor surgery, focusing on perioperative hemodynamics, inflammatory and stress responses, endotoxin (ET), nitric oxide (NO), oxidative stress, and postoperative recovery. A retrospective analysis was conducted on 229 pediatric patients who underwent intracranial tumor resection between June 2022 and August 2024, of whom 122 received ketamine anesthesia and 107 received sevoflurane. Propensity score matching was applied, yielding 62 patients in each group with balanced baseline characteristics. Perioperative indicators, including mean arterial pressure (MAP), heart rate (HR), C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), epinephrine, cortisol, ET, NO, superoxide dismutase (SOD), and malondialdehyde (MAD), were assessed at five timepoints (T_1-T_5). Postoperative outcomes included visual analogue scale (VAS) scores, Ramsay sedation scores, Pediatric Anesthesia Emergence Delirium (PAED) scores, emergence time, surgical duration, and adverse events. Results showed that the ketamine was associated with significantly lower MAP at T_3-T_4 but higher MAP at T_5, and with consistently lower HR at T_3-T_5 compared with the sevoflurane (all $P<0.01$). Levels of CRP, IL-6, TNF-α, epinephrine, and cortisol were significantly lower in the ketamine group at T_3-T_5, suggesting reduced inflammatory and stress responses, while ET and NO levels were higher at T_2-T_4. Oxidative stress markers (SOD and MAD) were also lower in the ketamine group at T_3-T_5, indicating stronger antioxidant properties. In contrast, the sevoflurane group demonstrated lower VAS scores at 1-24 h, higher Ramsay scores at 6-24 h, and lower PAED scores at 30 min-3 h (all $P<0.05$), reflecting better postoperative analgesia, sedation, and reduced agitation. Emergence time was significantly longer in the ketamine group ($P<0.001$), though surgical duration and incidence of adverse events showed no significant difference between groups. In conclusion, ketamine provides superior intraoperative hemodynamic stability and reduces inflammatory, stress, and oxidative responses, whereas sevoflurane offers better postoperative analgesia, sedation, and recovery. Individualized anesthetic selection is recommended based on patient and surgical characteristics.

Keywords: Ketamine, sevoflurane, pediatric anesthesia, intracranial tumor

Introduction

Intracranial tumors are among the most challenging conditions in pediatric neurosurgery. Since lesions involve critical brain structures, surgical resection is often accompanied by severe intracranial pressure fluctuations, tissue manipulation, and prolonged operative times, all of which can trigger significant physiological and neurological stress responses in pediatric patients [1, 2]. Children inherently have relatively limited blood volume reserves, and their sympathetic-parasympathetic nervous systems are incompletely developed, resulting in distinct pharmacokinetic and pharmacodynamic characteristics of anesthetic agents compared with adults. Consequently, they are more vulnerable to perioperative hemodynamic instability, massive release of inflammatory mediators and stress hormones, and elevated oxidative stress levels [3]. These factors not only compromise intraoperative vital-sign stability but may also exacerbate postoperative neurological dysfunction, prolong

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hospitalization and recovery, and potentially increase complication risks.

The major challenge in anesthetic management for pediatric intracranial tumor surgery is to suppress stress and inflammatory responses while maintaining adequate anesthetic depth, safety, and optimal postoperative recovery [4]. Evidence from network meta-analyses of preoperative sedative for pediatric elective procedures shows that agents such as dexmedetomidine, midazolam, and ketamine differ significantly in sedation efficacy, agitation control, and adverse-effect profiles, emphasizing the importance of rational anesthetic agent selection [5].

Ketamine, functioning as an N-methyl-D-aspartate (NMDA) receptor antagonist, has excellent analgesic and anesthetic properties. By stimulating the sympathetic nervous system, it maintains or increases blood pressure and heart rate (HR), thereby reducing intraoperative hypotensive episodes [6]. Qian et al. [7] reported that intranasal dexmedetomidine combined with ketamine provided superior sedative effects compared to dexmedetomidine alone, shortened sedation onset time, and improved pediatric cooperation during parental separation and mask acceptance. Additionally, ketamine inhibits inflammatory mediator release and reactive oxygen species scavenging, helping to attenuate intraoperative inflammatory responses and oxidative injury. A meta-analyses [8] comparing ketamine versus tramadol for postoperative analgesia following pediatric adenotonsillectomy showed that tramadol was superior in early analgesia, though ketamine still demonstrated good potential. Salman et al. [9] further observed that intramuscular ketamine achieved higher success rates and shorter scan times compared to intravenous administration for pediatric MRI sedation, with greater technician satisfaction.

Sevoflurane is characterized by rapid onset, easy titration of anesthetic depth, and quick emergence, suitable for high-precision neurosurgical procedures. Its postoperative sedative and analgesic effects are also notable. Kim et al. [10] found a moderate correlation between Bispectral Index (BIS) and Patient State Index (PSI) during pediatric sevoflurane anesthesia, though the reliability of both indices for monitoring anesthetic depth in children requires further investigation. However, sevoflurane may be inferior to ketamine in maintaining blood pressure and mitigating inflammation and oxidative stress.

Given these pharmacological and clinical differences, we retrospectively analyzed pediatric patients undergoing intracranial tumor resection and employed propensity score matching to balance baseline characteristics. The research comprehensively compared perioperative hemodynamic stability, inflammatory markers, stress hormones, endotoxin, nitric oxide, oxidative stress indicators, and postoperative outcomes, and adverse events, aiming to provide evidence-based guidance for optimizing anesthetic protocols in this high-risk pediatric population.

Methods and materials

Sample size calculation

Based on the study by Fang et al. [11], who compared different anesthetic approaches in pediatric patients and reported significant differences in perioperative parameters, we referred to their methodology to estimate sample size. In our cohort, the Pediatric Anesthesia Emergence Delirium (PAED) score at 30 minutes after extubation demonstrated a between-group difference of approximately 2 points with a pooled standard deviation of ~1.2. Using a two-sided test with $\alpha=0.05$ and statistical power of 90%, the minimum theoretical sample size was calculated to be ~29 patients per group. Considering potential attrition, bias, and the need for propensity score matching (PSM), we planned to include at least 30-40 patients per group to ensure robustness and generalizability. Ultimately, our matched cohort included 65 patients in each group, exceeding the estimated requirement.

Sample collection

Baseline demographic and clinical data were retrospectively collected from 229 pediatric patients with intracranial tumors who underwent surgical resection at our institution between June 2022 and August 2024. According to anesthetic approach, patients were stratified into the ketamine group (n=122, receiving ketamine anesthesia) and the sevoflurane group (n=107, receiving sevoflurane anesthe-

sia). This study was approved by the Ethics Committee of the National Children's Medical Center & Children's Hospital of Fudan University.

Inclusion and exclusion criteria

Inclusion criteria: Pediatric patients aged 5-12 years scheduled for intracranial tumor surgery; American Society of Anesthesiologists (ASA) classification I or II; elective intracranial tumor resection under general anesthesia; availability of complete perioperative clinical data.

Exclusion criteria: Severe cardiac, pulmonary, hepatic, or renal dysfunction; history of epilepsy, psychiatric disorders, or neurodevelopmental abnormalities; requirement for intraoperative cardiopulmonary resuscitation or occurrence of major anesthetic complications; known allergy to ketamine, sevoflurane, or related; concurrent systemic malignancies or combined surgical procedures.

Anesthetic protocols

Patients in both groups received identical preinduction preparation. All patients fasted for 8 hours and restricted water intake for 2 hours before surgery. Penehyclidine hydrochloride (0.01 mg/kg) was administered intramuscularly 30 minutes preoperatively.

Upon operating room entry, blood pressure, oxygen saturation, and HR monitoring were established. After 3 minutes of preoxygenation with 100% oxygen, anesthesia was induced with intravenous vecuronium (0.15 mg/kg), etomidate (0.2 mg/kg), and fentanyl (2.5 μg/kg) to facilitate tracheal intubation.

During maintenance, the ketamine group received a continuous ketamine infusion at 8 mg/(kg·h) with propofol 8 mg/(kg·h). The sevoflurane group maintained anesthetic depth with 5% sevoflurane inhalation combined with propofol 8 mg/(kg·h). At the end of surgery, anesthetic agents were discontinued, and patients were extubated once fully awake, then transferred to recovery room for routine monitoring and postoperative management.

Laboratory indicators and functional score assessment

Perioperative indicators were assessed at five timepoints: T_1 (pre-anesthetic induction), T_2 (immediately post-intubation), T_3 (surgery initiation), T_4 (surgery completion), and T_5 (5 minutes post-extubation). Mean arterial pressure (MAP) and HR were monitored using the Philips IntelliVue MP70 multiparameter monitor.

Inflammatory factors - including C-reactive protein (CRP, PC190), interleukin-6 (IL-6, PI325), and tumor necrosis factor-α (TNF-α, PT518) were sourced from Beyotime Biotechnology. Stress indicators epinephrine (ml105376) and cortisol (Cor, ml711149) were obtained from Shanghai Enzyme-linked Biotechnology, measured using the BioTek Epoch 2 microplate reader.

Endotoxin (ET) and nitric oxide (NO) were detected using commercial kits from Shanghai Sigma (catalog SG-ET200 and SG-NO150, respectively). Oxidative stress indicators (superoxide dismutase [SOD] and malondialdehyde [MDA]) were measured using Nanjing Jiancheng detection kits (SOD, colorimetric method, JC-SOD05; MDA, thiobarbituric acid method, JC-MDA10) on a Guoguang GCS-220 biochemical analyzer.

Postoperative assessments included visual analogue scale (VAS), Ramsay sedation scale, and PAED scale. Two trained researchers independently scored patients at the designated timepoints, and results were averaged.

Clinical data collection

Clinical data were obtained from electronic medical records and the surgical anesthesia information systems. Baseline demographic information included age, sex, body mass index (BMI), ASA classification, and tumor pathological type.

Perioperative vital signs (MAP and HR) were collected at five timepoints: T_1-T_5.

Laboratory biochemical indicators included inflammatory factors (CRP, IL-6, TNF-α), stress hormones (epinephrine and cortisol), ET, NO, and oxidative stress indicators (SOD, MDA). Peripheral blood samples were collected intraoperatively at the designated time points for biochemical analysis.

Postoperative recovery was assessed using VAS [12], Ramsay sedation scale [13], and PAED scale [14] at 1 h, 6 h, 12 h, and 24 h post-

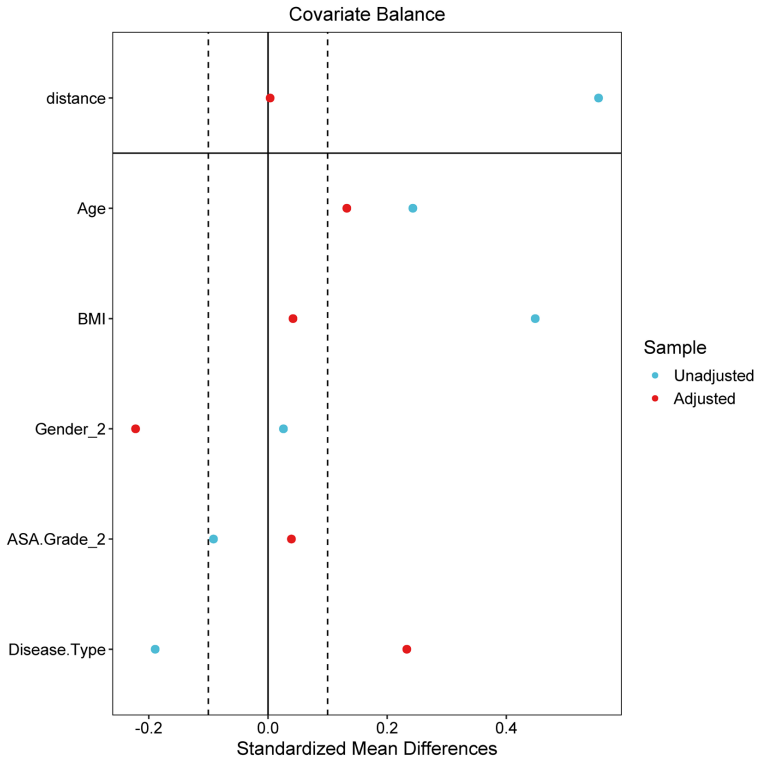

Figure 1. Standardized mean differences of covariates before and after matching. Note: Blue dots represent covariate distribution differences for unmatched samples (Unadjusted), red dots represent matched samples (Adjusted), vertical axis shows variable names, horizontal axis shows standardized mean differences; BMI: Body Mass Index, ASA: American Society of Anesthesiologists, PSM: Propensity Score Matching, SMD: Standardized Mean Differences.

operatively. Adverse events, including nausea, vomiting, shivering, and emergence agitation, were identified from progress notes and anesthetic recovery records. All data were cross-checked by two investigators to ensure completeness and accuracy.

Outcome measurements

Primary outcomes: Dynamic changes in perioperative MAP and HR; postoperative analgesia, sedation, and agitation scores assessed by VAS, Ramsay scale, PAED scores, respectively.

Secondary outcomes: Changes in inflammatory markers (CRP, IL-6, TNF-α); stress hormone levels (epinephrine, cortisol); concentrations of ET and NO; oxidative stress indicators (SOD, MDA); incidence of postoperative adverse events (nausea, vomiting, shivering, emergence agitation); baseline characteristic balance before and after propensity score matching (PSM).

Statistical analysis

Data analyses were performed using R software (version 4.3.3). Continuous variables were first tested for normality. Normally distributed variables were expressed as mean ± standard deviation ($\bar{x} \pm s$), and between-group comparisons were conducted using independent samples t-test. Non-normally distributed variables were expressed as median and interquartile range [M (P25, P75)], with between-group comparisons using Wilcoxon rank-sum test. Categorical variables were expressed as counts (%) and compared using the χ^2 test or Fisher's exact test, as appropriate.

Repeated measurement data were analyzed using repeated-measures analysis of variance (ANOVA) or paired non-parametric tests to evaluate time effects and group-time interaction. PSM was performed with 1:1 nearest-neighbor matching, using age, sex, BMI, ASA classification, and tumor type as covariates; a caliper width of 0.02 was applied. Post-matching baseline characteristic balance was assessed to confirm comparability. All tests were two-sided, with $P<0.05$ considered statistically significant.

Results

Assessment of baseline characteristic balance before and after propensity score matching

Following PSM, the standardized mean differences of covariates, including age, BMI, sex, ASA classification, and tumor type, were markedly reduced, with more balanced distributions between the ketamine and sevoflurane groups. A total of 130 patients were matched, yielding 65 patients per group. Q-Q plots demonstrated substantial overlap in propensity score distributions between groups post-matching, indicating improved sample comparability (**Figures 1**, **2**).

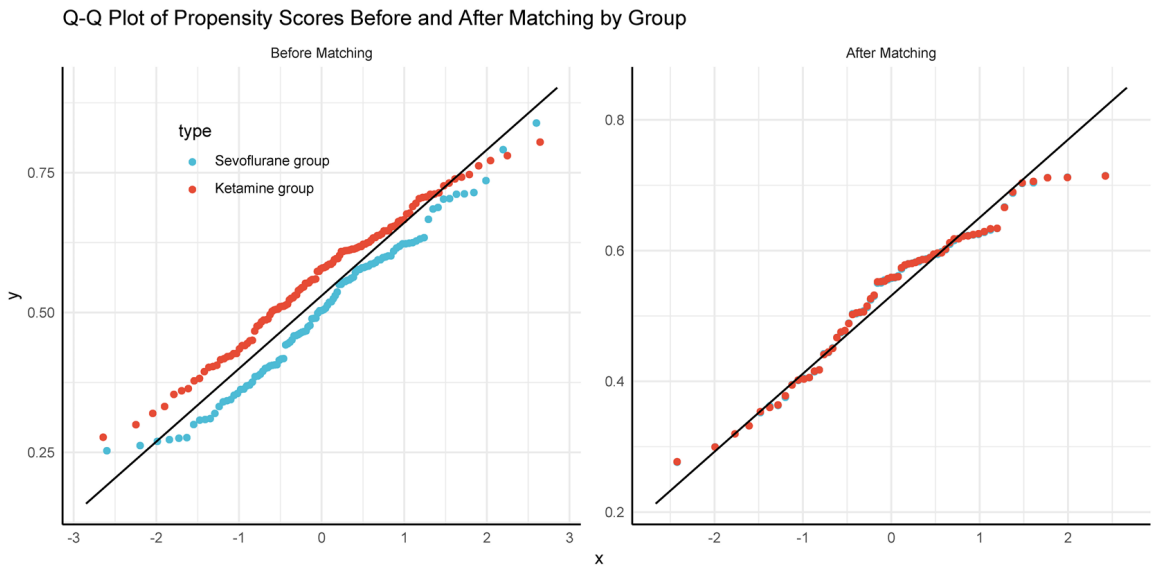

Figure 2. Q-Q plots of propensity scores before and after matching by group. Note: Blue and red dots represent propensity score distributions for the sevoflurane and ketamine groups, respectively. The left plot shows pre-matching, and the right plot shows post-matching.

Baseline characteristics of pediatric patients

Before PSM, significant differences were observed between the ketamine and sevoflurane groups in age (P=0.021) and BMI (P=0.001), whereas sex distribution, ASA classification, and tumor type were comparable (all P>0.05). After PSM, all baseline characteristics were well-balanced, with no significant between-group differences (all P>0.05), confirming successful matching and enhanced comparability (**Table 1**).

Surgical duration and emergence time

Surgical durations were comparable between the two groups both before and after PSM (all P>0.05). However, emergence time was consistently and significantly longer in the ketamine group compared with the sevoflurane group in both analyses (P<0.001), demonstrating that sevoflurane was associated with faster postoperative recovery (**Table 2**).

Hemodynamic parameters (MAP and HR)

MAP was similar between groups at early timepoints (T_1 and T_2, P>0.05). During surgery, MAP became significantly lower in the ketamine group at T_3 and T_4 (both P<0.001) but was higher at T_5 (P=0.003). HR showed a similar trend, with no significant differences at T_1 and T_2 (P>0.05) but significantly lower in the ketamine group at T_3 to T_5 (P<0.001). These findings indicate a time-dependent divergence in hemodynamic profiles between anesthetic regimens (**Table 3**).

Inflammatory biomarkers (CRP, IL-6, TNF-α)

CRP, IL-6, and TNF-α levels were similar between groups at T_1 and T_2 (all P>0.05). Levels of these markers increased significantly during surgery in both groups but remained consistently lower in the ketamine group at T_3, T_4, and T_5 (all P<0.001), suggesting a superior anti-inflammatory effect of ketamine (**Table 4**).

Stress hormones (epinephrine and cortisol)

Both epinephrine and cortisol concentrations increased significantly over time in both groups. No significant differences were observed at T_1 and T_2 (P>0.05). From T_3 to T_5, however, both hormones were consistently lower in the ketamine group than in the sevoflurane group (all P<0.001), indicating stronger suppression of perioperative stress responses with ketamine anesthesia (**Table 5**).

Endotoxin and nitric oxide levels

ET and NO levels were comparable at baseline (T_1, P>0.05) and T_5 (P>0.05). However, at T_2, T_3,

Table 1. Comparison of baseline characteristics between the two groups before and after PSM propensity score matching

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
Age (years) median [IQR]	7.00 [6.00, 8.00]	7.00 [5.00, 8.00]	2.262/0.021	7.00 [7.00, 8.00]	7.00 [5.00, 9.00]	1.254/0.21
BMI (kg/m^2) median [IQR]	22.50 [21.22, 23.58]	21.63 [20.48, 23.21]	3.181/0.001	22.21 [21.11, 23.16]	22.19 [20.82, 23.52]	0.244/0.807
Sex: Male n (%)	76 (62.30%)	68 (63.55%)	0.039/0.844	45 (69.23%)	38 (58.46%)	1.633/0.201
Sex: Female n (%)	46 (37.70%)	39 (36.45%)		20 (30.77%)	27 (41.54%)	
ASA I n (%)	99 (81.15%)	83 (77.57%)	0.447/0.504	51 (78.46%)	52 (80.00%)	0.047/0.829
ASA II n (%)	23 (18.85%)	24 (22.43%)		14 (21.54%)	13 (20.00%)	
Tumor: Osteoblastoma n (%)	61 (50.00%)	48 (44.86%)	2.771/0.25	28 (43.08%)	33 (50.77%)	2.23/0.328
Tumor: Craniopharyngioma n (%)	43 (35.25%)	34 (31.78%)		24 (36.92%)	25 (38.46%)	
Tumor: Others n (%)	18 (14.75%)	25 (23.36%)		13 (20.00%)	7 (10.77%)	

Note: ASA: American Society of Anesthesiologists, BMI: Body Mass Index, PSM: Propensity Score Matching.

Table 2. Comparison of surgical duration and emergence time between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
Emergence Time (min)	22.29±5.87	15.70±5.07	9.111/P<0.001	22.43±6.30	15.92±5.27	-6.390/P<0.001
Surgical Time (min)	156.49±9.93	157.50±9.00	-0.802/0.423	157.48±10.01	157.88±8.99	0.240/0.811

Note: PSM, Propensity Score Matching.

Table 3. Comparison of hemodynamic parameters between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
MAP (mmHg)						
T1	73.99±6.32	73.55±6.80	0.497/0.62	73.07 (69.27, 78.77)	74.61 (70.88, 79.07)	0.528/0.597
T2	78.61±7.33	77.78±7.57	0.836/0.404	78.43 (74.06, 83.10)	78.19 (73.22, 84.18)	-0.277/0.782
T3	74.68±5.87	78.17±5.97	4.452/P<0.001	75.34 (70.55, 78.98)	78.56 (73.11, 82.14)	3.106/0.002
T4	71.69±5.76	75.02±6.15	4.209/P<0.001	71.24 (68.48, 74.28)	75.37 (70.58, 78.48)	3.353/P<0.001
T5	86.22±6.94	80.53±7.42	5.959/P<0.001	85.40 (80.82, 90.30)	79.82 (76.15, 87.22)	-2.936/0.003
Within-group Stat/P	94.249/P<0.001	16.670/P<0.001		109.681/P<0.001	32.372/P<0.001	
HR (beats/min)						
T_1	106.28 (99.72, 112.72)	104.44 (96.91, 113.47)	1.216/0.224	106.44±10.55	104.02±13.26	-1.153/0.251
T_2	119.37 (109.30, 129.17)	123.41 (115.19, 130.85)	1.558/0.119	120.11±16.03	122.72±13.60	1/0.319

T_3	97.55 (90.15, 105.52)	114.37 (107.83, 124.01)	9.664/P<0.001	96.76±10.88	115.63±11.82	9.47/P<0.001
T_4	96.98 (89.24, 104.28)	105.32 (98.48, 110.59)	6.306/P<0.001	97.30±10.44	105.57±9.09	4.821/P<0.001
T_5	98.58 (90.62, 105.47)	108.77 (99.86, 116.86)	5.832/P<0.001	98.39±10.25	106.10±12.55	3.833/P<0.001
Within-group Stat/P	199.572/P<0.001	126.003/P<0.001		44.925/P<0.001	28.710/P<0.001	

Note: MAP: Mean Arterial Pressure, HR: Heart Rate, PSM: Propensity Score Matching, T_1: Timepoint 1, T_2: Timepoint 2, T_3: Timepoint 3, T_4: Timepoint 4, T_5: Timepoint 5.

Table 4. Comparison of perioperative inflammatory biomarkers between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
CRP (mg/L)						
T_1	56.10±6.88	56.84±6.18	0.854/0.394	55.64±6.56	57.36±5.40	1.630/0.106
T_2	65.93±8.50	67.49±8.23	1.413/0.159	65.90±8.45	66.69±8.38	0.534/0.595
T_3	93.82±10.81	115.08±13.63	12.952/P<0.001	95.37±10.99	116.61±13.62	9.784/P<0.001
T_4	115.50±12.34	128.46±12.51	7.872/P<0.001	116.84±12.06	128.58±12.87	5.366/P<0.001
T_5	133.23±14.70	144.41±15.48	5.581/P<0.001	131.89±14.83	142.88±15.50	4.130/P<0.001
Within-group Stat/P	1026.856/P<0.001	1099.823/P<0.001		541.083/P<0.001	642.513/P<0.001	
IL-6 (ng/L)						
T_1	25.79±3.02	25.86±3.31	0.156/0.876	26.24±2.45	25.95±3.08	-0.591/0.555
T_2	31.88±3.67	31.54±3.89	0.672/0.503	31.98±3.39	31.30±3.78	-1.076/0.284
T_3	40.95±4.41	54.62±5.94	19.561/P<0.001	40.07±4.42	54.52±5.40	16.699/P<0.001
T_4	52.09±5.36	62.40±6.41	13.105/P<0.001	51.50±5.25	61.14±6.05	9.695/P<0.001
T_5	67.33±6.43	74.39±7.09	7.857/P<0.001	67.45±6.96	74.03±7.17	5.304/P<0.001
Within-group Stat/P	1497.409/P<0.001	1454.287/P<0.001		802.551/P<0.001	925.980/P<0.001	
TNF-α (ng/L)						
T_1	45.98 (42.87, 49.83)	45.65 (41.67, 48.22)	1.677/0.093	45.30 (42.68, 48.75)	45.50 (41.67, 47.82)	-0.538/0.591
T_2	49.69 (46.12, 53.11)	49.68 (46.48, 54.30)	0.727/0.467	49.03 (46.28, 53.06)	50.78 (46.41, 55.08)	1.339/0.181
T_3	55.49 (51.59, 59.21)	62.67 (58.38, 67.03)	6.998/P<0.001	55.35 (50.86, 58.85)	63.61 (59.14, 68.13)	5.380/P<0.001
T_4	61.61 (56.23, 67.41)	70.22 (64.03, 74.73)	6.729/P<0.001	60.91 (56.31, 68.01)	71.33 (63.88, 74.65)	4.857/P<0.001
T_5	70.12 (65.46, 73.84)	76.46 (72.22, 81.62)	7.000/P<0.001	70.40 (65.08, 73.89)	76.84 (72.75, 83.33)	5.625/P<0.001
Within-group Stat/P	401.553/P<0.001	410.625/P<0.001		212.998/P<0.001	247.632/P<0.001	

Note: CRP: C-reactive Protein, IL-6: Interleukin-6, TNF-α: Tumor Necrosis Factor-alpha, PSM: Propensity Score Matching, T_1: Timepoint 1, T_2: Timepoint 2, T_3: Timepoint 3, T_4: Timepoint 4, T_5: Timepoint 5.

Table 5. Comparison of stress hormone levels between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
Epinephrine (ng/mL)						
T_1	39.18 (34.78, 42.19)	39.76 (36.27, 43.71)	1.509/0.131	38.83±4.82	39.76±5.10	1.069/0.287
T_2	50.44 (45.78, 53.95)	51.19 (47.42, 55.54)	1.147/0.252	50.75±5.48	51.56±5.68	0.821/0.413
T_3	61.69 (54.62, 67.14)	76.11 (72.05, 82.72)	10.533/P<0.001	60.60±7.74	78.29±8.55	12.367/P<0.001
T_4	78.17 (73.21, 85.18)	86.91 (78.98, 93.29)	5.747/P<0.001	79.37±9.71	86.67±8.94	4.458/P<0.001
T_5	53.71 (50.59, 57.50)	68.93 (64.37, 73.80)	11.791/P<0.001	54.75±5.52	68.91±7.45	12.308/P<0.001
Within-group Stat/P	472.826/P<0.001	441.821/P<0.001		331.596/P<0.001	429.440/P<0.001	
Cortisol (pg/mL)						
T_1	148.44 (136.01, 159.77)	148.59 (136.75, 158.09)	0.124/0.901	148.66 (135.35, 159.64)	149.74 (136.88, 157.63)	-0.037/0.97
T_2	170.94 (159.76, 180.46)	168.72 (154.31, 179.96)	1.327/0.184	170.89 (159.64, 178.77)	165.62 (154.16, 180.86)	-1.062/0.288
T_3	187.72 (170.02, 199.37)	234.44 (215.76, 253.17)	10.966/P<0.001	190.53 (170.13, 200.90)	234.44 (215.59, 254.11)	8.165/P<0.001
T_4	205.18 (188.98, 221.07)	271.13 (250.48, 290.24)	12.477/P<0.001	204.99 (188.90, 221.48)	271.50 (250.22, 292.23)	9.203/P<0.001
T_5	192.13 (178.30, 205.32)	222.34 (206.76, 233.45)	9.582/P<0.001	192.17 (180.13, 206.03)	221.89 (206.26, 233.24)	7.115/P<0.001
Within-group Stat/P	297.687/P<0.001	435.332/P<0.001		159.859/P<0.001	265.474/P<0.001	

Note: Cor: Cortisol, PSM: Propensity Score Matching, T_1: Timepoint 1, T_2: Timepoint 2, T_3: Timepoint 3, T_4: Timepoint 4, T_5: Timepoint 5.

Table 6. Comparison of endotoxin and nitric oxide levels between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
ET (ng/L)						
T_1	83.78±11.11	84.85±12.32	0.685/0.494	83.87 (77.11, 91.36)	84.53 (76.85, 94.26)	0.421/0.673
T_2	106.56±15.86	91.70±9.08	8.827/P<0.001	104.63 (96.49, 113.03)	92.21 (86.37, 97.67)	-5.301/P<0.001
T_3	109.31±14.53	84.00±7.84	16.667/P<0.001	108.08 (96.60, 114.92)	83.79 (80.00, 88.74)	-8.225/P<0.001
T_4	102.83±13.95	85.87±7.57	11.609/P<0.001	101.42 (89.41, 108.77)	87.04 (81.53, 91.12)	-6.293/P<0.001
T_5	97.21±12.14	94.45±12.23	1.709/0.089	98.38 (91.20, 105.73)	92.32 (85.00, 103.90)	-1.762/0.078
Within-group Stat/P	67.925/P<0.001	22.710/P<0.001		86.988/P<0.001	46.063/P<0.001	
NO (μmol/L)						
T_1	79.77±7.89	81.28±7.63	1.469/0.143	80.15±8.04	81.52±7.81	0.984/0.327
T_2	96.35±10.62	90.35±9.06	4.616/P<0.001	96.76±10.76	90.28±9.58	-3.627/P<0.001
T_3	102.86±11.38	94.48±8.82	6.265/P<0.001	101.91±12.61	94.25±9.39	-3.928/P<0.001
T_4	103.25±11.38	81.94±9.37	15.538/P<0.001	103.88±11.94	82.22±10.50	-10.987/P<0.001
T_5	109.56±12.11	109.45±11.22	0.075/0.940	109.31±13.10	111.12±11.05	0.851/0.397
Within-group Stat/P	139.374/P<0.001	174.614/P<0.001		63.181/P<0.001	105.418/P<0.001	

Note: ET: Endotoxin, NO: Nitric Oxide, PSM: Propensity Score Matching, T_1: Timepoint 1, T_2: Timepoint 2, T_3: Timepoint 3, T_4: Timepoint 4, T_5: Timepoint 5.

and T_4, both ET and NO levels were significantly higher in the ketamine group (P<0.001), indicating transient intraoperative elevations (**Table 6**).

Oxidative stress markers (SOD and MDA)

SOD and MDA levels did not differ significantly between groups at T_1 and T_2 (P>0.05). At T_3, T_4, and T_5, both markers were significantly lower in the ketamine group (P≤0.009), indicating a more favorable oxidative stress profile under ketamine anesthesia (**Table 7**).

Postoperative recovery scores (VAS, Ramsay, PAED)

VAS scores were consistently higher in the ketamine group at all postoperative time points, with differences reaching notable significance at 1 h, 6 h, and 12 h (P<0.001) and a smaller yet significant difference at 24 h (P=0.034-0.045). Ramsay sedation scores were significantly higher in the sevoflurane group at 6 h, 12 h, and 24 h (P<0.001), indicating deeper postoperative sedation. PAED agitation scores were significantly lower in the sevoflurane group at 30 min, 1 h, and 3 h postoperatively (P<0.001), confirming superior agitation control (**Table 8**).

Postoperative adverse events

No significant differences were found between the two groups regarding postoperative nausea and vomiting, shivering, emergence agitation, or overall adverse event incidence, both before and after PSM (all P>0.05), suggesting comparable safety profiles (**Table 9**).

Discussion

Pediatric intracranial tumor surgery poses considerable challenges because of the involvement of critical brain structures, marked intracranial pressure fluctuations, and prolonged operative duration, all of which demand exceptional anesthetic management. Perioperative hemodynamic instability, inflammatory and stress responses, and oxidative stress can exacerbate neurological injury and increase complication risks [15]. Given the immaturity of the pediatric autonomic nervous system and limited circulating blood volume, responses to anesthetic agents differ significantly from those in adults, making protocol selection particularly crucial.

Ketamine maintains hemodynamics and suppresses inflammation through NMDA receptor antagonism, while sevoflurane offers rapid onset, easy adjustment, and swift emergence [16]. This study comprehensively compared these anesthetic agents in terms of hemodynamics, inflammation, stress response, ET/NO levels, oxidative stress, and postoperative recovery. Propensity score matching (PSM) was employed to improve result reliability and provide evidence-based guidance for optimizing anesthetic management in pediatric intracranial tumor surgery.

Comparison of perioperative hemodynamics and postoperative recovery

Ketamine anesthesia demonstrated significant advantages in maintaining perioperative hemodynamic stability. During the intraoperative period, MAP remained lower at critical surgical phases (T_3-T_4) compared to sevoflurane, while HR was consistently lower from T_3 to T_5. These findings suggest that ketamine effectively prevents excessive intraoperative fluctuations and provides relative stability. Previous studies support this observation: Laws et al. [17] showed that ketamine reduces intracranial pressure and improves cerebral perfusion in children with severe traumatic brain injury, while Liu et al. [19] reported that S(+)-ketamine combined with propofol stabilizes hemodynamics in pediatric congenital heart disease. Clinically, ketamine's sympathetic stimulation prevents intraoperative hypotension and is particularly valuable for surgeries with marked intracranial pressure changes, such as intracranial tumor resections.

In contrast, sevoflurane was associated with more favorable postoperative recovery outcomes. Patients receiving sevoflurane reported lower pain scores in the first 24 hours, higher Ramsay sedation scores at 6-24 h, and reduced agitation based on PAED scores within the early postoperative period. Furthermore, emergence time was significantly shorter compared to ketamine, indicating more rapid recovery of consciousness and smoother transition from anesthesia. These results highlight sevoflurane's superiority in providing postoperative comfort and facilitating efficient recovery room management. Clinically, this translates to reduced risk of emergence agitation, shorter monitoring requirements, and improved patient and care-

Table 7. Comparison of oxidative stress markers between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
SOD (U/L)						
T_1	454.99 (352.42, 528.18)	453.98 (377.71, 507.59)	0.443/0.658	459.62±110.23	431.60±110.63	-1.447/0.15
T_2	411.81 (351.32, 499.38)	421.98 (374.69, 495.74)	0.736/0.462	419.49±105.97	418.16±98.16	-0.074/0.941
T_3	360.27 (287.38, 418.78)	405.75 (356.84, 475.39)	3.918/P<0.001	352.40±103.08	407.94±104.18	3.055/0.003
T_4	336.88 (255.34, 398.33)	386.43 (299.61, 442.90)	3.315/P<0.001	326.56±100.31	380.60±108.94	2.942/0.004
T_5	373.80 (301.51, 457.84)	419.95 (366.40, 480.72)	3.53/P<0.001	366.72±107.54	410.79±80.34	2.647/0.009
Within-group Stat/P	75.699/P<0.001	23.610/P<0.001		17.225/P<0.001	2.138/0.077	
MDA (mmol/mL)						
T_1	4.88 (4.53, 5.26)	4.81 (4.25, 5.30)	0.841/0.401	4.86 (4.53, 5.20)	4.70 (4.18, 5.24)	-0.847/0.397
T_2	4.83 (4.49, 5.27)	4.81 (4.43, 5.30)	0.094/0.925	4.72 (4.45, 5.20)	4.81 (4.37, 5.32)	0.491/0.623
T_3	5.03 (5.02, 5.04)	5.62 (4.96, 6.24)	5.887/P<0.001	5.03 (5.02, 5.04)	5.69 (5.02, 6.22)	4.749/P<0.001
T_4	5.16 (4.50, 5.87)	5.95 (5.06, 7.08)	4.43/P<0.001	5.13 (4.51, 5.90)	5.93 (5.11, 7.10)	3.213/0.001
T_5	4.71 (4.25, 5.36)	5.40 (4.46, 6.21)	3.628/P<0.001	4.63 (4.31, 5.44)	5.42 (4.68, 6.32)	3.474/P<0.001
Within-group Stat/P	19.436/P<0.001	71.709/P<0.001		14.264/0.006	53.415/P<0.001	

Note: SOD: Superoxide Dismutase, MAD: Malondialdehyde, PSM: Propensity Score Matching, T_1: Timepoint 1, T_2: Timepoint 2, T_3: Timepoint 3, T_4: Timepoint 4, T_5: Timepoint 5.

Table 8. Comparison of postoperative recovery between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
VAS (1 h)	3.00 (2.00, 3.00)	2.00 (2.00, 2.00)	5.216/P<0.001	3.00 (2.00, 3.00)	2.00 (2.00, 2.00)	-4.17/P<0.001
VAS (6 h)	3.00 (3.00, 3.00)	3.00 (2.00, 3.00)	5.028/P<0.001	3.00 (3.00, 3.00)	3.00 (2.00, 3.00)	-3.632/P<0.001
VAS (12 h)	5.00 (4.00, 5.00)	4.00 (4.00, 4.00)	6.898/P<0.001	5.00 (5.00, 5.00)	4.00 (4.00, 4.00)	-5.597/P<0.001
VAS (24 h)	5.00 (5.00, 6.00)	5.00 (5.00, 5.00)	1.713/0.045	5.00 (5.00, 6.00)	5.00 (5.00, 5.00)	-1.837/0.034
Ramsay (6 h)	2.00 (2.00, 2.00)	3.00 (2.00, 3.00)	5.943/P<0.001	2.00 (2.00, 2.00)	3.00 (2.00, 3.00)	4.5/P<0.001
Ramsay (12 h)	2.00 (1.00, 2.00)	2.00 (2.00, 2.00)	5.256/P<0.001	2.00 (1.00, 2.00)	2.00 (2.00, 2.00)	4.4/P<0.001
Ramsay (24 h)	1.00 (1.00, 1.00)	2.00 (1.00, 2.00)	5.912/P<0.001	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	3.783/P<0.001
PAED (30 min)	11.00 (10.00, 12.00)	9.00 (9.00, 10.00)	6.848/P<0.001	11.00 (10.00, 12.00)	9.00 (9.00, 10.00)	-4.847/P<0.001
PAED (1 h)	7.00 (7.00, 8.00)	6.00 (6.00, 7.00)	7.268/P<0.001	7.00 (7.00, 8.00)	6.00 (6.00, 7.00)	-5.441/P<0.001
PAED (3 h)	6.00 (6.00, 7.00)	5.00 (5.00, 6.00)	6.893/P<0.001	6.00 (6.00, 7.00)	5.00 (5.00, 6.00)	-6.642/P<0.001

Note: VAS: Visual Analogue Scale, Ramsay: Ramsay Sedation Scale, PAED: Pediatric Anesthesia Emergence Delirium Scale, PSM: Propensity Score Matching.

Table 9. Comparison of postoperative adverse events between the two groups before and after PSM

Variable	Pre-PSM			Post-PSM		
	Ketamine (n=122)	Sevoflurane (n=107)	t/Z/P	Ketamine (n=65)	Sevoflurane (n=65)	t/Z/P
Nausea & Vomiting, n	4	2	0.063/0.801	2	1	-/>0.999
Shivering, n	5	3	0.034/0.853	2	2	-/>0.999
Emergence Agitation, n	3	1	0.139/0.709	2	0	-/0.496
Total, n	12	6	0.884/0.347	6	3	0.478/0.490

Note: PSM, Propensity Score Matching.

giver satisfaction, making sevoflurane a more suitable choice when rapid recovery and effective postoperative analgesia are prioritized.

Regarding postoperative recovery, the sevoflurane group demonstrated lower pain scores in the early postoperative period, higher sedation levels, lower agitation scores, and significantly shorter emergence time compared with the ketamine group. These findings indicate that sevoflurane provides superior performance in terms of postoperative analgesia, sedation, and rapid recovery. Previous studies have also emphasized sevoflurane's advantages in rapid emergence and sedation. For instance, Xiao et al. [20] reported that prophylactic propofol administration (3 mg/kg) significantly reduced the incidence of pediatric agitation after sevoflurane anesthesia without prolonging recovery room stay. Nevertheless, the use of sevoflurane is often associated with emergence agitation, and adjunctive pharmacological strategies are commonly required to optimize outcomes [18]. In contrast, the ketamine group in our study exhibited higher postoperative pain and agitation scores as well as delayed emergence, which may be explained by ketamine's dissociative anesthetic properties and central nervous system effects. To address these limitations, multimodal strategies combining ketamine with other agents have been explored. Biricik et al. [21] demonstrated that a propofol-ketamine combination in a 3:1 ratio effectively reduced postoperative agitation, while Han et al. [24] showed that a midazolam-fentanyl-ketamine regimen decreased intraoperative spontaneous movement and postoperative agitation, improving surgeon satisfaction. Moreover, ketamine combined with lidocaine has been shown to attenuate intraoperative heart rate fluctuations, consistent with the hemodynamic benefits observed in our cohort.

Mechanistically, ketamine stabilizes blood pressure and HR via sympathetic nervous system activation and increased catecholamine release, thereby reducing intraoperative hypotension risk. Literature indicates [22] that ketamine, when used as adjunctive sedation in critically ill children, demonstrates a favorable safety profile with a low incidence of drug-related adverse events. Sevoflurane, on the other hand, enables rapid emergence and easy anesthetic depth adjustment due to rapid metabolism, resulting in faster postoperative recovery and more pronounced sedative-analgesic effects. However, its vasodilatory action may contribute to intraoperative HR elevation. A meta-analysis of randomized controlled trials [23] further revealed that, compared with sevoflurane, propofol anesthesia significantly reduced the incidence of emergence agitation, postoperative nausea and vomiting, and postoperative pain in children, while sevoflurane was associated with shorter times to eye opening and extubation.

Sevoflurane's advantages in rapid induction and recovery for neurosurgical procedures are well established, though its potential cardiovascular depressive effects warrant close monitoring.

Hebbar et al. [25] reported that intranasal atomized dexmedetomidine produced deeper sedation than intranasal atomized ketamine in pediatric spinal dysraphism surgery, though both showed comparable performance in facilitating intravenous access and mask acceptance. Recent meta-analyses [26] indicate that isoflurane significantly reduces the incidence of postoperative agitation in children compared to sevoflurane, underscoring the influence of inhalational anesthetic selection on postoperative recovery quality.

Our results align with existing literature, demonstrating ketamine's advantages in maintaining hemodynamic stability during high-risk surgeries, while sevoflurane excels in postoperative recovery speed, analgesia-sedation, and comfort improvement. Clinical practice should tailor anesthetic protocols to surgical characteristics and individual patient needs.

Regulation of inflammatory response, stress hormones, and oxidative stress

Our analysis revealed that the ketamine group exhibited consistently lower levels of inflammatory factor (CRP, IL-6, and TNF-α) than the sevoflurane group at multiple intraoperative timepoints. Stress hormone (epinephrine and cortisol) levels were also markedly lower under ketamine anesthesia, indicating its distinct advantages in suppressing inflammatory and stress responses. Sahoo et al. [27] reported that although subanesthetic ketamine was inferior to caudal block for postoperative analgesia, it demonstrated protective effects on inflammatory mediators, particularly IL-6 and TNF-α. Regarding oxidative stress, SOD activity and lipid peroxidation product MDA levels in the ketamine group were consistently lower than the sevoflurane group during the perioperative period, reflecting protective effects in reducing oxidative damage. Clinically, excessive perioperative inflammatory and stress responses can exacerbate brain injury, prolong recovery, and increase the risk of infection and other complication. Ketamine's comprehensive anti-inflammatory, anti-stress, and antioxidant effects help protect neurological function and simplify postoperative management. Wang et al. [28] demonstrated that perioperative S(+)-ketamine application effectively alleviated pediatric postoperative acute pain and reduced opioid consumption, closely related to its anti-inflammatory and anti-stress properties. Conversely, relatively higher inflammatory and oxidative stress levels in the sevoflurane group may render postoperative recovery more challenging, necessitating additional anti-inflammatory and protective management.

Mechanistically, ketamine suppresses inflammatory pathways such as nuclear factor-κB (NF-κB) through NMDA receptor antagonism, reducing the release of inflammatory factors including CRP, IL-6, and TNF-α. It simultaneously inhibits the secretion of epinephrine and cortisol to reduce stress responses. Ketamine also alleviates oxidative damage by scavenging reactive oxygen species and reducing lipid peroxidation product generation [29].

Meta-analyses have shown that ketamine-propofol combination provides superior protection against hypotension compared with either agent alone, which may related to ketamine's anti-inflammatory properties [30]. Sevoflurane, on the other hand, may induce stronger inflammatory and oxidative stress responses through volatile anesthetic metabolites or immunomodulatory effects, though the precise mechanisms require further investigation. Furthermore, meta-analyses indicate that midazolam-ketamine combination enhances pediatric cooperation during venipuncture compared to midazolam alone, possibly related to ketamine's anti-stress effects [31].

Changes in ET and NO levels

Perioperative data indicated that ET concentrations were generally higher in the ketamine group than in the sevoflurane group during surgery, while postoperative levels became comparable. NO levels followed a similar pattern, remaining relatively elevated in the ketamine group, suggesting that ketamine may influence ET clearance and NO generation. Clinically, intraoperative ET elevation may reflect compromised intestinal barrier function or reduced clearance capacity, warranting attention to postoperative infection risk. NO elevation helps maintain vascular tone and microcirculatory perfusion, though excessive vasodilation may predispose patients to tissue hypoperfusion. Mechanistically, ketamine promotes NO generation through sympathetic nervous system activation and NO synthase stimulation, while potentially affecting hepatointestinal ET metabolism [32]. Sevoflurane, by contrast, may reduce NO release via inhibitory effects on vascular endothelium, potentially limiting microcirculatory support [33]. Although evidence suggests that ketamine modulates vascular function through NO pathways, the specific effects of sevoflurane on ET and NO remain insufficiently characterized and require further investigation. These two anesthetic agents demonstrate differences in ET clearance and vascular regulation, underscoring the need for individualized selection based on surgical characteristics and pediatric physiological status.

Study limitations and future directions

This study employed PSM methodology to balance baseline characteristics and comprehensively evaluated multidimensional indicators, including hemodynamics, inflammation, stress response, ET/NO levels, oxidative stress, and postoperative recovery. This provided the first systematic comparison of the pharmacodynamic profiles of ketamine and sevoflurane in pediatric intracranial tumor surgery, providing evidence-based guidance for clinical anesthetic protocol optimization.

However, several limitations should be acknowledged. As a single-center retrospective study, it remains subject to selection bias, limited sample size, insufficient safety assessment, and lack of long-term neurological function and cognitive recovery assessment. In-depth analysis of dosage differences and individualized metabolic influences was not performed.

Clinically, anesthetic choice can be selected based on pediatric ASA classification, tumor type, and surgical complexity. Ketamine can be prioritized for maintaining intraoperative hemodynamic stability and mitigating inflammatory stress, whereas sevoflurane may be preferred for its advantages in postoperative analgesia, sedation and rapid emergence. Management can be optimized by combining ketamine with sedatives or enhancing HR monitoring during sevoflurane anesthesia. Ma et al. [34] propose comparing remimazolam versus sevoflurane regarding postoperative agitation per pediatric adenotonsillectomy, providing new research directions for further pediatric anesthetic protocol optimization.

Future research should include multicenter retrospective trials incorporating long-term neurological function and cognitive follow-up, investigate ET/NO and oxidative stress molecular mechanisms, evaluate advantages and disadvantages of sequential or combined drug use, and integrate genomics and pharmacokinetics to advance individualized pediatric anesthetic strategy development.

Conclusion

In pediatric intracranial tumor surgery, ketamine demonstrates superior perioperative hemodynamic stability and significant reduction of inflammatory responses, stress reactions, and oxidative stress compared to sevoflurane. However, it is associated with weaker postoperative analgesic and sedative effects and a higher risk of agitation. Sevoflurane excels in postoperative analgesia, sedation, and rapid emergence, but induces stronger inflammatory and stress responses. Differences in ET and NO dynamics suggest distinct effects of these two anesthetics on ET clearance and vascular regulatory function. Anesthetic selection should be individualized according to pediatric conditions and surgical complexity, with appropriate optimization of postoperative management strategies.

Disclosure of conflict of interest

None.

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