Effect of Intravenous Anesthesia With Remimazolam Besylate on Hemodynamics and Neuroprotection in Patients Undergoing Surgery for Craniocerebral Injury

Ann. Ital. Chir., 2025 96, 4: 543–549
https://doi.org/10.62713/aic.3867

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AIM: This study aimed to investigate the effect of intravenous anesthesia with remimazolam besylate on hemodynamics and neuroprotection in patients undergoing surgery for craniocerebral injury.
METHODS: This retrospective study analyzed the clinical data from 92 patients with craniocerebral injury who underwent craniotomy at Peking University International Hospital between May 2021 and August 2023. Based on anesthesia method applied, patients were divided into the observation group (n = 49) and the conventional group (n = 43). The conventional group underwent conventional anesthesia, and the observation group received intravenous anesthesia with remimazolam besylate. All patients were followed up for 3 months after surgery. Furthermore, perioperative hemodynamic indicators and neurological function were compared between the two groups at different time points, such as T0 (before surgery), T1 (30 minutes after anesthesia), T2 (at the end of surgery), and T3 (24 hours post-surgery). Additionally, perioperative indicators, postoperative adverse reactions, and prognosis were statistically analyzed.
RESULTS: From T0 to T1, heart rate (HR), peripheral capillary oxygen saturation (SpO_2), and mean arterial pressure (MAP) showed an increasing trend in both groups. Afterwards, HR and MAP demonstrated a decreasing trend in both groups, and ultimately restoring to T0 level. However, SpO_2 remained stable and then decreased slightly. The differences in HR, SpO_2, and MAP levels between the two groups and across different time points were statistically significant ($p < 0.05$). At T3, the levels of Tau protein, neuron-specific enolase, and glial fibrillary acidic protein were lower in the observation group than in the conventional group ($p < 0.05$). Furthermore, the observation group demonstrated shorter spontaneous breathing recovery time, eye-opening time, orientation recovery time, extubation time, length of intensive care unit (ICU) stays, and total hospital stay than the conventional group ($p < 0.05$). Additionally, the incidence rates of arrhythmia and pulmonary infection were lower in the observation group than in the conventional group ($p < 0.05$). Similarly, the observation group exhibited a better overall prognosis than the conventional group ($p < 0.05$).
CONCLUSIONS: Intravenous anesthesia with remimazolam besylate in patients undergoing surgery for craniocerebral injury can maintain stable hemodynamics, protect neurological function, and promote post-surgery recovery.

Keywords: remimazolam besylate; intravenous anesthesia; surgery for craniocerebral injury; hemodynamics; neurological function

Introduction

Craniocerebral injury, physical damage to brain tissue, is caused by external mechanical force, potentially leading to transient or permanent neurological dysfunction, coma, or skull bone fractures. The fatality rate of severe craniocerebral injury can reach up to 40% [1]. Currently, surgical treatment remains the primary approach in clinical practice. However, due to the complex neuronal network of the brain, surgical procedures and anesthesia require stringent standards, which include maintaining stable anesthesia depth to ensure unconsciousness and pain-free interventions, as well as maintaining hemodynamic parameters effectively. Furthermore, promptly identifying and managing surgical risks can enhance procedural safety and minimize postoperative recovery time and complications. Therefore, improving perioperative anesthesia management is crucial to increasing patient outcomes during craniocerebral surgery.

To meet these standards, various anesthetic regimens have been implemented in clinical practice, such as the combination of oxycodone and remifentanil with propofol [2] and the use of dexmedetomidine along with scalp nerve block [3]. While these common anesthetic and sedative drugs offer rapid analgesic and sedative effects, they are also associated with substantial adverse effects, including elevated oxidative stress in brain tissue and an increased incidence of postoperative complications, which can significantly impact prognosis. Remimazolam besylate, a benzodiazepine derivative, has emerged as a novel sedative, and is now being applied in various surgical procedures requiring anesthesia [4,5].

Submitted: 14 December 2024 Revised: 5 February 2025 Accepted: 14 February 2025 Published: 10 April 2025
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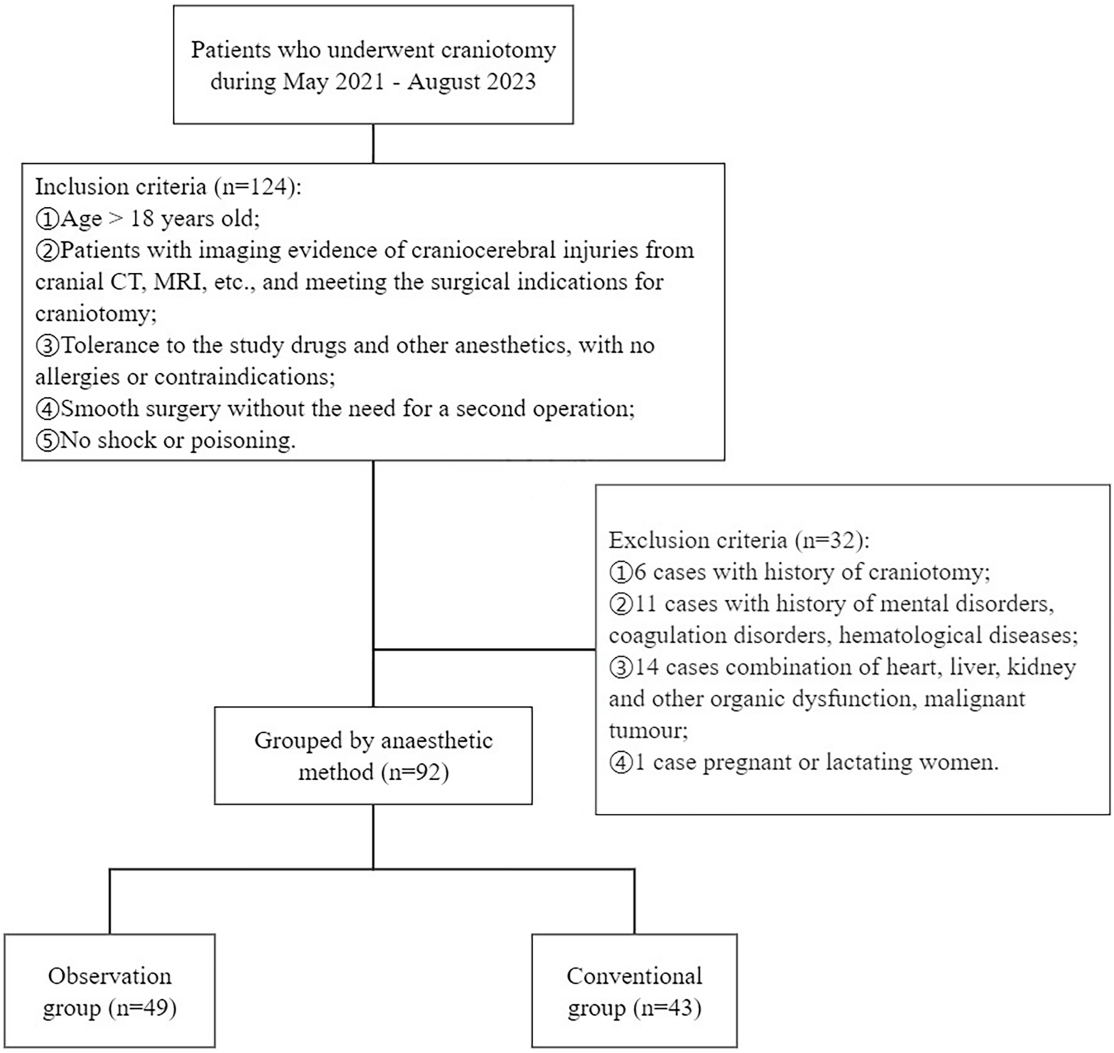

Fig. 1. A flow chart of patient enrolment and their grouping. Note: CT, computed tomography; MRI, magnetic resonance imaging.

However, research on the use of remimazolam besylate in craniotomy for craniocerebral injury remains limited. Therefore, this retrospective study analyzed clinical data collected from 92 patients with craniocerebral injury who underwent craniotomy at Peking University International Hospital, China, between May 2021 and August 2023. The aim was to investigate the effects of intravenous remimazolam besylate anesthesia on hemodynamic stability and neuroprotection in these patients.

Materials and Methods

Study Participants

This retrospective study collected clinical data from 92 patients with craniocerebral injuries who underwent craniotomy at Peking University International Hospital, China, between May 2021 and August 2023.

Inclusion criteria were set as follows: ① patients age >18 years, ② imaging-confirmed craniocerebral injury through cranial computed tomography (CT) or magnetic resonance imaging (MRI) and meeting the surgical indications for craniotomy [6], ③ ability to tolerate the study drugs and other anesthetics, with no known allergies or contraindications, ④ successful surgery completion without requiring a second operation, and ⑤ no history of shock or poisoning. While exclusion criteria included ① previous history of craniotomy, ② history of mental disorders, coagulation diseases, or hematological conditions, ③ significant organ dysfunction (heart, liver, kidney) or malignant tumour, and ④ pregnant or lactating women.

The patients were divided into an observation group (n = 49) and a conventional group (n = 43) based on the method of anesthesia. Following hospital admission, data on gender, age, glasgow coma scale (GCS) [7], cause of craniocerebral injury, and education level were obtained. The patient recruitment method is summarized in Fig. 1.

Treatment Protocols

Both groups of patients received standard preoperative and intraoperative management for craniotomy, which included:

(1) Preoperative fasting, water restriction, skin preparation, and airway clearance to ensure unobstructed respiration. Patients with brain herniation underwent mannitol or other hypotensive agent treatment.
(2) During intraoperative monitoring, access to the central venous was established, a nasogastric tube was placed, and continuous monitoring of electrocardiogram (ECG) and blood pressure was conducted.
(3) Based on CT scan results, the attending physician determined the type of surgery. The same attending physician performed all craniotomy procedures in this study.

The conventional group of patients received standard anesthesia. General anesthesia was induced through intravenous infusion of the following drugs:

- Sufentanil citrate injection (0.6 μg/kg, specification 1 mL: 50 μg, National Drug Approval No. H20203650, Enhua Pharmaceutical Co., Ltd., Xuzhou, China).
- Propofol medium/long-chain fat emulsion injection (2.0 mg/kg, specification 50 mL: 0.5 g, National Drug Approval No. H20213605, Hengrui Pharmaceutical Co., Ltd., Lianyungang, China).
- Rocuronium bromide injection (0.6 mg/kg, Production Batch No. A189921, Xianju Pharmaceutical Co., Ltd., Xianju, China).

During the procedure, anesthesia was maintained through intravenous infusion of propofol at a rate of 4 mg/kg·h combined with injectable remifentanil (specification 5 mg, National Drug Approval No. H20030200, Renfu Pharmaceutical Co., Ltd., Yichang, China) at a rate of 0.1 μg/kg-min, and 2% sevoflurane inhalation (specification: 250 mL, Production Batch No. H20160431, Baxter Co., Deerfield, IL, USA).

However, patients in the observation group received intravenous anesthesia with remimazolam besylate, and general anesthesia was induced through intravenous pumping of remimazolam besylate (specification: 50 mg, National Drug Approval No. H20227087, Renfu Pharmaceutical Co., Ltd., Yichang, China) and sufentanil at a dosage of 0.6 μg/kg. Moreover, anesthesia was maintained in this group, administering remimazolam besylate at a rate of 0.5 mg/kg·h during surgery.

Clinical Indicators

Patients were monitored by assessing the following clinical indicators.

(1) Hemodynamic indicators: A multifunctional monitor (M1205A, Philips, Amsterdam, Netherlands) was used to evaluate perioperative hemodynamic indicators in both groups at four-time points: preoperative (T0), 30 min after anesthesia (T1), at the end of surgery (T2), and 24 h after surgery (T3). These parameters included heart rate (HR), peripheral capillary oxygen saturation (SpO_2), and mean arterial pressure (MAP).
(2) Neurological function evaluation: A 3mL of venous blood was collected from each patient at T0 and T3 time points. After static stratification, blood samples were centrifuged (3000 r/min, 10 min), and serum was collected for further analysis. Neurological function indicators, including Tau protein (Suzhou Medical Device Registration 20212400825, Realmind Biotechnology Co., Ltd., Nanjing, China), neuron-specific enolase (Suzhou Medical Device Registration 20232400712, Realmind Biotechnology Co., Ltd., Nanjing, China), glial fibrillary acidic protein (Xiang Medical Device Registration 20242400299, Vazyme Biotechnology Co., Ltd., Chenzhou, China) were assessed using an automatic chemiluminescence analyzer (Suzhou Medical Device Registration 20192220813, Baiming Biotechnology Co., Ltd., Suzhou, China).
(3) Perioperative indicators: These parameters included surgical duration, intraoperative bleeding, spontaneous breathing recovery time, eye-opening time, orientation recovery time, extubation time, as well as the duration of the intensive care unit (ICU) stay, and the total hospital stay.
(4) Adverse reactions: The occurrence of adverse reactions (e.g., hypotension, arrhythmia, nausea/vomiting, etc.) was documented in both groups during the treatment period, and the incidence rate was calculated.
(5) Prognosis: Glasgow outcome score (GOS) [8] were used to assess the prognosis of the two groups 3 months after the surgery. The GOS grading criteria was as follows: Grade 1: Death; Grade 2: Persist vegetative states with minimal response, including sleep/wake cycles and eye-opening; Grade 3: Severe disability, conscious but requiring assistance for daily activities; Grade 4: Moderate disability, able to perform daily activities and work independently; Grade 5: Mild deficit, with minimal impact on normal life. Grades 1–3 indicate a poor prognosis, while grades 4–5 show a good prognosis.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics (version 24.0, SPSS Inc., Chicago, IL, USA). Count data were expressed as cases (%) and analyzed employing the χ^2 test. The Shapiro–Wilk test was used to assess data normality. Furthermore, measurement data were presented as mean ± standard deviation, and data following normal distribution were compared using an independent samples *t*-test. Comparisons between groups at multiple time points were assessed using Two-way Repeated-Measures Analysis of Variance (ANOVA). If significant main effects were observed, post-hoc tests were performed using Bonferroni

Table 1. Comparison of baseline data between the observation and conventional groups.

Group	Observation group (n = 49)	Conventional group (n = 43)	χ^2/t	p-value
Gender (male/female)	33/16	24/19	1.292	0.256
Age ($\bar{x} \pm$ s)	57.47 ± 7.64	59.62 ± 6.37	1.454	0.149
GCS score ($\bar{x} \pm$ s)	12.34 ± 1.31	12.05 ± 1.43	1.015	0.313
Causes of craniocerebral injury				
Traffic accidents [n (%)]	21 (42.86%)	19 (44.19%)	0.016	0.898
Fall from height [n (%)]	20 (40.82%)	13 (30.23%)	1.115	0.291
Smash [n (%)]	5 (10.20%)	6 (13.95%)	0.306	0.580
Other [n (%)]	3 (6.12%)	5 (11.63%)	0.318	0.573
Education level				
Junior high school and or below [n (%)]	22 (44.9%)	13 (30.23%)	2.090	0.148
Junior high school or above [n (%)]	27 (55.10)	30 (69.77%)	2.090	0.148

Note: GCS, glasgow coma scale.

Table 2. Comparison of perioperative haemodynamic indicators between the observation and conventional groups ($\bar{x} \pm$ s).

Group	n	HR (beat/min)				SpO_2 (%)				MAP (mmHg)			
		T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
Observation group	49	68.24 ± 9.70	78.71 ± 8.26*#	72.40 ± 7.11*#	68.52 ± 7.73	95.74 ± 1.47	98.66 ± 0.73*#	98.61 ± 0.48*#	96.28 ± 0.59*#	76.37 ± 5.57	86.94 ± 4.90*#	83.92 ± 4.83*#	77.34 ± 5.61
Conventional group	43	69.58 ± 9.36	84.05 ± 9.15*	76.88 ± 8.39*	69.79 ± 7.67	95.26 ± 1.22	96.90 ± 0.45*	97.75 ± 0.64*	97.17 ± 0.66*	75.82 ± 5.35	89.69 ± 4.25*	87.14 ± 5.21*	76.28 ± 5.27
$F/p_{inter\text{-}group}$		2.431/<0.001				3.631/<0.001				0.533/0.043			
F/p_{time}		26.032/<0.001				51.340/<0.001				51.071/<0.001			
$F/p_{interaction}$		0.842/0.234				10.820/<0.001				1.642/0.006			

Note: Compared to the T0, $^*p < 0.05$, compared to the conventional group, $^{\#}p < 0.05$. HR, heart rate; SpO_2, peripheral capillary oxygen saturation; MAP, mean arterial pressure.

Table 3. Comparison of neurological function between the observation and conventional groups ($\bar{x} \pm$ s).

Group	n	Tau protein (ng/L)		Neuron-specific enolase (μg/L)		Glial fibrillary acidic protein (ng/mL)	
		T0	T3	T0	T3	T0	T3
Observation group	49	7.64 ± 0.15	3.97 ± 0.20*	58.94 ± 1.35	30.83 ± 1.06*	0.59 ± 0.14	0.21 ± 0.05*
Conventional group	43	7.58 ± 0.19	4.28 ± 0.23*	59.33 ± 1.41	36.79 ± 0.90*	0.55 ± 0.12	0.28 ± 0.05*
t		1.691	6.916	1.354	28.852	1.461	6.700
p-value		0.094	<0.001	0.179	<0.001	0.148	<0.001

Note: Compared to the T0, $^*p < 0.05$.

correction. Moreover, rank sum tests were applied to compare hierarchical data. The statistically significant differences were defined as $p < 0.05$.

Results

Comparison of Baseline Data Between the Two Groups

This study included 92 patients who underwent craniotomy, including 49 patients in the observation group and 43 in the conventional group. The patients in the observation group had an age range of 28–73 years, while it was 25–75 years among the conventional group. The baseline characteristics between the two groups were comparable ($p > 0.05$, Table 1).

Comparison of Perioperative Haemodynamic Indicators Between the Two Groups

From the T0 to T1 period, both the observation and conventional groups showed a significant increase in HR, SpO_2, and MAP. During the T1 to T2 period, HR and MAP decreased in both groups, while SpO_2 remained stable. However, in the T2 to T3 period, HR and MAP was restored to T0 level, while SpO_2 was reduced. There were significant differences in HR between the two groups and at different time points ($p < 0.05$). For SpO_2 and MAP, there were significant differences between the two groups, at different time points, and in the interaction between groups and time ($p < 0.05$, Table 2).

Table 4. Comparison of perioperative indicators between the observation and conventional groups ($\bar{x} \pm s$).

Group	n	Surgical duration (h)	Intraoperative bleeding (mL)	Spontaneous breathing recovery time (min)	Eye-opening time (min)	Orientation recovery time (min)	Extubation time (min)	ICU stay (d)	Total hospital stays (d)
Observation group	49	1.94 ± 0.25	360.08 ± 51.65	8.37 ± 2.19	10.85 ± 2.27	15.06 ± 4.48	14.69 ± 3.88	9.27 ± 2.19	16.76 ± 3.20
Conventional group	43	2.06 ± 0.47	381.24 ± 63.88	10.96 ± 2.40	14.43 ± 3.34	20.17 ± 5.61	18.59 ± 3.73	12.63 ± 2.55	19.05 ± 3.78
t		1.555	1.756	5.412	6.075	4.853	4.898	6.800	3.147
p-value		0.124	0.083	<0.001	<0.001	<0.001	<0.001	<0.001	0.002

Note: ICU, intensive care unit.

Table 5. Comparison of adverse reactions between the observation and conventional groups [n (%)].

Group	n	Hypotension	Arrhythmia	Nausea/vomiting	Pulmonary infection	Others
Observation group	49	8 (16.33%)	2 (4.08%)	10 (20.41%)	2 (4.08%)	3 (6.12%)
Conventional group	43	10 (23.26%)	9 (20.93%)	15 (34.88%)	9 (20.93%)	5 (11.63%)
χ^2/t		0.699	6.032	2.425	6.032	0.318
p-value		0.403	0.014	0.119	0.014	0.573

Table 6. Comparison of prognosis between the observation and conventional groups [n (%)].

Group	n	Grade 2	Grade 3	Grade 4	Grade 5
Observation group	49	0 (0)	14 (28.57%)	27 (55.10%)	8 (16.33%)
Conventional group	43	2 (4.65%)	19 (44.19%)	19 (44.19%)	3 (6.98%)
Z			2.261		
p-value			0.024		

Assessment of Neurological Function in Both Groups

At the T0 time point, there were no significances in Tau protein, neuron-specific enolase, and glial fibrillary acidic protein between the two groups ($p > 0.05$). However, the levels of all three indicators decreased at the T3 time point in both groups, with significantly reduced levels observed in the observation group than in the conventional group ($p < 0.05$, Table 3).

Comparison of Perioperative Indicators Between the Two Groups

The surgical duration and intraoperative blood loss were comparable between the observation and conventional groups ($p > 0.05$). However, the observation group had a significantly shorter time for spontaneous breathing recovery, eye-opening time, orientation recovery time, extubation time, ICU stay, and total hospital stay than the conventional group ($p < 0.05$, Table 4).

Comparison of Adverse Reactions and Prognosis Between the Two Groups

The incidence of arrhythmia and pulmonary infection was significantly lower in the observation group than in the conventional group ($p < 0.05$). However, the incidence of postoperative hypotension, nausea/vomiting, and other adverse reactions were comparable between these two groups ($p > 0.05$, Table 5). Furthermore, the GOS grading was significantly higher in the observation group compared to the conventional group ($p < 0.05$, Table 6).

Discussion

Craniocerebral injury is associated with a high rate of death and disability, often requiring surgical treatment. However, postoperative adverse reactions and cognitive dysfunction remain common concerns. Previous studies have reported that its occurrence is affected by factors such as patient age, admission coma index, craniocerebral injury site, and postoperative complications [9,10]. Due to the large individual variability among patients with craniocerebral injury, the changes in haemodynamic indexes can be complex and may affect recovery during hospitalization [11].

Systematic neurological assessments were conducted at preoperative baseline (to establish baseline neurological status), 30 minutes post-anesthesia (to evaluate the acute effects of anesthetic agents), at the end of surgery (to assess post-procedure neurological recovery), and 24 hours postoperatively (to evaluate early postoperative neurological recovery) to offer valuable insights into the impact of anesthesia and surgery on neurological function. Therefore, the present study focuses on the anesthetic drug remazolam benzenesulfonate, assessing its impacts on haemodynamics and neurological function in patients undergoing craniocerebral.

In this study, the perioperative haemodynamic indexes, such as HR, SpO_2, and MAP, showed an overall increasing trend during the T0~T1 time period, followed by a decreasing trend from T1 to T3. Furthermore, substantial differences were found between the two groups and across different time points, suggesting that the fluctuation amplitude was smaller in the observation group. This result suggests that reamazolam benzenesulfonate intravenous anesthesia offers better hemodynamic stabilizing in patients undergoing craniocerebral surgery than conventional anesthesia. Moreover, psychological stress is a common response in surgical patients, resulting in elevated sympathetic excitability, which can impact haemodynamic stability and increase surgical risk [12]. Remimazolam besylate, an ultrashort-acting anesthetic, primarily acts on γ-aminobutyric acid (GABA) receptors, opening chloride channels and inhibiting neuronal activity. A study [13] confirmed its effectiveness in improving hemodynamics as well as reducing stress and pain in patients undergoing hysteroscopy. Furthermore, Xiao *et al*. [14] conducted a sequential trial and indicated valuable clinical insights into a specific dosage regimen of remimazolam besylate, supporting its use in this study.

Tau protein, neuron-specific enolase, and glial fibrillary acidic protein are known biomarkers of brain injury. The higher levels of these markers in blood stream after brain injury indicate greater neuronal or glial cell damage, associated with a poorer prognosis [15]. In this study, the levels of these three markers were significantly lower at 24 hours postoperatively in the observation group compared to the conventional group, indicating that intravenous remimazolam besylate anesthesia improved neurological function. Similarly, a study by Liu *et al*. [16] demonstrated that remimazolam besylate anesthesia has minimal impact on cognitive function in elderly patients undergoing gastroscopy, further validating its neuroprotective impacts.

In this study, the observation group showed shorter times for spontaneous respiration recovery, eye-opening time, orientation recovery time, extubation, ICU stay, and total hospital stay than the conventional group. These observations suggest that intravenous anesthesia with remazolam besylate facilitates rapid anesthesia recovery and promote better postoperative recovery. This effect can be due to remazolam besylate's rapid onset, rapid metabolism, and swift elimination, along with its minimal inhibitory effect on the respiratory and circulatory system and limited interaction with other analgesic and sedative drugs. Additionally, the reduced incidence of arrhythmia and pulmonary infection in the observation group, along with the higher GOS grades than the conventional group, further validate the safety and therapeutic advantages of remazolam besylate in clinical practices.

Despite several promising findings, this study has some limitations. Its retrospective design limits external validity and generalizability, while the small sample size may reduce statistical power. Moreover, the study did not consider the effects of patient age and intraoperative temperature on neurological outcomes, potentially leading to an incomplete interpretation of the findings. Future research should incorporate larger, multi-center samples and investigate these potential confounding factors to better understand the impact of anesthesia and surgery on the nervous system.

Conclusions

Intravenous anesthesia with remazolam besylate can effectively stabilize the haemodynamic levels in patients with craniocerebral injury, protect the neurological function, reduce post-surgery recovery, promote prognosis, and offer better safety. Hence, it is clinically recommended as a reference plan for clinical anesthesia management during craniocerebral surgery.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

HPL and LY designed the research study and wrote the first draft. KPL and HL performed the research. KPL, HL and JJG analyzed the data. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Medical Ethics Committee of Peking University International Hospital (Ethics Approval Number: YLL20210511). This study was conducted in compliance with the Declaration of Helsinki. All patients gave informed consent.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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