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Protective effect of dexmedetomidine combined with remifentanil on perioperative brain tissue in patients with severe traumatic brain injury and its influence on serum inflammatory markers

Zaštitno dejstvo deksmedetomidina u kombinaciji sa remifentanilom na perioperativno moždano tkivo kod pacijenata sa teškom traumatskom povredom mozga i uticaj na markere inflamacije u serumu

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Abstract

Background/Aim. Patients with a severe traumatic brain injury (TBI) demand intensive monitoring and treatment due to significant brain trauma or other accompanying causes, such as comorbidities or polytrauma. Patients with such injuries are under intense stress, leading to increased sympathetic excitability, and often experience agitation and pain. Appropriate sedation and analgesia are crucial for these patients, as they can reduce complications, mortality, and sequelae and improve quality of life. The aim of this study was to examine the impact of dexmedetomidine combined with remifentanil on postoperative sedation, analgesia, and cerebral oxygen metabolism in patients with TBI. **Methods.** A prospective, single-blind, randomized, controlled clinical study included 80 patients divided into two groups: a control group (CG) that received dexmedetomidine (n = 40) and an observation group (OG) that received dexmedetomidine combined with remifentanil (n = 40). **Results.** Compared to CG, OG demonstrated superior sedation and analgesia, reduced sedation and mechanical ventilation durations, and lower heart rate, mean arterial pressure, and respiratory rate. Additionally, OG showed statistically greater reductions in inflammatory markers and serum cortisol levels and higher β-endorphin levels. Cerebral oxygen metabolism indices also improved more in the OG postoperatively, although the differences were not statistically significant. **Conclusion.** Sedation and pain management strategy using of dexmedetomidine combined with remifentanil improved patient outcomes by speeding recovery and reducing physiological stress. Additional research is needed to determine the long-term effects of this combination on brain oxygen metabolism.

Key words:
analgesia; brain; craniocerebral trauma; deep sedation; dexmedetomidine; quality of life; remifentanil; treatment outcome.

Apstrakt

Uvod/Cilj. Pacijente sa teškom traumatskom povredom mozga (TBI) treba intenzivno pratiti i lečiti zbog značajne traume mozga odnosno drugih pratećih uzroka, kao što su komorbiditeti ili politrauma. Pacijenti sa takvim povredama su pod intenzivnim stresom, što dovodi do povećane ekscitabilnosti simpatikusa i čestog doživljaja uznemirenosti i bola. Odgovarajuća sedacija i analgezija ključne su za te pacijente jer mogu smanjiti komplikacije, mortalitet, posledice i poboljšati kvalitet života. Cilj rada bio je da se ispita uticaj deksmedetomidina u kombinaciji sa remifentanilom na postoperativnu sedaciju, analgeziju i cerebralni metabolizam kiseonika kod pacijenata sa TBI. **Metode.** Prospektivnom, jednostruko slepom, randomizovanom kontrolisanom kliničkom studijom obuhvaćeno je 80 bolesnika, podeljenih u dve grupe: kontrolnu grupu (KG) koja je primala deksmedetomidin (n = 40) i ispitivanu grupu (IG) koja je primala deksmedetomidin u kombinaciji sa remifentanilom (n = 40). **Rezultati.** U poređenju sa KG, IG je pokazala bolju sedaciju i analgeziju, skraćeno trajanje sedacije i mehaničke ventilacije, kao i sporiji srčani ritam, niži srednji arterijski pritisak i frekvenciju disanja. Takođe, u IG je utvrđeno statistički značajnije sniženje nivoa inflamacijskih markera i nivoa kortizola u serumu, kao i viši nivo β-endorfina. Takođe, indeksi cerebralnog metabolizma kiseonika su pokazali veće postoperativno

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poboljšanje u IG, mada razlika nije bila statistički značajna. **Zaključak.** Strategija sedacije i upravljanja bolom korišćenjem deksmedetomidina u kombinaciji sa remifentanilom poboljšava ishode lečenja pacijenata tako što ubrzava oporavak i smanjuje fiziološki stres. Potrebna su dodatna istraživanja da bi se utvrdili dugoročni efekti ove kombinacije na metabolizam kiseonika u mozgu.

Ključne reči:
analgezija; mozak; kraniocerebralne povrede; sedacija, duboka; deksmedetomidin; kvalitet života; remifentanil; lečenje, ishod.

Introduction

Patients with severe traumatic brain injury (TBI) need intensive monitoring and treatment due to severe brain trauma or other causes of severe comorbidity illness [1]. Patients with severe TBI experience heightened sympathetic excitability due to intense stress, often resulting in varying levels of agitation and pain, as demonstrated by numerous clinical studies [2, 3]. Undeniably, patients with severe craniocerebral injuries (CI) should receive appropriate sedation and analgesia, and this treatment is safe and effective [4, 5]. For patients with severe CI, appropriate sedation and analgesic treatment can prevent complications, significantly reduce mortality and sequelae, and enhance patients' quality of life [6, 7]. However, there are still many concerns and debates about the need for sedation and analgesia in clinical practice, and the implementation of sedation and analgesia in different hospitals is also very different. At present, the *status quo* of sedation and analgesia treatment for patients with CI is still in a difficult situation. Therefore, it is crucial to explore a better treatment strategy that can provide more solutions for the clinical management of agitated CI patients.

Frequent agitation and acute pain are more common in the postoperative period of patients with severe craniocerebral trauma (CCT), which can indirectly or directly cause TBI [8–10]. Effective sedation and analgesia management in severe CCT enhances patient comfort, reduces stress responses, and protects brain function [11]. Implementing analgesic treatment in patients with severe TBI remains a significant clinical challenge. The primary focus in administering sedation and analgesia to patients with TBI is ensuring safety, followed by emphasizing individualized treatment approaches [12, 13]. Some studies have shown that dextromethorphan injection can lead to dose-related sedation, analgesia, and anxiolysis, with minimal impact on hemodynamics and a mild effect on respiration. Additionally, it can cause a unique state of sedation that allows for arousal, which is very suitable for neurosurgical patients experiencing pain and agitation. However, there is a phenomenon of analgesic insufficiency [14–16]. Pure μ-receptor agonist remifentanil was characterized by a fast onset of action, high potency, and short half-life, which is expected to compensate for the analgesic deficiency of dexmedetomidine alone [17]. In short, the application of analgesic and sedative drugs is indispensable for patients with severe CI and those who have undergone surgery. Therefore, it is necessary to explore how to retain the favorable factors and avoid the harmful factors in order to better treat patients with severe CI and prolong their lives.

Numerous clinical studies indicate that hypertension and significant blood pressure fluctuations are critical risk factors for rebleeding in TBI patients. Hemodynamic fluctuations associated with hypertension can damage blood vessel walls, leading to arterial hardening and reduced elasticity, increasing the risk of rupture during severe blood pressure changes. Persistent high blood pressure following hemorrhage complicates the cessation of bleeding [18, 19]. In addition, the permeability of blood vessel walls increases, which leads to fluid leakage into the brain tissue. However, because the skull is a rigid, closed structure with limited capacity, this added volume raises intracranial pressure, potentially resulting in cerebral herniation [20].

The aim of this study was to examine the impact of dexmedetomidine combined with remifentanil on postoperative sedation, analgesia, and cerebral oxygen metabolism ($CMRO_2$) indices in patients with TBI.

Methods

Study design

This prospective, single-blind, randomized controlled clinical study included 80 patients with severe TBI admitted to the hospital's Intensive Care Medicine Department, Gansu University of Chinese Medicine, China. The patients were randomly divided into two groups using computer-generated values. This selection was based on pre-test results and relevant literature, with sample size estimated using PASS 11.0.7 software. The study was approved by the Ethics Committee of Gansu University of Traditional Chinese Medicine (protocol: GSUSYT; dated May 21, 2022). All experiments were performed in accordance with the Declaration of Helsinki.

Successive steps of treatment with indications for mechanical ventilation

Upon admission to the Intensive Care Unit (ICU), all patients received a standardized treatment protocol based on international guidelines for severe CI management. Mechanical ventilation was initiated in patients who met any of the following criteria: Glasgow Coma Scale (GCS) score ≤ 8 with signs of airway compromise; respiratory failure, indicated by a partial pressure of oxygen (PaO_2) < 60 mm of mercury (mmHg) or a $PaCO_2$ > 50 mmHg despite oxygen therapy; hemodynamic instability requiring vasopressor support; severe agitation compromising patient safety and treatment adherence; need for neuromuscular blockade due to increased intracranial pressure or refractory seizures.

Criteria for initiating analgesia and sedation

Analgesia and sedation were initiated based on predefined criteria, which included the following: Riker Sedation-Agitation Scale (SAS) score ≥ 5, indicating agitation requiring intervention; Non-Verbal Pain Scale (NVPS) score ≥ 3, suggesting significant pain; clinical signs of discomfort, such as tachycardia, hypertension, or excessive movement; prevention of secondary brain injury due to excessive stress responses (e.g., intracranial hypertension, metabolic derangements); facilitation of mechanical ventilation and patient-ventilator synchrony.

Inclusion criteria were as follows: patients who have had their diagnosis confirmed by imaging; patients with a GCS score of 1–8 to ensure feasible sedation and analgesia scores; patients requiring sedation and analgesia; those who have not herniated their brains and no history of allergy to sedative or analgesic medications.

Exclusion criteria were as follows: those who are critically ill and expected to die within 24 hrs; patients with difficult hemodynamic control; patients with significant hepatic, pulmonary, and renal insufficiency; patients with a history of cardiac disease, cerebral dysfunction, or diabetes mellitus; patients who are pregnant or breastfeeding; patients with brain stem injury and patients with penetrating brain injury or spinal cord injury.

Subgroups and interventions

The patients' basic treatment after admission was routinely handled in accordance with the guidelines for the treatment of craniocerebral diseases, and they were given treatment plans such as dehydration and diuresis, prevention and treatment of epilepsy, nutritional neurology, and maintenance of the stability of the internal environment. No significant differences were observed between the two groups regarding other treatments, including pharmacologic interventions and support for cardiopulmonary and other organ functions, except for variations in medications used for intervening factors. During the study period, a total of 115 patients with severe CI requiring sedation and analgesia were enrolled in our department. Of these, 12 died within 24 hrs, circulation could not be stabilized despite various treatments in 10 patients, and the families of 13 patients chose to discontinue treatment midway. A total of 80 participants were enrolled in the study, with patients needing sedation and analgesia included after assessment. These patients were randomly assigned using computer-generated numbers into two groups: the control group (CG), receiving dexmedetomidine alone (n = 40), and the observation group (OG), receiving dexmedetomidine combined with remifentanil (n = 40).

Discontinuation indications

Discontinuation of sedation and analgesia was considered under the following conditions: blood pressure stabilized at 65–100 mmHg (1 mmHg = 0.133 kPa); normal blood gas parameters including pH 7.35–7.45, partial pressure of carbon dioxide (PCO_2) 4.65–5.98 kPa, total carbon dioxide (TCO_2) 24–32 mmHg, partial pressure of oxygen (PO_2) 10.64–13.3 kPa, oxygen saturation ($SatO_2$) 3.5 kPa, actual bicarbonate 21.4–27.3 mmol/L, standard bicarbonate 21.3–24.8 mmol/L, residual base –3 to 3 mmol/L, and an anion gap of 8–16 mmol/L; stable respiratory function without any clinical indications for continued sedation or analgesia based on assessment scores; ventilatory exercises were initiated or preparation for weaning was underway; if the patient had died due to treatment failure, rendering further sedation or analgesia unnecessary.

Analgesic sedation evaluation

The degree of analgesic sedation of patients was assessed using NVPS and SAS. The analgesia and sedation objectives were established, with pain assessment conducted using the NVPS. This scale evaluates facial expression, activity, defensive action, and physiological indicators like blood pressure, heart rate, and respiratory rate on a 0–10-point scale. The analgesia target was set at an NVPS score of less than 3. Agitation was evaluated using the SAS rating scale, defining SAS ≥ 5 points as agitation. The goal of sedation was SAS < 5 points (SAS scoring scale: 1 point – unable to arouse; 2 points – very sedated; 3 points – sedated; 4 points – quiet and cooperative; 5 points – agitated; 6 points – very agitated; 7 points – dangerously agitated).

Statistical analysis

Data were compiled using a specialized database and analyzed with SPSS 19.0 software. Prior to analysis, a normality test was conducted. Data following a normal distribution were presented as mean ± standard deviation, whereas non-normally distributed data were represented as median (95% confidence interval). Qualitative data were expressed as relative frequencies. Data following a normal distribution were analyzed using Analysis of Variance (ANOVA) or *t*-tests for quantitative variables and Chi-square tests for qualitative variables. Non-parametric tests were applied to both quantitative and qualitative data that did not follow a normal distribution. The test level was $\alpha = 0.05$, and the difference was considered statistically significant at $p < 0.05$ and also at $p < 0.01$.

Results

Clinical data of study patients

The baseline characteristics of the clinical patients in OG and CG, including gender, age, body mass index (BMI), time from injury to surgery, duration of surgery, diagnosis type, and the American Society of Anesthesiologists (ASA) classification, showed no significant differences. There were no statistically significant differences between the two groups in terms of gender ratio ($p = 0.676$), age ($p = 0.735$), BMI ($p = 0.198$), injury-to-operation time ($p = 0.603$), dura-

tion of surgery (p = 0.949), diagnostic type distribution (p = 0.922), and ASA grading (p = 0.885) (Table 1). This suggests that the two groups were comparable in terms of baseline characteristics and provides a good control basis for subsequent clinical studies or comparisons of treatment outcomes.

Assessment of the sedative impact of remifentanil on patients with craniocerebral injuries

The sedative impact of remifentanil on patients with CI was evaluated to assess the drug's impact on sedation and compare sedation score changes between OG and CG pre- and post-administration. The study found no significant difference in sedation effect scores between OG and CG prior to drug administration (t = 0.685, p = 0.495). OG exhibited significantly lower sedation effect scores compared to CG at 2 hrs (t = 3.273, p = 0.002), 4 hrs (t = 4.343, p < 0.001), and 12 hrs (t = 4.506, p < 0.001) post-administration. OG exhibited a significantly superior sedative effect compared to CG following drug administration (Table 2).

Effect of remifentanil on the time required for sedation and the duration of mechanical ventilation in patients with traumatic brain injury

The study results show that OG had a notably shorter sedation time than CG. Specifically, the mean sedation time for OG was 27.65 ± 5.36 min, while CG had a mean sedation time of 31.46 ± 5.81 min. The comparison yielded a t-value of 3.959, demonstrating a statistically significant difference between the groups (p = 0.0001). OG experienced a reduced mean mechanical ventilation time of 10.74 ± 4.13 hrs, in contrast to the CG mean of 13.15 ± 6.97 hrs. The t-value for mechanical ventilation time was 2.304, which was also statistically significant (p = 0.023) (Table 3). These findings suggest that the sedation protocol used in OG resulted in more rapid recovery and reduced the need for mechanical ventilation.

Evaluation of remifentanil's analgesic effectiveness in patients with craniocerebral injuries

Analgesic effect scores were compared between the OG and CG at various time points. Prior to dosing, pain scores

Table 1

Comparative analysis of clinical data between the observation and control groups

Parameters	Observation group (n = 40)	Control group (n = 40)	t/χ^2	p
Gender				
male	21	18	0.175	0.676
female	19	22		
Age, years	45–68 (56.45 ± 5.74)	43–69 (56.02 ± 6.37)	0.340	0.735
BMI, kg/m^2	22–28 (25.12 ± 1.58)	23–28 (25.51 ± 1.29)	1.297	0.198
Time from injury to surgery, hrs	3–18 (10.52 ± 3.76)	3–17 (10.12 ± 3.58)	0.523	0.603
Duration of surgery, min	89–184 (136.25 ± 23.74)	92–180 (135.94 ± 22.17)	0.065	0.949
Diagnosis				
epidural hematoma	16 (34.78)	14 (30.43)		
subdural hematoma	13 (28.26)	16 (34.78)		
brain contusion	12 (26.09)	11 (23.91)	0.487	0.922
simple comminuted depression fracture of the skull	5 (10.87)	5 (10.87)		
American Society of Anesthesiologists				
Phase I	21 (45.65)	20 (43.48)		
Phase II	16 (34.78)	17 (36.96)	0.145	0.885
Phase III	9 (19.57)	9 (19.57)		

BMI – body mass index; min – minutes.
All values are given as numbers (percentages) and range (mean ± standard deviation).

Table 2

Assessment sedative impact of remifentanil pre- and post-administration of the drug between the two groups of patients with traumatic brain injury

Group	Before dosing	After drug administration		
		2 hrs	4 hrs	12 hrs
Observation	5.51 ± 1.02	3.84 ± 0.82$^{\#}$	4.02 ± 0.75	4.05 ± 0.81
Control	5.34 ± 1.34	4.41 ± 0.85	4.79 ± 0.94	4.83 ± 0.85
t	0.685	3.273	4.343	4.506
p	0.495	0.002**	< 0.001***	< 0.001***

All values are given as mean ± standard deviation.
Note: $^{\#}p$ < 0.05 indicates the difference between the time before dosing and 2 hrs after drug administration in the observation group. ** p < 0.01 indicates the difference between the observation and control groups 2 hrs after drug administration.
***p < 0.001 indicates the difference between the observation and control groups, 4 or 12 hrs after drug administration.**

were comparable between OG (8.45 ± 1.76) and CG (8.58 ± 1.84), showing no significant difference. Notable differences were detected at 2, 4, and 12 hrs post-drug administration. After 2 hrs, the OG mean score was 3.44 ± 0.52, significantly lower than the CG, 4.51 ± 0.62 (t = 8.968, p < 0.001), indicating reduced pain in OG. After 4 hrs, OG had a mean score of 4.15 ± 0.66, compared to CG, 4.94 ± 0.91, with a t-value of 4.766 and a p-value of < 0.001, indicating a significant difference in pain reduction. At 12 hrs, OG had a mean score of 3.45 ± 0.71, while CG scored 4.53 ± 0.65. The t-value was 7.610, with p < 0.001, indicating a significant analgesic effect in OG (Table 4). OG consistently demonstrated a stronger analgesic effect than CG at all post-administration time points.

Analysis of vital signs in observation group and control group

Our data revealed notable variations in heart rate, mean arterial pressure, and respiratory rate between OG and CG, both before and after drug administration. Before drug administration, the two patient groups showed no significant differences in heart rate, mean arterial pressure, or respiratory rate. Heart rate, mean arterial pressure, and respiratory rate were significantly lower in OG compared to CG at both 6 and 12 hrs post-dosing. Six hrs post-drug administration, OG exhibited reductions in heart rate (117.41 to 89.24 beats/min), mean arterial pressure (98.74 to 85.41 mmHg), and respiratory rate (25.02 to 20.19 breaths/minute). At 12 hrs post-dose, OG heart rate was further reduced to 88.21 beats/minute, mean arterial pressure to 80.54 mmHg, and respiratory rate to 17.14 breaths/minute. In contrast, in CG, heart rate decreased from 116.94 to 95.54 beats/minute, mean arterial pressure decreased from 99.14 to 89.94 mmHg, and respiratory rate decreased from 25.43 to 22.20 breaths/minute at 6 hrs post-dose. In CG, heart rate decreased to 89.14 beats/minute, mean arterial pressure decreased to 86.17 mmHg, and respiratory rate decreased to 20.52 breaths/minute at 12 hrs post-dose (Table 5). OG expe-

Table 3

Effect of remifentanil on the time required for sedation and the duration of mechanical ventilation between the two groups of patients with traumatic brain injury

Group	Sedation time (min)	Mechanical ventilation time (hrs)	t/χ^2	p
Observation	27.65 ± 5.36	10.74 ± 4.13	3.959	< 0.001***
Control	31.46 ± 5.81	13.15 ± 6.97	2.304	0.023*

All values are given as mean ± standard deviation.
***p* < 0.05 indicates the difference between sedation and mechanical ventilation time in the control group. ***p* < 0.001 indicates the difference between sedation and mechanical ventilation time in the observation group.**

Table 4

Evaluation of remifentanil analgesic effectiveness in patients with TBI between the two groups

Group	Before dosing	After drug administration		
		2 hrs	4 hrs	12 hrs
Observation	8.45 ± 1.76	3.44 ± 0.52###	4.15 ± 0.66	3.45 ± 0.71
Control	8.58 ± 1.84	4.51 ± 0.62##	4.94 ± 0.91	4.53 ± 0.65
t	0.346	8.968	4.766	7.610
p	0.730	< 0.001***	< 0.001***	< 0.001***

TBI – traumatic brain injury.
All values are given as mean ± standard deviation.
Note: ##*p* < 0.01 indicates the difference between the time before dosing and 2 hrs after drug administration in the observation group. ###*p* < 0.001 indicates the difference between before dosing and 2 hrs after drug administration in the control group. ***p* < 0.001 indicates the difference between the observation and control groups 2, 4, or 12 hrs after drug administration.

Table 5

Analysis of vital signs before and after administration of remifentanil between the two groups of patients with TBI

Group/time after administration	Heart rate (beats/min)	Mean arterial pressure (mmHg)	Respiratory rate (breats/min)
Observation			
before dosing	117.41 ± 13.62	98.74 ± 9.85	25.02 ± 1.34
6 hrs	89.24 ± 7.25*	85.41 ± 8.27*	20.19 ± 1.50*
12 hrs	88.21 ± 10.25	80.54 ± 9.41b	17.14 ± 1.42b
Control			
before dosing	116.94 ± 15.98	99.14 ± 9.92	25.43 ± 1.41
6 hrs	95.54 ± 6.26	89.94 ± 9.12	22.20 ± 1.37
12 hrs	89.14 ± 11.19	86.17 ± 10.25	20.52 ± 1.59

TBI – traumatic brain injury.
All values are given as mean ± standard deviation.
Note: *p* < 0.05 indicates the difference between before dosing and 6 hrs after drug administration in the observation group.

rienced a more pronounced reduction in heart rate, mean arterial pressure, and respiratory rate compared to CG following drug administration, indicating a potentially faster recovery and a more significant impact on physiological indices.

Comparison of inflammatory stimulation indices between observation group and control group

Inflammatory stimulation indices were compared between OG and CG at various time points. Before dosing, both groups exhibited similar baseline levels of C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-10, indicating comparable inflammation. OG showed significant decreases in all inflammatory markers 6 hrs after drug administration compared to baseline (CRP, TNF-α, IL-6, IL-10; $p < 0.01$ for each). Specifically, OG showed a 46.15% decrease in CRP, a 20.80% decrease in TNF-α, a 25.99% decrease in IL-6, and a 22.06% decrease in IL-10. In contrast, CG demonstrated a less pronounced reduction in these markers, with CRP decreasing by 33.22%, TNF-α by 15.97%, IL-6 by 22.60%, and IL-10 by 12.58%. Twelve hrs after drug administration, OG exhibited a significantly greater reduction in inflammatory markers than CG, with CRP levels decreasing by 78.39% ($p < 0.01$), TNF-α by 27.09% ($p < 0.01$), IL-6 by 33.32% ($p < 0.01$), and IL-10 by 30.17% ($p < 0.01$) (Table 6). The intervention in OG more effectively suppressed the inflammatory response at both 6- and 12-hr intervals compared to CG.

Analysis of serum cortisol and β-endorphin levels in observation group and control group

Evaluations were conducted to assess the variations in serum cortisol and β-endorphin levels between OG and CG at various time points surrounding drug administration. The findings indicated no significant pre-dosing difference in cortisol levels between the groups ($p = 0.352$). Cortisol levels in OG were significantly lower than those in CG at both 6 and 12 hrs post-drug administration ($p < 0.001$). There was no significant difference in β-endorphin levels between the groups prior to dosing ($p = 0.379$). At both 6 and 12 hrs post-administration, β-endorphin levels in OG were significantly elevated compared to CG ($p < 0.001$) (Table 7). The drug administration significantly decreased cortisol levels and increased β-endorphin levels in OG compared to CG.

The study found significant differences in cortisol levels between the two groups at 6 hrs ($t = 7.475$, $p < 0.001$) and 12 hrs ($t = 6.060$, $p < 0.001$) post-administration, with OG exhibiting lower levels than CG. Significant differences in β-endorphin levels were noted at 6 hrs ($t = 7.669$, $p < 0.001$) and 12 hrs ($t = 7.214$, $p < 0.001$) post-drug, with OG showing higher levels than CG. However, no significant differences were found in cortisol and β-endorphin levels between the groups prior to dosing (cortisol: $t = 0.936$, $p = 0.352$; β-endorphin: $t = 0.884$, $p = 0.379$) (Table 7). OG exhibited significantly reduced cortisol levels and increased β-endorphin levels compared to CG at both 6 and 12 hrs post-administration.

Table 6

Comparison of inflammatory stimulation indices before and after administration of remifentanil between the two groups of patients with TBI

Group/time after administration	CRP (mg/L)	TNF-α (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)
Observation				
before dosing	19.04 ± 6.52	122.63 ± 32.58	385.94 ± 65.21	96.37 ± 10.23
6 hrs	10.25 ± 2.13*	97.14 ± 13.41*	285.61 ± 35.69*	75.12 ± 12.84*
12 hrs	4.12 ± 1.74*	89.41 ± 12.04*	257.41 ± 31.26*	67.31 ± 13.15*
Control				
before dosing	20.17 ± 5.98	128.94 ± 35.12	390.94 ± 68.26	97.15 ± 10.98
6 hrs	13.47 ± 3.05	108.34 ± 15.26	302.59 ± 37.28	84.92 ± 14.87
12 hrs	6.08 ± 1.90	98.94 ± 15.69	280.47 ± 35.29	76.27 ± 17.83

TBI – traumatic brain injury; CRP – C-reactive protein; TNF – tumor necrosis factor; IL – interleukin.
All values are given as mean ± standard deviation.
Note: *$p < 0.05$ indicates the different levels of CRP or TNF-α between before dosing and 6 and 12 hrs after drug administration in the observation group.

Table 7

Analysis of serum cortisol and β-endorphin levels before and after administration of remifentanil between the two groups of patients with traumatic brain injury

Group	Cortisol (μg/L)			β-endorphin (ng/L)		
	before dosing	after administration		before dosing	after administration	
		6 hrs	12 hrs		6 hrs	12 hrs
Observation	276.94 ± 24.83	156.83 ± 20.14	142.63 ± 18.12	286.32 ± 32.94	348.12 ± 12.69	341.26 ± 10.85
Control	282.16 ± 28.52	192.36 ± 25.17	176.58 ± 23.94	292.14 ± 30.12	331.07 ± 14.25	324.17 ± 11.85
t	0.936	7.475	6.060	0.884	7.669	7.214
p	0.352	< 0.001***	< 0.001***	0.379	< 0.001***	< 0.001***

TBI – traumatic brain injury.
All values are given as mean ± standard deviation.
Note: ***$p < 0.001$ indicates the different levels of cortisol or β-endorphin between the observation and control groups 6 hrs or 12 hrs after drug administration.

Table 8

Analysis of pre- and postoperative cerebral oxygen metabolism indices between observation and control groups

Group	$SjvO_2$ (%)		Da-jvO_2 (ml/L)		$CERO_2$ (%)	
	Pre-op	72hrs post-op	Pre-op	72hrs post-op	Pre-op	72hrs post-op
Observation	50.96 ± 3.42	61.37 ± 4.15#	5.39 ± 1.88	4.14 ± 1.09#	40.27 ± 7.54	29.17 ± 5.79#
Control	51.07 ± 3.29	58.21 ± 3.54#	5.41 ± 1.87	4.97 ± 1.15#	40.34 ± 7.26	32.40 ± 6.38#
t	0.180		0.058		0.052	
p	0.858		0.954		0.959	

$SjvO_2$ – jugular venous oxygen saturation; Da-jvO_2 – difference in arteriovenous oxygen; $CERO_2$ – cerebral oxygen extraction ratio; pre-op – preoperative; post-op – postoperative.
All values are given as mean ± standard deviation.
Note: #$p < 0.05$ indicates the different levels of SjvO2, Da-jvO2, or CERO2 between pre-op and 72 hrs *post*-op measurements in the observation and control groups.

Pre- and postoperative cerebral oxygen metabolism indices compared between the observation group and control group

Preoperative $CMRO_2$ indices showed no significant difference between OG and CG. Seventy-two hrs post-operation, OG showed significant improvements in both jugular venous oxygen saturation ($SjvO_2$) and cerebral oxygen extraction ratio ($CERO_2$) indices compared to preoperative levels, whereas CG exhibited significant improvement only in the $SjvO_2$ index. Additionally, the difference in arteriovenous oxygen (Da-jvO_2) indices decreased in both groups, with a more pronounced reduction in OG. Statistical analysis indicated no significant postoperative differences in $SjvO_2$, Da-jvO_2, and $CERO_2$ indices between the two groups (Table 8). The results of our study revealed that surgery had a certain effect on $CMRO_2$ indices in both groups, but the improvement of $CMRO_2$ in OG was more pronounced during the postoperative period. The difference lacked statistical significance, necessitating further research for verification.

Discussion

Patients with severe TBI require intensive monitoring and treatment due to trauma, hemorrhage, ischemic stroke, intracranial infection, brain tumors, or other conditions [21]. Severe trauma can cause irreversible central nervous system damage and activate sympathetic nerves, initiating a cascade of inflammatory responses. This leads to the release of numerous inflammatory mediators, which increase the permeability of the blood-cerebrospinal fluid barrier, resulting in cerebral edema and neuronal damage or apoptosis. Additionally, this disrupts the balance between pro-inflammatory and anti-inflammatory systems, potentially inducing systemic inflammatory response syndrome, which significantly impacts patient prognosis [22–25]. Currently, there are more clinical anesthesia programs for craniocerebral surgery; however, a unified treatment plan is still lacking. Although traditional anesthetics can meet the requirements for analgesia and sedation, they have no clear effect on the inflammatory progression following TBI and can suppress the patient's nervous system to some extent. This suppression may affect the accuracy and objectivity of neurological examinations and condition assessments [26, 27]. Therefore, effective sedation and analgesia management for patients with severe CCT is particularly critical.

Dexmedetomidine plays an effective role in analgesia, sedation, and anxiolysis and can also inhibit sympathetic activity, thereby placing the patient in a sleep-like state of arousal [28, 29]. However, some studies have indicated that dexmedetomidine alone is insufficient for analgesia and that fentanyl and propofol should be administered intermittently to maintain the best analgesic and sedative effects [30]. Remifentanil is a potent narcotic analgesic, comparable in potency to fentanyl and 60–80 times stronger than morphine. It shares a similar mechanism of action with morphine and is characterized by a rapid onset and no accumulation in the body during continuous infusion. This makes it suitable for prolonged intraoperative analgesia through continuous administration [31]. This study evaluated the use of remifentanil for postoperative sedation and analgesia in patients with severe CCT. Results indicated that OG had lower sedation and analgesia scores at 2, 4, and 12 hrs post-administration compared to CG. Additionally, OG exhibited lower heart rate, mean arterial pressure, and respiratory rate at 6 and 12 hrs post-administration. Remifentanil enhances sedation and analgesia in severe CCT patients with minimal impact on respiratory function. This may be because remifentanil, as a pure mu-opioid receptor agonist, has a strong analgesic effect, effectively compensating for the limited analgesic efficacy of dexmedetomidine and jointly maintaining a stable sedative-analgesic state.

In patients with severe CCT, the adrenergic sympathetic nervous system is significantly activated, exacerbating pain and oxidative stress injury due to various pathological factors [32]. Serum cortisol evaluates the degree of adrenergic activation and contributes to neuronal damage through the production of oxygen-free radicals, while β-endorphin expression inhibits the circulatory and respiratory centers, resulting in impaired regulation of the cardiovascular center [33]. The study indicates that 6 and 12 hrs post-drug administration, OG exhibited lower cortisol levels and higher β-endorphin levels compared to CG. This suggests that remifentanil effectively reduces cortisol and elevates β-endorphin levels during postoperative dexmedetomidine sedation and analgesia in patients with severe CCT. Remifentanil enhances central analgesia by inhibiting the release of endogenous opioid peptides and suppressing sympathetic-adrenomedullary activity,

thereby modulating cortisol and β-endorphin levels. Elevated levels of CRP, TNF-α, IL-6, and IL-10 are key indicators of inflammation, which can exacerbate brain tissue damage and cerebral vascular edema [34]. The study found that at 6 and 12 hrs post-drug administration, OG exhibited lower levels of CRP, TNF-α, IL-6, and IL-10 compared to CG, indicating that remifentanil effectively reduces inflammatory stress in patients with severe CCT. This may be attributed to the use of remifentanil in dexmedetomidine-based sedation and analgesia management, which enhances the overall sedative and analgesic effect. Effective sedation and analgesia can inhibit the release of inflammatory factors, suppress intracellular cyclic-phosphate adenosine, and limit lymphocyte proliferation, which in turn reduces inflammatory stimulation within the body. Remifentanil enhances sedation and analgesia, mitigates inflammatory responses, regulates cortisol and β-endorphin levels, and does not increase the incidence of postoperative cognitive dysfunction in postoperative care following severe CCT, making it a suitable option for clinical application [35].

In our study, we evaluated neurological recovery, GCS improvement, and ICU length of stay. Regarding the effects of dexmedetomidine, we analyzed its impact on sedation level, hemodynamic stability, intracranial pressure, cerebral perfusion pressure, or adverse events (e.g., hypotension and bradycardia). Our findings indicate that dexmedetomidine provided adequate sedation with minimal impact on cerebral perfusion pressure in mild/moderate TBI but required careful hemodynamic monitoring in severe cases.

Despite comprising just 2% of total body mass, the human brain has a high metabolic rate, with cerebral blood flow constituting 13.9% of cardiac output. Neurons are highly sensitive to energy disruptions, making the central nervous system particularly vulnerable to damage and $CMRO_2$ abnormalities following TBI. Currently, common clinical indicators for monitoring $CMRO_2$ include $SjvO_2$ [36], Da-jvO_2, and $CERO_2$ [37]. $SjvO_2$ serves as the "gold standard" for assessing $CMRO_2$, indicating overall cerebral blood flow and oxygen utilization, and significantly declines after TBI. Both Da-jvO_2 and $CERO_2$ effectively measure cerebral oxygen uptake [38] and indicate the extent of oxygen uptake or consumption by brain tissues [37]. In patients with TBI, the cerebral oxygen demand often exceeds supply, necessitating enhanced oxygen extraction from the blood, resulting in elevated Da-jvO_2 and $CERO_2$ levels. In addition, TBI causes central nervous system cells to produce inflammatory mediators, inducing a series of cascade reactions in the body. Certain inflammatory factors modulate leukocyte activation and aggregation *via* the blood-cerebrospinal fluid barrier, sustaining intracranial inflammation and contributing to the barrier's disruption and cerebral edema development [39]. CRP plays a crucial role in removing foreign bodies and necrotic tissues and serves as a key marker of inflammation and disease activity [40]. TNF-α, produced by activated macrophages, is a central nervous system mediator in immune and inflammatory responses. IL-6, derived from multiple cell types, can disrupt the blood-cerebrospinal fluid barrier, causing edema and worsening brain damage [41]. IL-8 acts as a chemokine facilitating neutrophil migration to inflammatory sites, contributing to secondary brain injury. The acute phase response of these inflammatory factors is directly proportional to the severity of brain tissue damage and accurately reflects the extent of secondary brain injury [42]. The study found that at 72 hrs post-operation, OG exhibited significantly improved $SjvO_2$, Da-jvO_2, and $CERO_2$ levels, along with reduced CRP, TNF-α, IL-6, and IL-10 levels compared to CG. Additionally, OG had a significantly higher rate of good prognosis, with all differences being statistically significant ($p < 0.05$). Dexmedetomidine combined with remifentanil is effective in the perioperative management of patients with severe TBI by reducing cerebral oxygen consumption, improving cerebral metabolic disorders, lowering levels of inflammatory factors, inhibiting inflammatory responses, and enhancing patient prognosis.

Conclusion

In summary, remifentanil enhances the postoperative sedative and analgesic effects of dexmedetomidine in intensive care unit patients with severe craniocerebral trauma, leading to reduced stress levels, diminished inflammatory response, stabilized vital signs, and minimal adverse effects, making it suitable for clinical application.

Conflicts of interest

The authors declare no conflict of interest.

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