Am J Transl Res 2021;13(7):8403-8408
www.ajtr.org /ISSN:1943-8141/AJTR0131470

Original Article

Application of etomidate and propofol mixture in hematoma removal in patients with intracranial epidural hematoma

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Received February 5, 2021; Accepted March 26, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Objective: To innvestigate the application of etomidate and propofol mixture in the evacuation of hematoma in patients with epidural hematoma. Methods: 98 patients with epidural hematoma were randomly divided into two groups: the joint group (n=49, anesthesia induction with etomidate and propofol) and the etomidate group (n=49, anesthesia induction with etomidate) using a random number table. Hemodynamics, stress response and cerebral oxygen metabolism were compared between the two groups at T0 (pre-anesthesia induction), T1 (after endotracheal intubation), T2 (10 min after the beginning of the operation) and T3 (the end of the operation). Adverse reactions were also analyzed. Results: Compared with T0, the mean arterial pressure (MAP) at T1, T2 and T3 in the joint group decreased first and then increased, and the MAP at T1 was significantly lower than that in the etomidate group (P<0.05). Compared with T0, blood oxygen saturation of internal jugular vein bulb ($SjvO_2$) increased in T1-T3 groups, and $SjvO_2$ in the joint group was higher than that in the etomidate group (all P<0.05). Compared with T0, cerebral oxygen uptake rate ($CERO_2$) in the T1-T3 groups decreased significantly, and $CERO_2$ at T3 in the joint group was higher than that in the etomidate group (all P<0.05). Compared with T0, the levels of cortisol and superoxide dismutase (SOD) at T3 in the two groups were significantly lower, but those in the etomidate group were higher than those in the combination group (all P<0.05). There was no significant difference in the incidence of postoperative anesthesia-related adverse reactions between the two groups (P>0.05). Conclusion: Etomidate has less effect on hemodynamics and stress reaction during intravenous anesthesia, but its combination with propofol can improve cerebral oxygen metabolism to a certain extent with fewer adverse reactions.

Keywords: Etomidate, propofol, hematoma removal, hemodynamics, cerebral oxygen metabolism, stress response

Introduction

Epidural hematoma refers to the vascular brain edema caused by the rupture and hemorrhage of bridging vein between venous sinus and cortex, which can lead to pathological changes such as cerebral ischemia and hypoxia, abnormal brain metabolism, a rapid increase of intracranial pressure, and the mortality rate is as high as 60%-90% [1, 2]. Some studies have pointed out that if the hematoma is removed within 4 hours after the onset of the disease, patients' survival rate can be increased to about 70%, but some patients still die due to irreversible damage of brain function [3-5].

Evacuation of intracranial hematoma is an essential operation for the treatment of epidural hematoma. However, the use of anesthetics during the operation will impact on the outcome of the patients' hemodynamics and cerebral oxygen metabolism, which is not conducive to patients' postoperative recovery [6, 7]. Therefore, choosing a safe and effective anesthesia method has crucial clinical significance, such as reducing hemodynamics' fluctuation during the operation, reducing cerebral oxygen metabolism injury, and promoting patients' postoperative recovery.

Etomidate and propofol are commonly used intravenous anesthetics. Studies showed that intravenous anesthesia with etomidate has little effect on hemodynamics but a relatively significant impact on cerebral oxygen metabolism [8, 9]. However, whether the combination

with propofol can significantly improve cerebral oxygen metabolism in surgical patients has not been reported. Therefore, this study aims to compare etomidate's effect and its combination with propofol on the hemodynamics, stress response and cerebral oxygen metabolism.

Materials and methods

General data

In this prospective study, 98 patients with epidural hematoma who underwent hematoma removal in our hospital from October 2018 to January 2020 were divided into the joint group (n=49) and the etomidate group (n=49) according to the random number table method.

Inclusive criteria: 1) patients aged 25-65 years old; 2) patients with a clear history of trauma and diagnosed by brain CT or MRI; 3) patients with hematoma volume <200 mL; 4) patients with midline displacement <10 mm; 5) patients with elective hematoma removal; 6) patients with ASA classification of II-III [10].

Exclusion criteria: 1) patients with coagulation system dysfunction; 2) patients with complex systemic injury; 3) patients with other cerebrovascular diseases, such as cerebral infarction; 4) patients with malignant tumor; 5) pregnant or breast-feeding women; 6) patients who are allergic to drugs in this study; 7) patients who participated in other researches at the same time; 8) patients with mental diseases and unable to cooperate. All patients in this study signed informed consent and the medical ethics committee of our hospital approved this study.

Method

The patients in both groups were given an intramuscular injection of 0.5 mg atropine (Jiangsu Yuexing Pharmaceutical Co., Ltd., batch number: 180427) 30 min before the operation. After entering the room, venous access was established and regular oxygen inhalation was performed. In the etomidate group, 0.3 mg/kg etomidate (Jiangsu Enhua Pharmaceutical Co., Ltd., batch number: 181112), 3 μg/kg fentanyl (Jiangsu Enhua Pharmaceutical Co., Ltd., batch No.: 180805), 0.15 mg/kg vecuronium (Chongqing Yaoyou Pharmaceutical Co., Ltd., batch No.: 181120) were injected intravenously in turn for induction of anesthesia. Endotracheal intubation was performed after the muscle relaxation was satisfied, and the anesthesia was maintained by continuous infusion of etomidate 0.4-0.7 mg/(kg·h) with micropump during the operation. Anesthesia induction in the joint group was the same as that in the etomidate group. Propofol and etomidate were continuously pumped with a micropump to maintain anesthesia at 4-6 mg/(kg·h) and 0.2-0.4 mg/(kg·h), respectively during the operation. Vecuronium was injected intermittently according to the specific situation of patients during the operation.

Outcome measures

Primary outcome measures: (1) The hemodynamics including mean arterial pressure (MAP, normal range 70-105 mmHg) and heart rate (HR, normal range 60-100 beats/min) at T0, T1, T2 and T3 were compared between the two groups. T0, T1, T2 and T3 represented pre-anesthesia induction, after the endotracheal intubation, 10 min after the beginning of the operation and at the end of the operation, respectively. (2) The levels of cerebral oxygen metabolism indexes, including $CERO_2$ and $SjvO_2$ were compared between the two groups. (3) The stress indexes, including cortisol and superoxide dismutase (SOD) at T0 and T3 were compared between the two groups.

Secondary outcome measures: The incidence of adverse reactions (such as nausea, vomiting, dizziness, etc.) was calculated. Anesthesia-related postoperative adverse reactions such as nausea, vomiting and dizziness were compared between the two groups. The total incidence of adverse reactions = cases of adverse reactions/total cases * 100%.

Statistical analysis

SPSS 20.0 was used for data statistics. The counting data was expressed as (n/%). A Chi-square test was used for comparison. The measurement data was expressed as ($\bar{x} \pm s$). The paired t-test was used for comparison before and after the treatment in the same group. The independent t-test was used for comparison between the two groups. The difference was statistically significant when $P< 0.05$.

Table 1. Comparison of general data between the two groups (n, $\bar{x} \pm s$)

	Joint group (n=49)	Etomidate group (n=49)	χ^2/t	P
Gender (n)			0.653	0.419
Male	26	22		
Female	23	27		
Age (year)	46.6±5.9	47.2±6.4	0.483	0.631
BMI (kg/m^2)	23.33±2.10	23.18±1.75	0.384	0.702
Time from injury to admission (h)	2.02±0.88	2.13±0.79	0.651	0.517
Hematoma volume (mL)	143.28±20.93	145.04±22.28	0.403	0.688
Midline shift (mm)	6.68±1.89	6.43±1.77	0.676	0.501
Causes of injury (n)			1.646	0.649
Fall from a height	13	10		
Violent injuries	10	12		
Traffic accident	18	15		
Others	8	12		
ASA classification (n)			2.003	0.157
Grade II	29	22		
Grade III	20	27		

Note: BMI: body mass index; ASA: American Society of anesthesiologists.

Table 2. Hemodynamic changes during anesthesia in two groups ($\bar{x} \pm s$)

Groups	Time	MAP (mmHg)	HR (times/min)
Joint group (n=49)	T0	98.89±10.88	73.30±5.44
	T1	94.48±9.66*,#	73.98±5.93
	T2	104.40±10.80*	74.03±6.49
	T3	103.22±8.64*	73.39±5.93
Etomidate group (n=49)	T0	99.57±11.95	73.86±6.11
	T1	102.08±10.76	73.77±6.44
	T2	101.94±11.48	74.20±5.49
	T3	100.77±11.45	74.08±5.89

Note: MAP: mean arterial pressure; HR: heart rate. Compared with T0, *P<0.05; compared with etomidate group at the same time, #P<0.05.

Results

General information

There was no significant difference in the general information between the two groups (all P>0.05). The two groups were comparable. See **Table 1**.

Hemodynamics

There were no significant MAP and HR changes at T0-T3 in the etomidate group and HR at T0-T3 in the joint group (all P>0.05). The MAP at T1, T2 and T3 in the joint group decreased first and then increased compared with that at T0 and the difference was statistically significant. MAP at T1 was significantly lower than that in the etomidate group (P<0.05). See **Table 2**.

Cerebral oxygen metabolism index

Compared with T0, the $SjvO_2$ of the two groups increased significantly at T1-T3, and the $SjvO_2$ of the joint group was higher than that of the etomidate group at the same time (all P<0.05). Compared with T0, $CERO_2$ of both groups decreased significantly at T1-T3, and $CERO_2$ of the joint group at T3 was higher than that of the etomidate group (all P<0.05). See **Table 3**.

Stress indexes

Compared with T0, the levels of cortisol and SOD in the two groups at T3 were significantly lower, but the cortisol and SOD levels in the etomidate group were higher than those in the joint group (all P<0.05). See **Table 4**.

Adverse reactions

There was no significant difference in the incidence of postoperative anesthesia-related ad-

Table 3. Changes of cerebral oxygen metabolism during anesthesia in two groups ($\bar{x} \pm s$)

Groups	Time	$CERO_2$	$SjvO_2$
Joint group (n=49)	T0	39.98±2.99	63.98±3.77
	T1	34.60±3.02*	84.49±4.88*,#
	T2	36.10±2.85*	77.79±4.30*,#
	T3	38.09±3.04*,#	74.46±3.84*,#
Etomidate group (n=49)	T0	40.04±3.20	64.40±3.02
	T1	35.49±3.33*	78.88±4.97*
	T2	35.48±3.20*	70.05±3.38*
	T3	34.44±3.82*	67.74±3.08*

Note: $CERO_2$: cerebral oxygen uptake rate; $SjvO_2$: blood oxygen saturation of internal jugular bulb. Compared with T0, *P<0.05; compared with etomidate group at the same time, #P<0.05.

Table 4. Changes of stress response indexes during anesthesia in two groups ($\bar{x} \pm s$)

Group	Index	T0	T3
Joint group (n=49)	Cortisol (mmol/L)	355.37±20.98	238.90±19.83*,#
	SOD (U/L)	104.40±9.93	89.48±8.77*,#
Etomidate group (n=49)	Cortisol (mmol/L)	356.55±18.70	273.30±17.47*
	SOD (U/L)	103.96±10.04	97.78±7.46*

Note: SOD: superoxide dismutase. Compared with T0 time in the same group, *P<0.05; compared with the Etomidate group at the same time, #P<0.05.

Table 5. Comparison of the incidence of adverse reactions between the two groups

Group	Nausea	Vomiting	Dizzy	Blurred vision	Total incidence
Joint group (n=49)	5 (10.20)	2 (4.08)	1 (2.04)	1 (2.04)	9 (18.37)
Etomidate group (n=49)	4 (8.16)	1 (2.04)	0 (0.00)	1 (2.04)	6 (12.24)

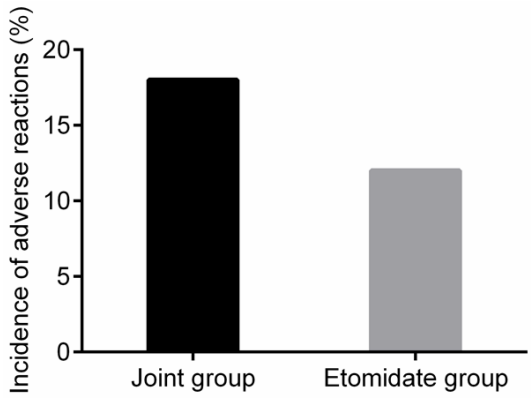

Figure 1. Comparison of the incidence of adverse reactions between the two groups.

verse reactions between the two groups (P> 0.05). See **Table 5** and **Figure 1**.

Discussion

Evacuation of intracranial hematoma is the primary operation method of epidural hematoma, but anesthetics will inevitably affect the body's hemodynamics and cerebral oxygen metabolism [11, 12]. So it is vital to find safe and effective drugs to reduce the adverse impact of surgery on patients.

Etomidate and propofol are commonly used clinical intravenous anesthesia induction drugs, which have fast onset, fast recovery after an operation, and fewer adverse reactions caused by anesthesia. However, a single induction of etomidate has a more significant impact on the hemodynamics of patients. Propofol can directly inhibit the systolic cardiac function, affect the circulatory system, and reduce cardiac output [13, 14]. There were no significant changes in MAP and HR at T0-T3 in the etomidate group and HR at T0-T3 in the joint group in this study. The MAP at T1, T2 and T3 in the joint group decreased first and then increased compared with that at T0, and the difference was statistically significant. This phenomenon suggested that etomidate had less effect on hemodynamics during intravenous anesthesia than propofol. It was speculated that etomidate did not affect the tension discharge of the sympathetic nerve. It does not affect atrial function and conduction and does not inhibit the reflex of vascular baroreceptors, leading to less impact on fluctuation in heart rate and blood pressure [15]. The hemodynamics fluctuated more after the combination with propofol. This study is consistent with the results of Meyancı et al., which also pointed out that general anesthesia with etomidate can make patients'

hemodynamics more stable during the operation [16].

The imbalance of cerebral oxygen supply and demand is the leading cause of secondary brain injury in patients with intracranial epidural hematoma. Some studies [17] showed that reducing or restoring the imbalance of cerebral oxygen supply and demand as soon as possible can improve patients' prognosis after the removal of intracranial hematoma. The traditional detection of intracranial pressure and cerebral blood flow is not enough to reflect patients' cerebral oxygen metabolism because the detection of intracranial pressure ignores the influence of cerebrovascular resistance and the detection of cerebral blood flow can only reflect the body's hemodynamics. However, $CERO_2$ and $SjvO_2$ can directly affect the balance of cerebral oxygen supply and patients' demand [18]. $SjvO_2$ >75% indicates that brain tissue' oxygen supply increases and the cerebral blood flow is sufficient. The decrease of $SjvO_2$ indicates that the oxygen supply of brain tissue is decreased and the cerebral blood flow is decreased. The other characteristic of $SjvO_2$ is that $SjvO_2$ will decline abnormally before the brain tissue of patients shows symptoms of hypoxia, so it can be used as an early evaluation index of cerebral oxygen supply and demand imbalance [19, 20]. The results showed that compared with T0, the $SjvO_2$ of the two groups increased significantly at T1-T3, and the $SjvO_2$ of the joint group was higher than that of the etomidate group at the same time. Compared with T0, $CERO_2$ of both groups decreased significantly at T1-T3, and $CERO_2$ of the joint group at T3 was higher than that of the etomidate group, suggesting that compared with etomidate, propofol combined with etomidate can effectively improve cerebral oxygen metabolism of patients undergoing intracranial hematoma removal. It is speculated that propofol has a good blocking effect on non-selective calcium channels, which can inhibit the release and inflow of calcium ions, expand the arteries and veins, and improve cerebral oxygen balance supply and demand of patients [21]. This study's results are similar to that of Lee et al., which also pointed out that etomidate combined with propofol has less effect on oxygen metabolism in brain tissue [22].

Surgery and anesthetics are stressors for surgical patients, which will lead to different degrees of stress reaction. In this study, the cortisol and SOD levels of the two groups at T3 were significantly lower than those at T0. However, the cortisol and SOD levels of the etomidate group were higher than those of the joint group, suggesting that etomidate caused less stress response during intravenous anesthesia with etomidate and propofol. The reason may be that etomidate can inhibit the release of adrenocortical function and cortisol secretion [23].

Similar studies by Kaushal et al. also showed that etomidate has less stress response than propofol [24]. In terms of adverse reactions, no severe adverse reactions occurred in the two groups, and there was no significant difference in the incidence of anesthesia-related adverse reactions, suggesting that etomidate and propofol are safe for intravenous anesthesia. However, this study is a single-center study with limited sample size. Further studies are needed to confirm the effect of the combination of the two drugs on anesthesia patients.

In conclusion, compared with propofol, etomidate has less effect on hemodynamics and less stress reaction during intravenous anesthesia. However, etomidate combined with propofol can improve cerebral oxygen metabolism and with fewer adverse reactions.

Disclosure of conflict of interest

None.

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