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Original Article

The effect of the pre-hospital use of thrombin combined with propofol on the hemorrhaging and prognoses of craniocerebral injury patients

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Abstract: Objective: This study was designed to explore the effect of the pre-hospital treatment of thrombin (Tb) combined with propofol (Pr) on the hemorrhaging and prognoses of craniocerebral injury (CCI) patients. Methods: A total of 101 CCI patients admitted to Weinan Central Hospital from January 2016 to December 2018 were recruited as the study cohort, among whom 42 who were administered pre-hospital Pr treatment were included in the control group (CG), and 59 who were administered pre-hospital Tb combined with Pr therapy were included in the observation group (OG). The heart rates (HR), systolic blood pressures (SBP), diastolic blood pressures (DBP), intracranial pressures (ICP), and blood oxygen saturations (SpO_2) were compared between the two groups before and after the treatment. The patients' blood biochemical indexes, including blood loss, mean hemoglobin (Hb), and hematocrit (HCT), were measured using an automatic biochemical analyzer. Their coagulation function indexes, represented by Fibrinogen (Fib), and their activation partial thrombin times (APTT), prothrombin times (PT), and platelet aggregation rates (PAR) were measured using an automatic hemagglutination instrument. The incidences of adverse reactions, the sedation satisfaction times, the awakening times, and the Riker Sedation-Agitation Scale (SAS) scores were compared between the two groups, as well as the pre- and post-treatment Glasgow Coma Scale (GCS) scores. Results: The HR, DBP, SBP, and ICP were lower in OG than in the CG, but the SpO_2 levels showed no evident difference. The blood loss was reduced, but the mean Hb and HCT were increased in the OG compared with the CG. The OG had higher Fib and PAR levels but lower APTT and PT levels than the CG. The patients in the OG had better prognoses than the patients in the CG. The incidence of adverse reactions in the OG (6.78%) was lower than the incidence of adverse reactions in the CG (26.19%). The sedation in the OG was better than it was in the CG. Conclusions: The pre-hospital use of Tb combined with Pr yields relatively stable vital signs, excellent hemostatic effects, and favorable prognoses in patients with CCI.

Keywords: Thrombin, propofol, craniocerebral injury, hemorrhage, prognosis

Introduction

Craniocerebral injury (CCI), a common traumatic disease, can be divided into closed and open CCI according to whether the brain is exposed to the outside world [1]. It can lead to high mortality and neurological defects in patients [2]. CCI-induced secondary brain injury is the primary cause of adverse prognoses in CCI patients [3]. Also, CCI may impair the cardiovascular function. Boyarinov et al. found significant changes in the myocardial tissue and blood vessels of rats after inducing CCI [4]. CCI is a global problem in health care and society [5], so effective treatment is needed to improve the symptoms and prognoses of patients with the disease.

Because CCI causes a hemostasis disorder [6], it may lead to severe bleeding during the operation. Therefore, how to prevent and control CCI patients' bleeding is one a focus of current research. Thrombin (Tb) is a key enzyme for maintaining organisms' normal hemostatic functions [7], and its hemostatic value has been well demonstrated in surgery [8-10]. In CCI, Tb plays a non-negligible role and has been shown [11] to be the key mediator of epilepsy secondary to CCI. In addition to hemostasis disorders, analgesia and the sedation of

Table 1. General information

	OG (n=59)	CG (n=42)	χ^2/t	*P*
Gender			0.105	0.746
Male	37	25		
Female	22	17		
Average age	44.58±9.03	43.84±8.37	0.418	0.677
BMI	21.57±2.29	20.86±2.13	1.580	0.117
Preoperative GCS score*	6.12±1.28	6.07±1.07	0.207	0.837
Preoperative SAS score*	5.84±1.69	5.73±1.24	0.359	0.721
Cause of injury			2.802	0.246
Head impact	13	19		
High falling injury	21	12		
Traffic accident	25	11		
Type of injury			1.177	0.555
Cerebral contusion and laceration	17	14		
Subdural hematoma	19	16		
Epidural hematoma	23	12		
History of alcoholism			0.943	0.332
Yes	26	18		
No	33	24		
History of smoking			0.430	0.512
Yes	27	22		
No	32	20		

*GCS: Glasgow coma scale; *SAS: Riker Sedation-Agitation Scale.

patients with CCI are among the issues that should be taken into consideration in clinical medicine. Propofol (Pr), an intravenous anesthetic, can be applied in sedation anesthesia nursing or in general anesthesia induction in the clinic [12]. Pr may be beneficial for inhibiting oxidative stress, thus facilitating the recovery of CCI [13]. It also exerts sedative and hemodynamic effects on CCI [14, 15].

At present, there are few studies on the effect of Tb combined with Pr on hemorrhaging and sedation in CCI. In view of this, we recruited 101 patients with CCI brought to Weinan Central Hospital from January 2016 to December 2018 for analysis, with 42 patients in the control group (CG) who underwent pre-hospital Pr treatment, and 59 patients in the observation group (OG) who underwent pre-hospital Tb combined with Pr therapy. The effects of the two treatment methods on the hemorrhaging and prognosis of the CCI patients were compared, in order to provide reliable clinical data and to create strategies for the treatment of CCI.

Materials and methods

General information

One hundred and one patients with CCI admitted to our hospital from January 2016 to December 2018 were recruited as the study cohort and divided into the CG (n=42) and the OG (n=59) according to the treatment method each underwent. There were 25 males and 17 females in the CG, with an average age of 43.84±8.37 years, and a preoperative Glasgow Coma Score (GCS) of 6.07±1.07 points. In the OG, there were 37 males and 22 females with an average age of 44.58±9.03 years and a preoperative GCS of 6.12±1.28 points. There were no significant differences in terms of gender, average age, body mass index (BMI), preoperative GCS, preoperative Riker Sedation-Agitation Scale (SAS), cause of injury, type of injury, history of alcoholism, or smoking between the two groups, so they were comparable. The patients' general information is detailed in **Table 1**. Apart from routine emergency treatment, the patients in the CG were administered

pre-hospital Pr treatment, and the patients in the OG were given Tb combined with Pr therapy before their hospitalization. After their admission, the patients with surgical indications were promptly underwent surgery according to their conditions. All the patients signed the informed consent forms according to the Declaration of Helsinki, and this study was approved by the hospital ethics committee.

Inclusion and exclusion criteria

Inclusion criteria [1]: Patients who met the relevant diagnostic criteria for CCI and who were confirmed to have a traumatic intracranial hemorrhage using a cranial CT scan, and patients with a GCS of 3-8 points and an injury time of less than 6 hours. Exclusion criteria: Patients who were pregnant or lactating, patients with Tb or Pr contraindications, patients with a recent history of glucocorticoid, anti-inflammatory, anticoagulation, or anti-immunosuppression treatment, patients with severe cardiovascular diseases, patients with a spleen rupture or liver or kidney dysfunction, patients with severe hypertension, diabetes, or coagulation dysfunction complications, patients with mental disorders, and patients with infectious diseases.

Treatment methods

The patients in both groups underwent routine emergency treatment. Before admission, the OG underwent Tb combined with Pr therapy, and the CG underwent Pr treatment. Apart from routine first aid, the CG was additionally administered 0.6-2.5 mg/(kg•h) Pr (State Drug Approval document number: H20030115, Sichuan Guorui Pharmaceutical Co., Ltd.) for 8-12 hours for continuous sedation. The OG was given Tb in addition to the treatment given to the CG. The specific steps of the Tb application were as follows: 1 U Tb (Penglai Nuokang Pharmaceutical Co., Ltd., State Drug Approval document number: H20041419, 1 U/branch) + 10 mL 0.9% sodium chloride injection was used for the pre-hospital intramuscular injection, and then 1 U Tb + 250 mL 0.9% sodium chloride was injected intravenously after the establishment of an intravenous channel. After their admission, the patients with surgery indications promptly underwent surgery.

Outcome measures

The patients' heart rates (HR), systolic blood pressures (SBP), diastolic blood pressures (DBP), and intracranial pressures (ICP) were recorded. The blood oxygen saturation (SpO_2) was monitored using a GE blood gas analyzer, and the blood biochemical indexes, including blood loss, mean hemoglobin (Hb), and hematocrit (HCT) were quantified using an automatic biochemical analyzer. The coagulation function indexes, including fibrinogen (Fib), the activation partial thrombin times (APTT), the prothrombin times (PT), and the platelet aggregation rates (PAR), were measured using an automatic hemagglutination instrument. The postoperative GCS, the Riker sedation-agitation scores, the sedation satisfaction times, and the awakening times were recorded. The GCS reflects the coma degree, with a total possible score of 15 points: 12-15 points indicates a mild coma, 7-12 points indicates a moderate coma, and less than 7 points indicates a severe coma. The Riker SAS, with a score ranging from 1 to 7, was used to evaluate the patients' pain and sedation, and the sedative effect of the sedatives. The doctors were informed immediately when a total score was more than 5. The sedation satisfaction times and the awakening times can also be used to evaluate the sedation. Generally speaking, the higher the sedation satisfaction times or the shorter the awakening times, the better the sedation effect.

Statistical analysis

The measurement data are described as the mean ± mean standard error, and the counting data are recorded as n (%). KS tests confirmed that the data conformed to a normal distribution. Independent sample T tests and chi-square tests were employed to compare the data between the two groups. If the *P* value was lower than 0.05, the difference was statistically significant. SPSS 22.0 (IBM, USA) was the statistical analysis software used in this paper.

Results

Comparison of the hemodynamics

There were 25 males and 17 females in the CG, with an average age of 43.84±8.37 years, and a preoperative Glasgow Coma Score (GCS) of 6.07±1.07 points. In the OG, there were 37 males and 22 females with an average age of 44.58±9.03 years, and a preoperative GCS of 6.12±1.28 points. There were no significant differences in terms of gender, average age, body mass index (BMI), preoperative GCS, preopera-

Table 2. Comparison of the hemodynamics in the two groups

	OG (n=59)	CG (n=42)	t	*P*
HR (times/minute)*	85.69±6.28	95.75±7.99	7.079	<0.0001
SBP (mmHg)*	128.39±11.25	141.74±12.28	5.658	<0.0001
DBP (mmHg)*	74.67±9.07	83.21±9.14	4.649	<0.0001
SpO_2 ($\times10^{-2}$)*	96.28±2.85	96.07±2.19	0.401	0.689
ICP (mmHg)/*	10.92±1.74	14.52±1.97	9.494	<0.0001

*Note: HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; ICP: intracranial pressure; SpO_2: blood oxygen saturation.

Table 3. Comparison of the hemostatic effects of the two groups

	OG (n=59)	CG (n=42)	t	*P*
Blood loss (ml)	917.88±81.28	1357.17±92.75	25.240	<0.0001
Hb (g/L)	92.28±8.03	77.88±8.28	8.768	<0.0001
Hematocrit (%)	37.69±4.75	32.22±4.29	5.935	<0.0001

Note: Hb: hemoglobin; HCT: hematocrit.

Table 4. The coagulation function indexes of the two groups

	OG (n=59)	CG (n=42)	t	*P*
Fib*	3.18±0.32	3.02±0.36	2.351	0.021
APTT*	33.52±4.64	35.96±4.76	2.577	0.011
PT*	11.86±2.52	13.22±2.13	2.847	0.005
PAR*	43.79±6.23	40.42±6.39	2.651	0.009

*Note: Fib: fibrinogen; PAR: platelet aggregation rate; APTT: activation partial thrombin time; PT: prothrombin time.

tive Riker SAS, cause of injury, type of injury, or history of alcoholism and smoking between the two groups. See **Table 2** for a comparison of the hemodynamics (HR, SBP, DBP, ICP, and SpO_2) between the two groups. It shows that the SpO_2 level differed insignificantly between the OG and CG, but the HR, DBP, SBP, and ICP were lower in the OG than in CG.

Comparison of the hemostatic effects

Table 3 shows a comparison of the hemostatic effects between the two groups. After the treatment, the blood loss in the OG (917.88±81.28 ml) was less than it was in the CG (1357.17± 92.75), and the mean Hb and HCT in the OG (92.28±8.03 g/L, 37.68±4.75%) were higher than they were in the CG (77.88±8.28 g/l, 32.22±4.29%). This indicated that the hemostatic effect in the OG was better than it was in the CG.

Comparison of the coagulation function

Table 4 shows a comparison of the coagulation function between the two groups. The OG had higher Fib and PAR but lower APTT and PT than the CG. The above results showed that the coagulation function in the OG was better than it was in the CG.

Comparison of the GCS scores

Table 5 shows a comparison of the GCS scores in the two groups. In the OG, 43 cases scored 4-5 points, and 16 cases scored 1-3 points, for a good prognosis rate of 72.88%. In the CG, 22 cases scored 4-5 points and 20 cases scored 1-3 points, for a good prognosis rate of 52.38%. This indicates that the OG had a better prognosis than the CG (P=0.034).

Comparison of the adverse reactions

Table 6 shows a comparison of the adverse reactions in the two groups. In the OG, decreased blood pressure occurred in 1 case, respiratory depression in 2 cases, bradycardia in 1 case, and there was no injection pain, nausea and vomiting, or diarrhea. In the CG, there were 3 cases of decreased blood pressure, 1 case of respiratory depression, 3 cases of bradycardia, 2 cases of injection site pain, 1 case of nausea and vomiting, and 1 case of diarrhea. The incidence of adverse reactions in the OG (6.78%) was lower than it was in the CG (26.19%).

Comparison of the sedative effects

Table 7 shows a comparison of the sedation in the two groups. The sedation satisfaction times and awakening times (25.85±4.95 h, 10.57±7.24 h) in the OG were significantly shorter than they were in CG (33.25±6.74 h, 13.58±6.22 h), but the Riker SAS scores in OG (3.27±0.74) were lower than they were in the CG (5.04±0.82 h). The above results demonstrated that the sedation in the OG was better than it was in the CG.

Discussion

CCI is a common brain injury disease. Its treatment strategy should focus on how to prevent secondary injuries, avoid abnormal blood pressure and hypoxia, and maintain appropriate intracranial pressure, so as to optimize the

Table 5. Comparison of the GCS between the two groups

Score	OG (n=59)	CG (n=42)	χ^2	*P*
5	18 (30.51)	12 (28.57)		
4	25 (43.37)	10 (23.81)		
3	7 (11.86)	8 (19.05)		
2	4 (6.78)	5 (11.90)		
1	5 (8.47)	7 (16.67)		
Good prognosis*	43 (72.88)	22 (52.38)	4.495	0.034

*Note: 4-5 points indicate a good prognosis, and 1-3 points indicate a poor prognosis.

Table 6. Comparison of the adverse reactions in the two groups (n [%])

	OG (n=59)	CG (n=42)	χ^2	*P*
Decreased blood pressure	1 (1.69)	3 (7.14)		
Respiratory depression	2 (3.39)	1 (2.38)		
Bradycardia	1 (1.69)	3 (7.14)		
Pain at injection site	0	2 (4.76)		
Nausea and vomiting	0	1 (2.38)		
Diarrhea	0	1 (2.38)		
Incidence of adverse reactions	4 (6.78)	11 (26.19)	7.310	0.007

Table 7. A comparison of the sedation in the two groups

	OG (n=59)	CG (n=42)	t	*P*
Sedation satisfaction time	25.85±4.95	33.25±6.74	6.364	<0.0001
Awakening time	10.57±7.24	13.58±6.22	2.181	0.032
SAS*	3.27±0.74	5.04±0.82	11.330	<0.0001

*Note: SAS: Riker Sedation-Agitation Score.

brain recovery environment [16, 17]. However, there is currently a great controversy about clinical CCI treatment without optimal therapy [18].

Tb is a multifunctional serine protease activated by prothrombin that can realize hemostasis by promoting fibrin clot formation and platelet activation, so it is essential in secondary hemostasis [19, 20]. In this study, we found that, compared with the CG, the patients with CCI in the OG had reduced blood loss, increased mean hemoglobin and hematocrit, shortened APTT and PT, and increased Fib and PAR, which may be caused by Tb exerting a hemostatic effect in the body.

As a commonly used sedative, Pr can be used to alleviate patients' agitation, thus increasing their comfort and benefiting treatment [21]. The results of this study showed that compared with the CG, the sedative effect was more significant in the OG. This may be because the hemostatic effect produced by Tb reduces patients' brain tissue damage, thus protecting the nervous system from damage, so it is more favorable for Pr to exert the sedative effect. In addition to the sedative effect, another advantage of Pr in surgical anesthesia is to improve hemodynamics such as the blood pressure and the heart rate [22]. The results of this study showed that compared with the CG, the hemodynamics were better in the OG, which may be related to the promotion of Pr by Tb.

Based on the above results, we speculated that Tb and Pr can significantly reduce hemorrhage, ease restlessness, and improve the hemodynamics of CCI patients, which may help improve patient outcomes. Further, by comparing the adverse reactions between the CG and the OG, we observed that the incidence of adverse reactions was notably lower in the OG, and the good prognosis rate reflected by GCS was higher in the OG, indicating that the combination of Tb and Pr was safer and contributed to a favorable prognosis.

Of course, there are still some inadequacies in this study. Although there was a certain statistical significance, only 109 CCI patients were included in this study due to time constraints, so it was unable to reflect all the CCI symptoms. In addition, only the short-term efficacy of Tb combined with Pr on CCI was demonstrated, without a statistical analysis of the long-term effects, so a long-term follow-up should be supplemented in the follow-up studies to record the patients' long-term outcomes. Moreover, the relationship between Tb and Pr is worthy of exploration. Last but not least, the mechanism of Tb combined with Pr in treating CCI with intricate pathological mechanisms remains elusive, so it needs to be discussed by constructing a CCI model.

Taken together, this paper argues that the pre-hospital use of Tb combined with Pr in the treatment of patients with CCI yields relatively stable vital signs, and a superior hemostatic effect, significantly alleviates agitation and promotes a favorable prognosis. Therefore, the application of Tb combined with Pr in pre-hospital emergency treatment for patients with CCI is beneficial for reducing hemorrhaging and improving the prognosis, so it is worthy of further medical research.

Disclosure of conflict of interest

None.

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