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Original Article

The effects of edaravone and xingnaojing injections on the serum ET-1 concentrations and GCS of patients with cerebral vasospasm in the acute stage of SCCI

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Abstract: Objective: This study aims to analyze the effects of edaravone combined with xingnaojing injections on the endothelin-1 (ET-1) concentrations and Glasgow coma scores (GCS) of patients with cerebral vasospasm in the acute stage of severe craniocerebral injury (SCCI). Methods: 121 patients in the acute stage of SCCI in our hospital from January 2016 to February 2018 were retrospectively analyzed and divided into the control group (the CG, n=61, treated conventionally) and the observation group (the OG, n=60, treated conventionally with edaravone and xingnaojing injections). The ET-1 concentrations in CSF at various stages, the GCS, the intracranial blood flow velocities, and the incidences of cerebral vasospasm were compared between the two groups after the treatment. Results: (1) The concentrations of ET-1 in CSF, the GCS, and the incidence of cerebral vasospasms at 7 d and 14 d after the treatment were (34.25±1.25) pg/ml and (27.12±1.11) pg/ml, (12.98±1.42) and (13.59±1.89), 5% (3/60) and 3.33% (2/60) in the OG and (41.25±1.32) pg/ml and (32.19±1.22) pg/ml, (9.12±0.45) and (10.25±0.58), 16.39% (10/61) and 14.75% (9/61) in the CG (P<0.05). In addition, the average blood flow velocities of BA, VA, PCA, MCA, and ACA were lower in the OG (P<0.05). Conclusion: For patients in the acute stage of SCCI, the combination of edaravone and xingnaojing injections effectively reduces the incidence of cerebral vasospasm and the intracranial blood flow velocities with better prognoses and higher publicity values.

Keywords: SCCI, acute stage, cerebral vasospasm, edaravone, xingnaojing injections

Introduction

Clinically, SCCI is generally defined as cerebral contusion and laceration, intracranial hematoma, brainstem injury and extensive skull fracture caused by trauma. It has an association with a serious complication called cerebral vasospasm [1, 2] reported in about 30% of the cases [3] according to studies.

Presently, cerebral vasospasm after SCCI has become a research hotspot. The major cause of traumatic cerebral vasospasm is that as the brain is injured, the local vessels therein convulse subject to various factors, and narrow with increasing resistance. Consequently, insufficient blood is supplied, the brain tissues supplied by the involved vessels become anoxic and ischemic, and the patients finally die or become disabled [4, 5]. At present, there are various methods to prevent and treat cerebral vasospasm in the acute stage of SCCI, including intraarterial papaverine infusion, 3H therapy, CSF replacement, and calcium antagonists [6]. However, those methods have their limitations, even though they manage to ease up cerebral vasospasms in the acute stage of SCCI to a certain degree [7]. A lot of clinical studies have shown that xingnaojing injection combined with edaravone can achieve an ideal clinical effect in the treatment of SCCI, but the effects of combining the two in the prevention and treatment of cerebral vasospasm in the acute stage has been rarely reported [8]. Therefore, this study explored the effects of edaravone combined with xingnao-

jing injection on the serum ET-1 concentrations and the GCS of patients with cerebral vasospasm in the acute stage of SCCI, which has a certain innovation and feasibility.

By comparing the CG treated conventionally only with the OG treated conventionally with edaravone and xingnaojing injections, this study specifically analyzed the roles of edaravone and xingnaojing in preventing and treating cerebral vasospasm in the acute stage of SCCI to seek more effective and safer treatment methods.

Materials and methods

Materials

121 patients in the acute stage of severe brain injury treated in our hospital from January 2016 to February 2018 were retrospectively analyzed and divided into two groups, the CG (n=61, treated conventionally, 36 males and 25 females ranging in age from 17 to 56), and the OG (n=60, treated conventionally with edaravone and xingnaojing injections, 34 males and 26 females ranging in age from 18 to 57). (1) Inclusion criteria: patients who received treatment in a hospital within 24 h after their injury, patients who were in the acute stage, and patients who had no contraindications for edaravone and xingnaojing injections were included. Informed consents were obtained from their family members and approval was granted from the ethics committee of South Hospital of Jiaozhou People's Hospital. (2) Exclusion criteria: patients with vital sign disorders, patients with respiratory and circulatory failure when sent to the hospital, or patients with consciousness disorders due to other organ diseases, severe primary diseases in the kidneys, liver, lungs, or heart, or patients with hemorrhagic shock or multiple injuries complicated with lung contusions or hematopneumothorax were excluded.

Methods

After routine treatment, the patients in the CG were advised to lie in bed and were provided with continuous low-flow oxygen to make sure their respiratory tracts were unblocked. A tracheotomy was performed if necessary. For patients with encephaledema, effective actions were taken to reduce their intracranial pressure. Other treatments included a rapid intravenous drip of 125 ml of 20% mannitol (manufacturer: Shijiazhuang No. 4 Pharmaceutical Co., Ltd., approval no. GYZZ H5102-2149, specification: 250 ml: 50 g/bottle) and the administration of drugs to prevent the formation of fibrinolytic enzymes and to promote blood coagulation, including 2.0 g ethamsylate (manufacturer: Sinopharm Rongsheng Pharmaceutical Co., Ltd., approval no. GYZZ H20057257, specification: 2 ml: 0.5 g*10 pieces/box), 0.4 g PAMBA (approval no. GYZZ H43021565, manufacturer: Hunan Dongting Pharmaceutical Co., Ltd., specification: 10 ml: 0.1 g*5 pieces), 500 ml Ringer-Locke liquor (approval no. GYZZ H20100138, manufacturer: Hunan Kangyuan Pharmaceutical Co., Ltd., specification: 500 ml sodium chloride (3.0 g), natrium aceticum (1.90 g), potassium chloride (0.15 g) and calcium chloride (0.1 g)) by intravenous drip once a day. In addition, supportive nutritional therapy, anti-infection therapy with a mixture of 250 ml of normal saline and penicillin sodium (3.2 million units) (approval no. GYZZ H23021439, manufacturer: Harbin Pharmaceutical Group General Factory, specification: 0.48 g (800,000 units)) by intravenous drip, cooled with ice blankets as well as surgeries performed if necessary.

In addition to the treatments provided to the CG, the patients in the OG were intravenously dripped with a mixture of 100 ml normal saline and 30 mg edaravone (manufacturer: Nanjing Simcere Dongyuan Pharmaceutical Co., Ltd., approval no. GYZZ H20031342, specification: 5 ml: 10 mg × 6 pieces/box) twice a day, a mixture of 250 ml 5% glucose injection and 20 ml xingnaojing injection (manufacturer: Wuxi Jemincare Shanhe Pharmaceutical Co., Ltd., approval no. GYZZ Z320-20563, specification: 10 ml × 6 pieces/box) once a day. The treatment lasted for 14 d.

Observation indices

ET-1 concentration in CSF: a lumbar puncture was performed at 1 d, 7 d, and 14 d of treatment to collect 5 ml of a CSF sample. The sample was centrifuged at a speed of 3000 r/min for 10 min. The liquid supernatant was harvested and stored at -20°C to test the ET-1 concentrations using radioimmunoassays with test kits from the Beijing Puerwei Biotechnology Co., Ltd. [9].

GCS: the GCSs yielded by the two groups at 1 d, 7 d, and 14 d of treatment were compared

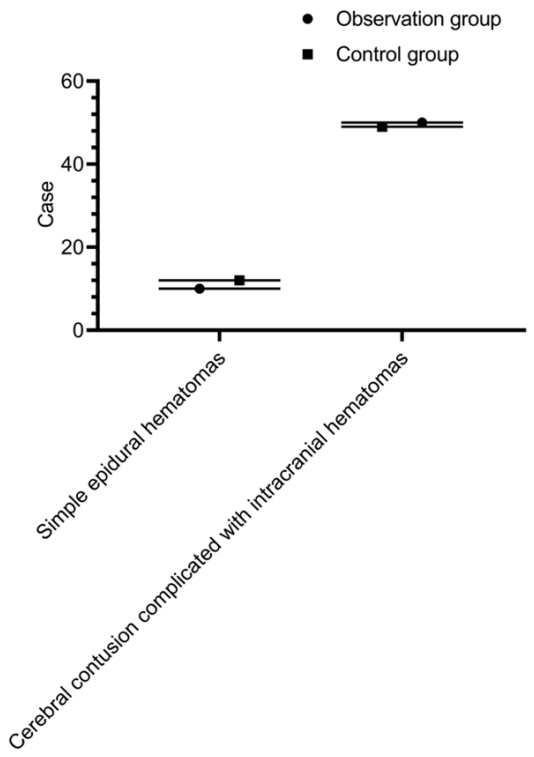

Figure 1. Analysis of the lesion types in the OG and the CG. Patients with simple epidural hematoma and cerebral contusions complicated with intracranial hematoma accounted for 16.67% and 83.33% in the OG and 19.67% and 80.33% in the CG (P>0.05).

and positively correlated to their states of consciousness [10]. GCS is the sum of points assigned to three aspects, i.e., physical movement, speech, and opening the eyes.

Intracranial blood flow velocities: transcranial doppler ultrasound examinations were conducted at 1 d, 7 d, and 14 d of treatment to obtain and compare the blood flow velocities in BA, VA, PCA, MCA and ACA.

Incidence of cerebral vasospasms: cerebral vasospasm was identified according to the following criteria, and the incidence was compared between the two groups at 1 d, 7 d, and 14 d of treatment. Patients satisfying any of the following criteria were considered to have cerebral vasospasm: an average blood flow velocity exceeding 80 cm/s in BA or VA, or 120 cm/s in MAC or ACA [11].

Statistical analysis

The statistical analysis was performed using SPSS 22.0. In the case of numerical data expressed as the mean ± standard deviation, comparison studies were carried out through independent-samples *t* tests for the data which were normally distributed, and Mann-Whitney U tests for the data which were not normally distributed. Paired t tests were used for the intragroup comparisons before and after the treatment. In the case of nominal data expressed as [n (%)], comparison studies were carried out using X^2 tests for the intergroup comparisons. For all the statistical comparisons, significance was defined as P<0.05.

Results

Intergroup comparisons of the patients' clinical data

There were 34 males (56.67%) and 26 females (43.33%) in the OG, with an age range and average age of 18-57 and (45.12±1.21) accordingly; there were 36 (59.01%) male and 25 (40.98%) female patients in the CG, ranging in age from 17 to 56, and with an average age of (45.09±1.19). The patients with simple epidural hematomas and cerebral contusions complicated with intracranial hematoma were 10 (16.67%) and 50 (83.33%) in the OG and 12 (19.67%) and 49 (80.33%) in the CG. The patients who were injured in traffic accidents, being hit by something, and falling were 12 (20.00%), 32 (53.33%) and 16 (26.67%) in the OG and 13 (21.31%), 31 (50.82%) and 17 (27.87%) in the CG. The two groups were not statistically different in terms of gender, average age, type of lesion (**Figure 1**), or cause of injury (P>0.05) (**Table 1**).

Intergroup comparison of the ET-1 concentrations in the CSF

The two groups were not statistically different in their ET-1 concentrations in the CSF at day one, which was (74.15±5.26) pg/ml in the OG and (75.02±5.12) pg/ml in the CG (t=0.922, P>0.05). At 7 d and 14 d, the ET-1 concentrations in the CSF were reduced to (34.25±1.25) pg/ml and (27.12±1.11) pg/ml in the OG and (41.25±1.32) pg/ml and (32.19±1.22) pg/ml in the CG (t=29.942, 23.899, P<0.05). The ET-1 concentration in the CSF was significantly reduced in both groups at 7 d and 14 d compared with that concentration at 1 d, and the ET-1 concentration in the CSF at 14 d was lower than it was at 7 d (P<0.05) (**Figure 2**).

Table 1. Intergroup comparison of the patients' clinical data [n (%)]/($\bar{x}$ ± s)

Characteristic		OG (n=60)	CG (n=61)	t/X^2	*P*
Gender (n)	Male	34 (56.67)	36 (59.01)	0.069	0.794
	Female	26 (43.33)	25 (40.98)		
Age (y)		45.12±1.21	45.09±1.19	0.138	0.890
Type of lesion					
Simple epidural hematoma		10 (16.67)	12 (19.67)	0.184	0.668
Cerebral contusion complicated with intracranial hematoma		50 (83.33)	49 (80.33)		
Causes of injury					
Traffic accident		12 (20.00)	13 (21.31)	0.023	0.888
Being hit		32 (53.33)	31 (50.82)		
Falling		16 (26.67)	17 (27.87)		

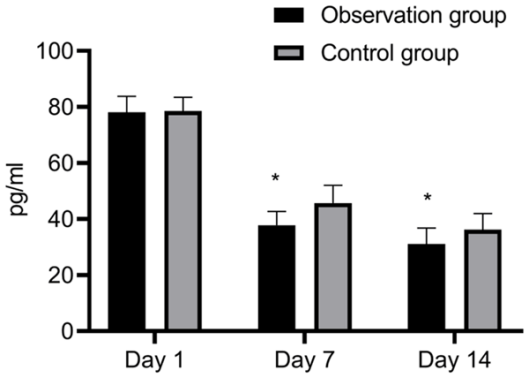

Figure 2. Intergroup comparison of the ET-1 concentration in the CSF. The ET-1 concentration in the CSF was not significantly different between the two groups at 1 d of treatment, but it was lower in the OG at 7 d and 14 d of treatment (P<0.05). *P<0.05 vs CG.

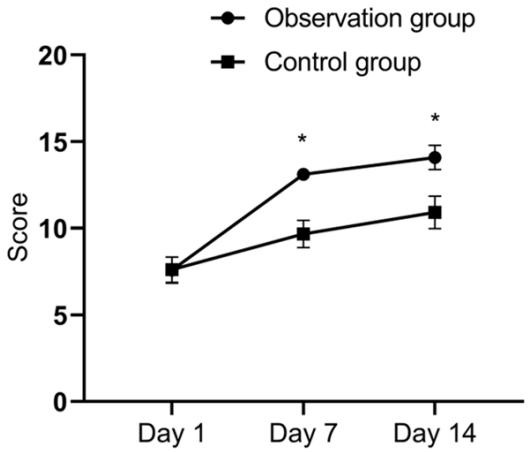

Figure 3. Intergroup comparison of the GCS. The GCS were not significantly different between the two groups at 1 d of treatment, but they were higher in the OG at 7 d and 14 d of the treatment (P<0.05). *P<0.05 vs CG.

Intergroup comparison of the GCS

No significant difference was found between the two groups in their GCS at 1 d, which were (7.05±0.12) in the OG and (7.09±0.11) in the CG (*t*=1.912, *P*>0.05). The scores rose to (12.98±1.42) and (13.59±1.89) in the OG and (9.12±0.45) and (10.25±0.58) in the CG as the treatment continued to 7 d and 14 d (*t*=20.225, 13.186, *P*<0.05). The GCS were significantly increased in both groups at 7 d and 14 d compared with the scores on day one, and the GCS at 14 d were higher than they were at 7 d (*P*<0.05) (**Figure 3**).

Intergroup comparison of the intracranial blood flow velocities

Average blood flow velocities in BA, VA, PCA, MCA, and ACA were compared between the two groups and found to be not significantly different at 1 d (P>0.05, **Table 2**) but they were lower in the OG at 7 d and 14 d of treatment (P<0.05, **Tables 3** and **4**). The average blood flow velocities in BA, VA, PCA, MCA, and ACA were significantly reduced in both groups at 7 d and 14 d compared with the velocities at 1 d, and the velocities at 14 d were lower than they were at 7 d (*P*<0.05).

Intergroup comparison of the incidence of cerebral vasospasm

The incidence of cerebral vasospasm was 3.33% (2/60), 5% (3/60), and 3.33% (2/60) in the OG and 3.28% (2/61), 16.39% (10/61) and 14.75% (9/61) in the CG at 1 d (X^2= 0.003, *P*>0.05), 7 d, and 14 d of treatment

Table 2. Intergroup comparison of the intracranial blood flow velocities at 1 d of treatment ($\bar{x}$ ± s, cm/s)

Group	BA	VA	PCA	MCA	ACA
CG (n=61)	68.12±2.52	75.12±2.63	96.12±1.25	129.52±8.52	99.86±5.63
OG (n=60)	68.19±2.48	75.19±2.52	96.19±1.18	129.59±8.48	99.92±5.59
t	0.154	0.149	0.317	0.045	0.059
P	0.878	0.882	0.752	0.964	0.953

Table 3. Intergroup comparison of the intracranial blood flow velocities at 7 d of treatment ($\bar{x}$ ± s, cm/s)

Group	BA	VA	PCA	MCA	ACA
CG (n=61)	72.12±1.25	73.69±2.33	93.36±1.18	110.26±5.12	91.25±4.16
OG (n=60)	64.02±1.15	64.12±1.25	83.12±1.12	100.02±4.08	80.12±3.12
t	37.079	28.086	48.945	12.154	16.628
P	0.000	0.000	0.000	0.000	0.000

Table 4. Intergroup comparison of the intracranial blood flow velocities at 14 d of treatment ($\bar{x}$ ± s, cm/s)

Group	BA	VA	PCA	MCA	ACA
CG (n=61)	66.12±0.22	68.96±1.26	87.69±1.06	105.63±4.22	89.96±3.22
OG (n=60)	60.12±0.85	62.02±0.58	80.02±0.88	95.12±3.22	75.63±2.12
t	53.348	38.809	43.269	15.383	28.863
P	0.000	0.000	0.000	0.000	0.000

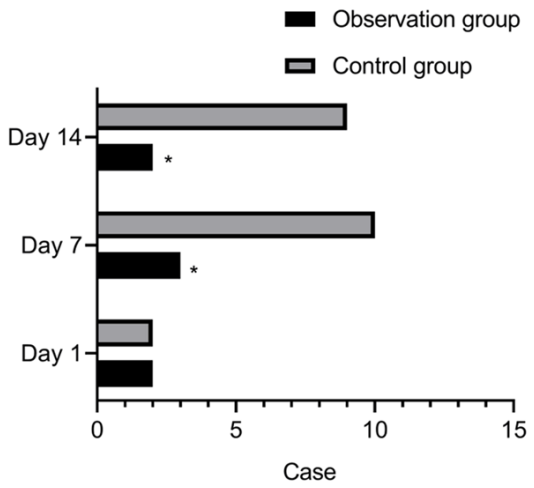

Figure 4. Intergroup comparison of the incidences of cerebral vasospasm. At 1 d of treatment, the incidence of cerebral vasospasm was 3.33% (2/60) in the OG and 3.28% (2/61) in the CG (P>0.05). As the treatment continued to the 7 d and the 14 d, the incidences were 5% (3/60) and 3.33% (2/60) in the OG and 16.39% (10/61) and 14.75% (9/61) in the CG respectively (P<0.05). *P<0.05 vs CG.

(X^2=4.095, 5.635, *P*<0.05) (**Figure 4**). The incidence of cerebral vasospasm was significantly reduced in both groups at 7 d and 14 d compared with the incidence at 1 d, and the incidence of cerebral vasospasm at 14 d was lower than it was at 7 d (*P*<0.05).

Discussion

Cerebral vasospasm after SCCI develops through a complicated pathological mechanism which is still unclear [12, 13], but the abnormality in blood constituents is generally accepted as one of its causes [14-16].

In this study, the incidences of cerebral vasospasm and GCS in the OG at 7 d and 14 d were lower than those in the CG. Also, at the same time points, the OG had lower average blood flow velocities than the CG (P<0.05). The findings jointly indicated that the combination of edaravone and xingnaojing injections to treat patients in the acute stage of severe brain injury can reduce the incidences of cerebral vasospasm and intracranial blood flow velocities and improve prognosis. The reason is that edaravone, a brain protector for intravenous administration, can pass through the blood-CSF barrier, eliminate the highly

cytotoxic hydroxyl groups in the brain, inhibit the peroxidation of nerve cells and vascular endothelial cells, and consequently alleviate the degree of injury to the brain tissue and cerebral ischemia [17, 18]. Many clinical experiments have reported a reduction of leukocyte infiltration, the inhibition of the expression of inflammatory cytokines, the alleviation of encephaledema and oxidative stress as well as various neurological symptoms when patients enter the acute stage of cerebral hemorrhage or cerebral infarction [19, 20], if edaravone was given to the patients within 24 h after onset. The active ingredients of xingnaojing injection include Radix curcumae, Cape jasmine, borneol, and musk. Radix curcumae can dredge channels, expel stagnation, reduce phlegm, activate blood circulation, and remove blood stasis. Cape jasmine can clear away heat and toxic materials and cool the blood. Borneol, with a fragrant odor, is a good substance for resuscitation and refreshment, and musk is well known for its roles in activating blood circulation, dispersing blood stasis, and opening up channels. Their joint application can achieve better effects [21, 22]. According to modern pharmacology, the active ingredients in xingnaojing injection after intravenous injection can directly pass through the blood-CSF barrier to exert effects on nerve cells [23]. Fang [24] et al. revealed in their study that xingnaojing injection mitigates the cerebral anoxia, ischemia and encephaledema in rats with craniocerebral injury, inhibits calcium overload, reduces capillary permeability, and protects the brain at the molecular level by eliminating free radicals. As a result, the conditions of the SCCI patients are improved. Scholars including Pan et al. [25] also analyzed the efficacy of xingnaojing injection in treating SCCI patients, and the results showed that, compared with the CG adopting conventional Western therapies, those using xingnaojing injection faced lower incidences of vasospasm after craniocerebral injury and cerebral infarction as the blood flow velocities in their intracranial vessels dropped.

After craniocerebral injury, many factors, including high intracranial pressure, angiotensin, arginine vasopressin, thrombin, oxygenated hemoglobin, and the anterior endothelin genes were activated to promote the generation and release of ET. Existing clinical studies have shown that a rapidly rising ET concentration, reperfusion, hypoxia, and ischemia of the brain tissues after craniocerebral injury can intensively promote the expression of mRNA (an ET receptor). As a result, the amount of ET released increases [26]. ET is a common and active substance for vascular contraction categorized into three subtypes, i.e., ET-1, ET-2 and ET-3. ET-1 participates in the development and progression of many vascular diseases by sharply increasing the blood pressure and promoting vascular contraction, especially the collateral vessels, so as to reduce local blood flow and improve the recovery of nerve functions. According to the findings of this study, the OG had a lower ET-1 concentration in the CSF at 7 d and 14 d of treatment ($P<0.05$), indicating that compared with conventional therapies, the combination of edaravone and xingnaojing injections in treating SCCI patients can reduce the concentration of ET-1 through their interaction.

In conclusion, the combination of edaravone and xingnaojing injections managed to bring down the incidence of cerebral vasospasm, the concentration of ET-1, and intracranial blood flow velocities in patients in the acute stage of severe brain injury, and effectively improve their prognoses.

However, this study included a small cohort, so its results are not sufficiently representative. In future in-depth studies, a larger cohort will be recruited.

Disclosure of conflict of interest

None.

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