Effects of early lumbar cistern drainage of cerebrospinal fluid and combination of edaravone and nimodipine on vasospasm, intracranial pressure, inflammatory factors in traumatic subarachnoid hemorrhage

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Sent for review: 8 January 2022
Revised accepted: 17 July 2022

Abstract

Purpose: To investigate the effect of early lumbar cistern drainage (LCD) of cerebrospinal fluid (CSF) and combination of edaravone and nimodipine on vasospasm, intracranial pressure (ICP), serum inflammation, S100 and vascular endothelial growth factor (VEGF) levels in traumatic subarachnoid hemorrhage (tSAH).

Methods: Treatment was administered to 136 patients divided into control group (n = 68) and study group (n = 68). Serum inflammation was determined by assessing the levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) while nitric oxide (NO), endothelin-1 (ET-1), S100 and VEGF levels were determined by enzyme-linked immunosorbent assay (ELISA). Serum C-reactive protein (CRP) level was measured by immunoturbidimetry. Perfusion weighted imaging was performed and the mean transit time (MTT), cerebral blood flow (CBF), cerebral blood volume (CBV), mean flow velocity (Vm) and pulsatility index (PI) were recorded. Glasgow coma scale (GCS) score and Montreal cognitive assessment (MoCA) score were used to compare the differences in therapeutic effect.

Results: Compared with values before treatment, Vm, PI, NO, CBF, CBV, GCS score and MoCA score were significantly increased (p < 0.05), while ICP, serum levels of TNF-α, IL-6, CRP, ET-1, S100 and VEGF and MTT significantly decreased (p < 0.05). Therapeutic response rate of the study group (89.71%) was higher than that of control group (66.18%) (p < 0.05).

Conclusion: Early LCD of CSF and combination of edaravone and nimodipine reduces the degree of cerebral vasospasm and contribute to brain function recovery in the treatment of patients with tSAH. This therapeutic strategy requires further clinical trials before application in clinical practice.

Keywords: Early lumbar cistern drainage, Cerebrospinal fluid, Edaravone, Nimodipine, Traumatic subarachnoid hemorrhage

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a clinical syndrome caused by rupture of a blood vessel in the brain, causing blood to flow into the subarachnoid space. The main clinical symptoms of SAH are meningeal irritation sign, vomiting, nausea and headache [1]. Traumatic SAH (tSAH) is a common type of SAH which damages cerebrovascular endothelial cell function. In the
early stage, due to systemic inflammatory reaction, platelet activation, cerebral ischemia and hypoxia, cerebrovascular endothelial cell function was impaired, resulting in cerebral vasospasm. Increased intracranial pressure (ICP), and decreased cerebral blood flow (CBF), leading to impaired neurological function in patients [2].

Common complications of SAH are convolution, hydrocephalus, rebleeding, and cerebral vasospasm. Among these complications, cerebral vasospasm has a relatively higher incidence, and it often causes severe delayed ischemic brain damage or local cerebral ischemia [3]. Studies have shown that cerebral vasospasm may be closely related to the production of vasoactive substances, calcium influx, and mechanical stimulation of blood vessels [4]. Currently, there is no specific drug for tSAH. Nimodipine is able to selectively expand the cerebral blood vessels through the blood-brain barrier, thereby exerting a certain therapeutic effect on tSAH [5].

Edaravone is an oxygen free radical scavenger, which improves the neurological function and vasospasm in patients with tSAH [6]. Despite the efficacy of the combination of the two drugs in the treatment of tSAH, the prognosis and improvement of neurological function are still unsatisfactory in some patients. From clinical studies, early lumbar cistern drainage (LCD) of cerebrospinal fluid (CSF) showed an excellent clinical effect on patients with tSAH [7]. This study investigated the effects of early LCD of CSF and the combination of edaravone and nimodipine on vasospasm, ICP, serum inflammation, levels of S100 and VEGF in tSAH.

METHODS

Patients

A total of 136 patients with tSAH treated in Shanghai Songjiang District Central Hospital, Department of Neurosurgery from May 2018 to January 2020 were enrolled in this study. The study was approved by the Ethics Committee of Shanghai Songjiang District Central Hospital (approval no 2017SH10SD6). The study was conducted following the guidelines of Declaration of Helsinki [8]. All patients and/or guardians signed written informed consents [9].

Inclusion criteria

(1) patients diagnosed with tSAH, (2) Hunt-Hess class I-IV, (3) patients agreed to participate in and signed informed consent form.

Exclusion criteria

(1) patients complicated with severe dysfunction of heart, liver or kidney, (2) those accompanied by severe leukemia, aplastic anemia or other severe blood system diseases, (3) those complicated with immune deficiency, (4) those with disturbance of consciousness or nervous system disease, (5) those allergic to drugs used in the study, (6) pregnant or lactating patients, (7) those who needed surgical intervention due to intracranial hematoma or cerebral contusion, or (8) those who had poor compliance or quit halfway.

Treatments

The patients were grouped based on random number table: control group (n = 68); observation group (n = 68). Patients in both groups received nutritional support and Electrolyte balance treatment. Control group was treated with 10 mL of nimodipine (NMPN H20023122, CISEN Pharmaceutical) dissolved in 500 mL of normal saline and intravenously injected twice a day, and 20 mL of edaravone (NMPN H20031342, Nanjing Simcere Pharmaceutical Group) dissolved in 500 mL of normal saline was also intravenously injected twice a day for 2 consecutive weeks. Patients in observation group underwent early LCD of CSF, as follows: Local anesthesia catheter was used for puncture and drainage.

After anesthesia, L5S1 or L4-5 intervertebral space was routinely punctured at a depth of about 5 - 6 cm using a special puncture needle. A drainage tube was inserted into the skin from the puncture point and withdrawn from the neck, and connected to the ventricular drainage bag. The height of the drainage bag was adjusted, and the drainage rate was controlled at 1 - 3 drops/min. The pressure of CSF was measured and the drainage bag was replaced every day.

Evaluation of parameters/indices

Serum inflammatory factors

Fasting venous blood (5 mL) was drawn the next morning after admission, and centrifuged for 10 min (4 °C, 2000 g). The serum separated was stored in a refrigerator at -75 °C if not detected immediately. The TNF-α and IL-6 were determined by enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Zeye Biological Technology Co. Ltd.) and serum C-reactive protein (CRP) was by immunoturbidimetry.
Nitric oxide (NO) and endothelin-1 (ET-1)

The levels of serum NO, ET-1, serum S100 and VEGF were determined via ELISA strictly according to the instructions of kits (Beijing Diagreat Biotechnology Co. Ltd).

Brain microcirculation

Perfusion weighted imaging was performed using a 64-slice spiral CT machine (CE, USA), and the contrast agent was injected via the elbow vein at 5 mL/sec, followed by continuous dynamic scanning at a slice thickness of 8 cm based on the sella turcica layer. The mean transit time (MTT), cerebral blood flow (CBF), cerebral blood volume (CBV), mean flow velocity (Vm) and pulsatility index (PI) were recorded.

Glasgow coma scale (GCS) score and Montreal cognitive assessment (MoCA) score

The GCS scale includes three categories of body movement, verbal response and eye-opening response on a scale of 1 - 5, with a total of 15 points. The lower score corresponds to the severer disturbance of consciousness: ≤ 8 points = coma, 9 - 11 points = moderate disturbance of consciousness, 12 - 14 points = mild disturbance of consciousness, and 15 points = clear consciousness. The MoCA scale was composed of 11 items in 8 cognitive domains of orientation, calculation, conceptual thinking, view structure skill language, memory, executive function, attention and concentration, with a total score of 30 points [11,12].

Intracranial pressure (ICP)

This was measured using an indwelled probe. The efficacy was evaluated by Chinese Guidelines on Diagnosis and Treatment of Subarachnoid Hemorrhage (2015 edition) [12]:

1. ineffective: decreased blood flow in the middle cerebral artery (MCA) < 10 %, and no improvement in clinical symptoms;
2. effective: decreased blood flow in MCA blood flow > 10 %, basic disappearance of clinical symptoms, significant enhancement of muscle strength, good recovery, and basic self-care ability;
3. markedly effective: decreased blood flow in MCA blood flow > 20 %, disappearance of clinical symptoms, good recovery, and no related sequelae.

Statistical analysis

Statistical Software for Social Sciences (SPSS) 19.0 (SPSS Inc., Chicago, IL, USA) was used for data processing. Measurement data are expressed as mean ± standard deviation (SD) and compared by t-test. Enumeration data are expressed as (n (%)) and compared by chi-square test. P < 0.05 was considered statistically significant.

RESULTS

Baseline patient information

In the control group (n = 68), patients were 41.32 ± 4.65 years old while in the study group (n = 68), their mean age was 41.55 ± 4.68 years. There were no statistical differences between the groups with regard to age, gender, duration from injury to admission, Hunt-Hess class, and type of injury (p > 0.05) (Table 1).

Serum inflammatory factors

Serum TNF-α, IL-6 and CRP decreased after treatment in both groups, and the decrease was more remarkable in study group (p < 0.05; Table 2).

Table 1: Comparison of baseline data between the two groups (n=68)

| Parameter                                      | Control group (n = 68) | Observation group (n = 68) | t/χ² | P-value |
|-----------------------------------------------|-----------------------|---------------------------|------|---------|
| Age (year)                                    | 41.32 ± 4.65          | 41.55 ± 4.68              | 0.287| 0.387   |
| Male/female (n (%))                           | 40 / 28               | 38 / 30                   | 0.120| 0.729   |
| Duration from injury to admission (h)         | 6.35 ± 1.22           | 6.47 ± 1.18               | 0.583| 0.280   |
| Hunt-Hess class (n (%))                        |                       |                           |      |         |
| I                                             | 17 (25.00)            | 15 (22.06)                |      |         |
| II                                            | 20 (29.41)            | 21 (30.88)                | 0.186| 0.996   |
| III                                           | 13 (19.12)            | 14 (20.59)                |      |         |
| IV                                            | 18 (26.47)            | 18 (26.47)                |      |         |
| Type of injury (n (%))                         |                       |                           |      |         |
| Traffic injury                                 | 38 (55.88)            | 36 (52.94)                | 0.119| 0.731   |
| Falling injury                                 | 13 (19.12)            | 15 (22.06)                | 0.180| 0.671   |
| Slipping injury                                | 9 (13.24)             | 8 (11.76)                 | 0.067| 0.795   |
| Blow injury                                    | 8 (11.76)             | 9 (13.24)                 | 0.067| 0.795   |
Table 2: Comparison of serum inflammatory factors (n = 68)

| Group    | Time       | TNF-α (μg/L) | IL-6 (μg/L) | CRP (mg/L) |
|----------|------------|--------------|-------------|------------|
| Control  | Before     | 0.87±0.06    | 66.18±3.65  | 52.16±4.58 |
| Study    | Treatment  | 0.86±0.07    | 65.96±3.71  | 52.24±4.62 |
| t        |            | 0.894        | 0.349       | 0.101      |
| P-value  |            | 0.186        | 0.364       | 0.460      |
| Control  | After      | 0.48±0.03@   | 55.26±3.51@ | 40.18±3.69@|
| Study    | Treatment  | 0.21±0.05@   | 43.69±3.48@ | 24.84±2.98@|
| T        |            | 38.184       | 19.303      | 26.670     |
| P-value  |            | <0.001       | <0.001      | <0.001     |

*p < 0.05 vs. before treatment

Table 3: Comparison of serum levels of NO and ET-1

| Group    | Time       | NO (μmol/L) | ET-1 (ng/L) |
|----------|------------|-------------|-------------|
| Control  | Before     | 33.15±4.58  | 78.98±6.87  |
| Study    | Treatment  | 33.09±4.62  | 78.69±7.02  |
| T        |            | 0.076       | 0.243       |
| P-value  |            | 0.470       | 0.404       |
| Control  | After      | 48.69±7.85@ | 67.59±5.48@ |
| Study    | Treatment  | 56.36±7.91@ | 59.87±4.89@ |
| T        |            | 5.676       | 8.668       |
| P-value  |            | <0.001      | <0.001      |

*p < 0.05 vs. before treatment

Serum NO and ET-1

Serum NO increased remarkably, while serum ET-1 decreased after treatment in both groups, while the changes were greatly obvious in study group (p < 0.05; Table 3).

Vm, PI and ICP

The Vm and PI were remarkably higher, while the ICP was lower in both groups after treatment, especially in the study group (p < 0.05, Table 4).

Brain microcirculation

The two groups had significantly shorter MTT, and significantly smaller CBF and CBV after treatment, these trends were more significant in study group (p < 0.05) (Table 5).

Serum levels of S100 and VEGF

Serum S100 and VEGF were lower in both groups after treatment, but the study group presented lower values (p < 0.05; Table 6, Figure 1).

Table 4: Comparison of Vm, PI and ICP

| Group    | Time       | Vm (cm/s) | PI   | ICP (Kpa) |
|----------|------------|-----------|------|-----------|
| Control  | Before     | 66.71±0.86| 0.75±0.15| 4.25±0.23 |
| Study    | Treatment  | 66.79±0.91| 0.74±0.13| 4.31±0.21 |
| T        |            | 0.047     | 0.415| 1.589     |
| P-value  |            | 0.481     | 0.399| 0.057     |
| Control  | After      | 87.58±12.36@| 0.97±0.16@| 2.54±0.19@|
| Study    | Treatment  | 103.58±13.54@| 1.15±0.17@| 1.54±0.15@|
| T        |            | 17.197    | 6.358| 34.065    |
| P-value  |            | <0.001    | <0.001| <0.001    |

*p < 0.05 vs. before treatment

Table 5: Comparison of brain microcirculation indices

| Group    | Time       | MTT (s)   | CBF (mL/min/100g) | CBV (mg/g) |
|----------|------------|-----------|-------------------|------------|
| Control  | Before     | 4.71±0.38 | 28.96±3.48        | 1.58±0.15  |
| Study    | Treatment  | 4.73±0.52 | 28.29±3.81        | 1.56±0.17  |
| T        |            | 0.256     | 0.112             | 0.727      |
| P-value  |            | 0.399     | 0.456             | 0.234      |
| Control  | After      | 3.78±0.25@| 34.52±4.05@       | 1.89±0.17@ |
| Study    | Treatment  | 3.15±0.31@| 38.21±4.33@       | 2.21±0.23  |
| T        |            | 13.045    | 6.132             | 9.226      |
| P-value  |            | <0.001    | <0.001            | <0.001     |

*p < 0.05 vs. before treatment
Table 6: Comparison of serum levels of S100 and VEGF

| Group     | Time          | S100 (μg/L)  | VEGF (ng/L)  |
|-----------|---------------|--------------|--------------|
| Control   | Before treatment | 0.38±0.06   | 208.69±13.56 |
| Study     | t-value       | 0.825        | 0.090        |
| P-value   |               | 0.806        | 0.464        |
| Control   | After treatment | 0.29±0.05@  | 148.69±8.97@ |
| Study     | T-value       | 24.042       | 19.833       |
| P-value   |               | <0.001       | <0.001       |
@ P < 0.05 vs. before treatment

Table 7: Comparison of GCS and MoCA scores

| Group     | Time          | GCS score | MoCA score |
|-----------|---------------|-----------|------------|
| Control   | Before treatment | 9.21±2.54 | 18.45±3.26 |
| Study     | t-value       | 0.116     | 0.145      |
| P-value   |               | 0.454     | 0.443      |
| Control   | After treatment | 11.87±2.69 | 22.59±3.51 |
| Study     | T-value       | 2.393     | 3.697      |
| P-value   |               | 0.009     | <0.001     |
@ P < 0.05 vs. before treatment

GCS and MoCA scores

The GCS and MoCA scores were significantly higher in both groups after treatment, but was more significantly higher in the study group (p < 0.05; Table 7).

Clinical efficacy

Therapeutic response rate of treatment was significantly higher in observation group (89.71%) than that in control group (66.18%; p < 0.05; Table 8).

DISCUSSION

Vascular endothelial cell function damage in patients with tSAH is closely related to neurological damage and cerebral vasospasm. The vascular endothelial cell function is usually evaluated using ET-1 and NO secreted by vascular endothelial cells [13]. The NO inhibits platelets and expand blood vessels effectively, while ET-1 induces platelet adhesion and aggregation and trigger vasospasm [14]. Under normal physiological conditions, ET-1 and NO are in a dynamic balance state in patients. However, systematic pathological stimuli, such as inflammatory response and cerebral hypoxia and ischemia, the vascular endothelial cell function is damaged, and the synthesis of NO is decreased, while that of ET-1 is increased, thereby resulting in increased ICP, decreased CBF and cerebral vasospasm [15].

Then increased ICP and cerebral vasospasm enhance the degree of cerebral ischemia and hypoxia in patients, which may form a vicious circle and worsen disease condition.

Nimodipine is a frequently-used calcium channel antagonist able to effectively inhibit Ca\(^{2+}\) transformation, maintain the normal concentration of Ca\(^{2+}\) in cells. It can also dilate blood vessels and effectively relieve cerebral vasospasm [15]. It can be seen that nimodipine prevented cerebral vasospasm in patients to a certain extent, and inhibited voltage-dependent Ca\(^{2+}\) channels, but it had no obvious effect on receptor-operated Ca\(^{2+}\) channels. Edaravone is an active antioxidant able to effectively suppress the formation of lipid peroxides and capture...
hydroxyl free radicals, thereby preventing peroxidative damage to cerebral vascular endothelial cells, effectively preventing cerebral edema, and inhibiting cerebral vasospasm [16].

Brain microcirculation, characterized by blood-CSF barrier and automatic regulation of CBF, supplies oxygen and glucose to brain tissues, maintains normal physiological function of brain tissues [17]. The diameter of cerebral microvessels is altered according to the changes in arterial pressure to keep CBF in a stable state. Blood-CSF barrier limits the exchange of substances between brain tissues and blood. Therefore, brain microcirculation helps to maintain the brain homeostasis, and its dysfunction can directly cause functional damage to brain tissues [18].

The tSAH leads to a certain degree of microcirculation disorder. In this study, nimodipine in combination with edaravone improved the brain microcirculation and prognosis of patients to a certain extent. Studies have demonstrated that tSAH induces a series of immune-inflammatory responses, and inflammatory factors such as TNF-α, IL-6 and CRP play important roles during cerebral vasospasm, leading to vasoconstriction, increased vascular permeability, intima damage and neuron damage [19].

VEGF is a member of the growth factor family that promotes angiogenesis and endothelial cell division while S100 proteinase is a central nerve-specific protein in astrocytes and oligodendrocytes [20]. This report shows that nimodipine and edaravone alleviated the inflammatory response to and ameliorate the levels of serum S100 and VEGF in patients. In addition, both GCS score and MoCA score were greatly improved after treatment compared with those before treatment. It can be inferred that nimodipine effectively inhibits calcium overload, increased blood flow, expanded cerebral blood vessels, and prevented vasospasm, all of which provided conditions for the recovery of brain function in patients.

In study group, the above related indices were more significantly improved compared with those of the control group, indicating that early LCD of CSF in combination with edaravone and nimodipine can better improve degree of cerebral vasospasm and induce the recovery of brain function in patients with tSAH. There would be need for further studies on a larger population to establish strategies for clinical treatments of patients.

CONCLUSION

Early LCD of CSF in combination with edaravone and nimodipine is effective in reducing ICP and serum S100 and VEGF levels, relieve the inflammatory response, improve degree of cerebral vasospasm and induce the recovery of brain function in patients with tSAH. There would need for further studies on a larger population to establish strategies for clinical treatments of patients.

DECLARATIONS

Acknowledgements
None provided.

Funding
None provided.

Ethical approval
None provided.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest
No conflict of interest associated with this work.

Contribution of Authors
We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Wenjie Tong and Jun Fang conceived and designed the study, and drafted the manuscript. Wenjie Tong, Yongliang Jiang and Bo Huang collected, analyzed and interpreted the experimental data. Yongliang Jiang and Bo Huang revised the manuscript for important intellectual content. All authors read and approved the final manuscript.
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