Effects of fasudil injection on stress hormone and inflammatory factors in the treatment of traumatic brain injury

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ABSTRACT

Objective: To investigate the effect of fasudil injection on stress hormone and inflammatory factors in the treatment of traumatic brain injury. Methods: 120 cases of traumatic brain injury were divided into control group and observation group according to the odd and even number of the group, 60 cases each. The control group was given conventional therapy including hemostasis, intracranial pressure control, neurotrophic drugs and anti-infection, the observation group was given fasudil injection on the basis of routine treatment, compare the serum stress hormones adrenocorticotrophic hormone (ACTH), Norepinephrine (NE), norepinephrine (Cor) and inflammatory factors IL-1, IL-6, TNF-α levels between two groups before treatment (T0) and after treatment 3 d (T1) and 7 d (T2). Results: The ACTH, NE, Cor and IL-1, IL-6, and TNF-α levels in T0 serum were not significantly different between the two groups (all \( P > 0.05 \)). As the treatment progressed, serum ACTH, NE, and Cor levels of T1 and T2 were lower than T0 in both groups, when T2 was lower than T1, which showed a gradual downward trend, two groups of T1 serum IL-1, IL-6 and TNF-α levels were higher than T0, when T2 was lower than T1 and T0, it showed increased first and then decreased, the difference was statistically significant (\( P < 0.05 \)); Observation group T1 serum ACTH, NE, Cor and IL-1, IL-6 and TNF-α levels were (67.23±9.8) pg/mL, (685.71±181.83) pg/mL, (251.65±50.35) ng/mL, (6 276.38±52.05) pg/mL, (231.34±29.05) pg/mL, (92.21±15.25) ng/mL respectively, significantly lower than those in T1 of the control group; Observation group T2 serum ACTH, NE, Cor and IL-1, IL-6 and TNF-α levels were (55.16±8.05) pg/mL, (426.72±150.14) pg/mL, (202.36±39.18) ng/mL, (108.37±38.38) pg/mL, (111.36±21.15) pg/mL, (40.72±13.42) ng/mL respectively, significantly lower than those in T2 of the control group, the differences were statistically significant (\( P < 0.05 \)). Conclusion: Fasudil injection can relieve the stress reaction and control the level of inflammatory factors in patients with brain trauma.

1. Introduction

Traumatic brain injury is a high traumatic neurosurgical disease, some patients need surgery, long-term clinical study found that patients with traumatic brain injury with varying degrees of stress and inflammatory response, which can affect the effect of surgical treatment, and increase the risk of complications[1]. In recent years, the application of fasudil injection in cardiovasular and cerebrovascular diseases are becoming more and more widely in relieving cerebral vasospasm, has good effect[2] on improving the blood supply to the brain. Some scholars began to apply it to the treatment of patients with traumatic brain injury, and confirmed its good efficacy and safety[3], the study began in 2015, the application of fasudil injection in the treatment of traumatic brain injury, found which has a good effect in patients with brain trauma to improve the level of stress hormones and inflammatory factors , the report is as follows.

2. Materials and methods

2.1. Study subjects

120 consecutive patients with traumatic brain injury from January
2015 to October 2016 were randomly divided into the control group and the observation group according to the odd and even number of the entry serial number, 60 cases each. The control group: male 38 cases, female 22 cases, age 22–58 years old, average age (41.55±14.62), Glasgow coma score 5–14, average (8.75±2.55), including 25 cases of epidural hematoma, subdural hematoma in 26 cases, 9 cases of cerebral hemorrhage; Observation group: male 39 cases, female 21 cases, age 20-59 years old, the average (42.25±14.75), Glasgow coma score 5–13, average (8.55±2.75), including 24 cases of epidural hematoma, subdural hematoma in 26 cases, 10 cases of cerebral hemorrhage; Clinical data of the two groups were basically the same, the difference was not significant (P>0.05).

2.2. Inclusion and exclusion criteria

Inclusion criteria: (i) History, clinical symptoms and CT and/or MRI imaging consistent with traumatic brain injury hematoma performance, and in line with surgical treatment of evidence; (ii) aged 18–60 years; (iii) American Society of Anesthesiologists (ASA) grading: II–III; (iv) Informed consent of family members, with treatment and signed informed consent form; (v) Medical information and laboratory examination data improved; Exclusion criteria: (i) critically ill, postoperative death; (ii) combined infection, endocrine, cardiovascular and malignant tumors and other diseases; (iii) combined with other parts of the trauma; (iv) nearly 1 month application of immune agents, glucocorticoids.

2.3. Treatment

The control group: after the admission to actively deal with trauma, as soon as possible to improve the laboratory and imaging studies to determine compliance with surgical indications, according to the bleeding site, hematoma size, conduct craniotomy hemostasis and hematoma removal. Given intensive care and sub-temperature intervention after operation, antihypertensive drugs to control blood pressure, hemostatic acid to stop bleeding. Under the premise of stable circulation, given mannitol, glycerol fructose or furosemide to dehydration, reduce pressure. Appropriate amount of antibiotics to prevent infection, promote brain metabolism or nutritional drugs to promote brain repair, famotidine prevention of stress ulcers, enough fluid to ensure that water and electrolyte, acid-base balance, the same period to give other symptomatic treatment.

The observation group: On the basis of the conventional treatment in craniotomy and control group, fasudil injection (manufactured by Nagase Pharmaceuticals Plant, Asahi Kasei Pharma Corporation, approval number H20150252, specification: 30 mg/sup), 30 mg with 5% glucose injection intravenous infusion treatment, 2 times/d, continuous treatment for 7 d.

2.4. Observation indicators

(i) The levels of serum stress hormones before treatment (T0), treatment 3 d (T1), and 7th day (T2) in the two groups were compared, including adrenocorticotropic hormone (ACTH), Norepinephrine (NE), norepinephrine (Cor), measured by radioimmunoassay, the normal range is: 10–52 pg/mL, 104–548 pg/mL, 50–280 ng/mL; (ii) The levels of inflammatory cytokines in T0, T1 and T2 were compared between the two groups, including interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) levels, using enzyme-linked immunosorbent assay (ELISA), the normal range are respectively. 0–100 pg/mL, 0–6.4 pg/mL, 0.74-1.54 ng/mL.

2.5. Statistical analysis

The data were analyzed by SPSS19.0 statistical software. The measurement data were expressed as \( \bar{x} \pm s \), obey the normal distribution, multi-time comparison by one-way repeated analysis of variance analysis + t test, if \( P<0.05 \), the difference was significant.

3. Results

3.1. Comparison of serum levels of stress hormones before and after treatment

There was no significant difference in ACTH, NE and Cor levels between the serum T0 in two groups (all \( P>0.05 \)). As the treatment progressed, the ACTH, NE and Cor levels in T1, T2 were lower than T0, when the T2 was lower than T1, the difference was statistically significant (all \( P<0.05 \)). The observation group ACTH, NE and Cor in serum T1 were respectively (67.23±9.8) pg/mL, (685.71±181.83) pg/mL and (251.65±50.35) ng/mL, significantly lower than the control group T1. The observation group T2 serum ACTH, NE and Cor were respectively (55.16±8.05) pg/mL, (426.72±150.14) pg/mL, (202.36±39.18) ng/mL, significantly lower than the control group T2 (\( P<0.05 \)). See Table 1.

3.2. Comparison of serum inflammatory factors before and after treatment in two groups

There was little difference between the two groups serum IL-6 and IL-1 and TNF-α levels of T0 (\( P>0.05 \)); As the treatment progressed, both groups of T1 serum IL-1, IL-6 and TNF-α levels were higher than those of T0, when T2 was lower than that of T1 and T0, the
differences were statistically significant ($P<0.05$); Observation group T1 serum IL-1, IL-6 and TNF-α levels were (6276.38±52.05) pg/mL, (231.34±29.02) pg/mL, and (92.21±15.25) ng/mL, respectively, significantly lower than the control group T1, the observation group T2 serum IL-1, IL-6 and TNF-α levels were (108.37±38.38) pg/mL, (111.36±21.15) pg/mL, (40.72±13.42) ng/mL, respectively, significantly lower than the control group T2 ($P<0.05$). See Table 2.

4. Discussion

In recent years, with the rapid development of Chinese economy and society, traumatic patients was significantly increased, patients with traumatic brain injury occupied a higher proportion in the department of neurosurgery, part of the condition is more critical, especially in patients with severe brain injury often progressed rapidly, cerebral hernia formation rate and the deterioration rate is high, need surgical treatment[4]. In recent years, a large number of clinical studies have shown that patients with different levels of brain trauma associated with stress, a large number of ACTH, NE and Cor released into the blood, induced cerebral vasospasm and abnormal blood supply adverse reactions, causing serious impact on the surgical effect, and even leading to stress ulcers, secondary cerebral hemorrhage and other complications[5]. In addition, a large number of clinical studies at home and abroad showed that brain trauma can cause systemic inflammatory response syndrome, severe inflammatory response syndrome can aggravate cerebral edema, increase other organ damages beyond brain and the risk of infection. On which the over-release of inflammatory mediators has an important effect, the inflammatory factors such as IL-1, IL-6, and TNF-α have been found to have a high sensitivity in evaluating the degree of inflammatory response after traumatic brain injury[6,7].

Recent domestic and international clinical studies have shown that the application of fasudil in patients with traumatic brain injury is more and more widely, including application of fasudil hydrochloride combined with nimodipine in the treatment of brain traumatic subarachnoid hemorrhage[8], results showed that fasudil helps alleviate cerebral vascular spasm in patients with trauma, improve the cerebral blood flow velocity, and improve the prognosis of nerve function. Wang et al confirmed through animal experiments, fasudil can reduce hypoxic ischemic brain damage, improve the function of brain tissue oxidative damage and inflammatory reaction[9]. This study shows that the treatment of fasudil in patients with brain trauma after treatment 3, 7 d plasma, the ACTH, NE and Cor levels were significantly lower than before treatment, suggesting that fasudil can effectively reduce the traumatic brain injury in patients with stress response. To observe the inflammatory reaction of brain trauma patients, the serum IL-1, IL-6 and TNF-α levels in patients with traumatic brain injury 3 d after operation increased compare with before treatment, but decreased significantly 7 d after the operation, the possible reasons may be related with the relatively obvious early inflammatory reaction and the release of inflammatory mediators and inflammatory process in surgical brain trauma patients. However, serum IL-1, IL-6 and TNF-α levels in fasudil treatment patients 3D postoperative increase to a lesser degree, and decreased significantly after 7 d , suggesting that fasudil helps to control inflammatory response in patients with traumatic brain injury surgery.

Fasudil is a novel 5-isouquinolinesulfonamide derivative and is

Table 1

| Table 1 |
| Levels of serum stress hormones before and after treatment (n=60, $\pm x$). |
| --- | --- | --- |
| Group | Time | ACTH (pg/mL) | NE (pg/mL) | Cor (ng/mL) |
| Observation group | T0 | 85.35±11.02 | 780.41±205.73 | 352.85±92.38 |
| | T1 | 67.23±9.85 | 685.71±181.83 | 251.6±50.35 |
| | T2 | 55.16±8.05 | 426.72±150.14 | 202.36±39.18 |
| Control group | T0 | 86.06±12.18 | 791.58±211.54 | 356.39±90.73 |
| | T1 | 72.38±9.25 | 702.37±186.23 | 282.67±58.36 |
| | T2 | 62.38±8.35 | 478.25±155.38 | 242.72±45.29 |

Compared with T0, $P<0.05$; compared with T1, $P<0.05$; compared with the control group at the same time, $P<0.05$.

Table 2

| Table 2 |
| Comparison of serum inflammatory factors between the two groups before and after treatment (n=60, $\pm x$). |
| --- | --- | --- |
| Group | Time | IL-1 (pg/mL) | IL-6 (pg/mL) | TNF-α (ng/mL) |
| Observation group | T0 | 226.38±56.44 | 226.36±61.45 | 89.26±23.16 |
| | T1 | 276.38±52.05 | 231.34±29.02 | 92.21±15.25 |
| | T2 | 108.37±38.38 | 111.36±21.15 | 40.72±13.42 |
| Control group | T0 | 228.55±60.18 | 233.59±55.83 | 91.74±24.17 |
| | T1 | 291.28±53.08 | 261.34±33.23 | 105.38±16.22 |
| | T2 | 132.06±8.26 | 132.5±23.61 | 64.26±14.17 |

Compared with T0, $P<0.05$; compared with T1, $P<0.05$; compared with the control group at the same time, $P<0.05$. 

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a Rho (serine/threonine) protein kinase inhibitor. Fasudil dilates blood vessels primarily by increasing the activity of myosin light chain phosphatase, to inhibit vasospasm, improve brain microcirculation and protect ischemic brain tissue, thereby improving the prognosis[10,11]. There is no report on fasudil improve the mechanism of stress response at home and abroad, the reason may be related to the drug in the early stage of the brain trauma can quickly relieve cerebral vasospasm, promote rapid recovery of blood supply of brain tissue and brain cell metabolism[12–17]. Xing reports that fasudil inhibits Rho kinase, can increase the production of NO, which has a protective role in brain injury[18]. In addition, domestic animal studies show that fasudil antagonistic Rho kinase is helpful to improve the stability of the cell membrane, increase the expression of Nogo myelin related protein and NF200 in brain tissue and improve the stability of the cell membrane, increase the expression of Nogo myelin related protein and NF200 in brain tissue and thereby reducing the release of inflammatory mediators, thereby reducing inflammatory reaction, at the same time, it also plays an important role in inhibiting proteolysis and apoptosis[19–22].

In conclusion, fasudil injection can effectively reduce the stress response of patients with brain trauma surgery, control the level of inflammatory factors, and it is worthy of clinical application.

References


