Int J Clin Exp Med 2020;13(5):3736-3744
www.ijcem.com /ISSN:1940-5901/IJCEM0107361

Original Article

Analysis of high risk factors of secondary infection after ventricle drainage and their correlation with changes of NSE, LDH and ADA levels in cerebrospinal fluid

Weijun Wu, Yirong Yuan, Yuan Hu, Zhigen Len, Wenxing Liu, Jianxiong He, Bohe Li

Department of Neurosurgery, Yichun People's Hospital, Yichun, Jiangxi, China

Received January 4, 2020; Accepted April 2, 2020; Epub May 15, 2020; Published May 30, 2020

Abstract: Objective: To explore high risk factors of secondary infection after ventricle drainage and their correlation with changes of neuron specific enolase (NSE), lactate dehydrogenase (LDH) and adenosine deaminase (ADA) levels in cerebrospinal fluid (CSF). Methods: Sixty patients with traumatic brain injury (TBI) or intracerebral hemorrhage (ICH) who received ventricle drainage in our hospital from January 2017 to February 2019 were selected and divided into a normal group (n=28) and an infection group (n=32) according to the postoperative intracranial infection. Forward selection and backward selection were employed to all variables of high risk factors of infection, and then stepwise regression was conducted. Afterwards, related risk factors that may bring about postoperative infection were first analyzed by the univariate Logistic regression to select important variables, and major independent risk factors were selected through a multivariate logistic regression model. CSF was sampled from patients in the two groups, and the NSE, LDH, and ADA in the fluid of the two groups were analyzed. Results: There was no significant difference in general data between the two groups (P>0.05). Univariate analysis revealed that the two groups were largely different in sampling frequency of CSF, catheter retention time, urokinase perfusion, intubation, and subcutaneous tunnel (all P<0.05), and multivariate analysis revealed that sampling frequency of CSF, catheter retention time, urokinase perfusion, intubation, and subcutaneous tunnel were independent risk factors for postoperative infection. The infection group showed significantly higher NSE, LDH, and ADA levels than the normal group (all P<0.05). Elevated levels of NSE, LDH and ADA in CSF may be associated with secondary infection after ventricular external drainage (P<0.05). Conclusion: Sampling frequency of CSF, catheter retention time, urokinase perfusion, intubation, and subcutaneous tunnel are independent risk factors for postoperative infection, and the NSE, LDH and ADA levels in CSF of infected patients are increased.

Keywords: Ventricle drainage, secondary infection, high risk factor analysis, cerebrospinal fluid, NSE, LDH, ADA

Introduction

Traumatic brain injury is a complex pathological change with an abnormal energy metabolism, which generates and intensifies microcirculation disturbance in the body without limitation. With the increase of free radicals, energy metabolism and microcirculation dysfunction, brain tissue will show necrosis and degeneration of various degrees [1]. With extremely high incidence and morbidity, traumatic brain injury usually makes survivors suffer from severe limb dysfunction and compromised living and recovery ability and life quality [2]. Ventricle drainage is commonly regarded as one of the most common and important life-saving procedures in the neurological intensive care unit (ICU), and it may be beneficial to many acquired brain injuries, such as intracranial hemorrhagea accompanied by ventricular dilation, subarachnoid hemorrhage, traumatic brain injury, and bacterial meningitis [3]. Some studies concluded that monitoring of intracranial pressure was crucial to the treatment of severe brain injury, and ventricle drainage could control the intracranial pressure through cerebrospinal fluid (CSF) drainage [4, 5]. Moreover, the use and management of ventricle drainage is crucial, which may affect the long-term outcome of patients and the incidence of ventriculitis and cerebral ischemia delay in the patients. Therefore, ventriculoperitoneal shunting, intensive care unit, and hospitalization time are required [6]. Ventricle drainage is prone to cause infec-

tion. Ventricular drainage infection is a very common complication, with incidence of 36.2% among patients [7]. It is prone to cause prolonged hospitalization and intensive care stay, and may also bring about financial and econimic impacts [8]. Although various prevention strategies have been adopted to reduce infection, most patients may still be infected [9]. This study aimed to explore the risk factors related to ventricular drainage infection to prevent infection.

Materials and methods

General data

A total of 60 patients with traumatic brain injury (TBI) or intracerebral hemorrhage who received ventricle drainage in our hospital from January 2017 to February 2019 were enrolled, and divided into a normal group (n=28) and an infection group (n=32) according to the postoperative intracranial infection. The normal group consisted of 17 males and 11 females with average height of 166.37±5.29 cm, including 10 patients younger than 25 years and 18 patients equal to 25 years or older, 16 patients with body mass index (BMI) lower than 22 kg/m^2 and 12 patients with BMI equal to 22 kg/m^2 or higher, while the infection group consisted of 23 males and 9 females with an average height of 167.48±5.25 cm, including 15 patients younger than 25 years and 17 patients equal to 25 years or older, and 18 patients with BMI lower than 22 kg/m^2 and 14 patients with BMI equal to ≥22 kg/m^2 or higher.

Exclusion and inclusion criteria

The inclusion criteria of the patients were as follows: Patients confirmed with traumatic brain injury and those with detailed clinical data [10]. The patients and their family members signed informed consent forms after understanding the study, and the study was carried out under the permission of the Ethics Committee of Yichun People's Hospital.

The exclusion criteria of the patients were as follows: Patients with severe hematologic diseases, immune diseases, or severe infectious diseases; patients with hepatic or kidney function obstacle; patients comorbid with other severe major diseases; patients with psychosis; and patients allergic to drugs during treatment.

Treatment methods

Before operation, the hair of the patient was removed, and he/she was fasted. Then the brain part far away from the brain lesion site of the patient was selected as the puncture point, anesthetized, disinfected, and cut by a scalpel. The skull was punctured using a sleeve-type skull drill with a sleeve, and the drill was pulled out, leaving the sleeve in it. Subsequently, a drainage tube was inserted, and fixed at the site 10-15 cm above the ventricle. The sleeve was pulled out and connected with a sterile drainage bottle. Antibiotics were properly administered throughout the perioperative period to prevent infection, and staff were arranged to observe the basic information such as intracranial pressure, control drainage flow, and the color of the drainage flow.

Observation indices

Aseptic lumbar puncture was carried out on patients in the two groups as follows: 1.5 ml of CSF was sampled routinely, and it was centrifuged by a centrifuge (MicroSep Biotechnology Co. Ltd.) at 10 g and 4°C for 15 min to take the supernatant after being sampled, and stored in a refrigerator at -20°C for later determination of neuron specific enolase (NSE), lactate dehydrogenase (LDH), and adenosine deaminase (ADA). The NSE level was determined using an enzyme-linked immuno sorbent assay (ELISA) kit (Suzhou Elisa Biotechnology Co., Ltd.), and the LDH level was measured through agarose gel electrophoresis. The ADA level was analyzed using the continuous monitoring method of adenosine deaminase coupled with glutamate dehydrogenase reaction. The instrument was a full-automatic biochemistry analyzer (Beijing Sike Nuosi Biotechnology Co., Ltd.), and ADA antibody was purchased from Wuhan Fine Biotech Co., Ltd.

Statistical analysis

In this study, the data were analyzed statistically using SPSS 21.0 (SPSS, Inc., Chicago, Illinois, United States). Measurement data were expressed as the mean ± standard deviation (x±sd), and comparison of the data between groups was carried out using the t test. Enumeration data were expressed as the number of cases/percentage [n (%)], and comparison of the data between groups was conducted by the chi-square test. Forward selection and

backward selection were employed to all variables of high risk factors of infection, and then stepwise regression was adopted. Afterwards, related risk factors that may bring about postoperative infection were first analyzed by univariate Logistic regression to select important variables, and major independent risk factors were selected through a multivariate logistic regression model. P<0.05 indicated a significant difference.

Results

Univariate analysis of risk factors related to postoperative infection

There was no significant difference between the two groups in sex, age, BMI, height, nationality, marital status, place of residence, education background, diabetes mellitus history, hypertension history, smoking history, drinking history, Glasgow coma score (GCS) at admission, combination treatment with craniotomy, the number of catheters left in the body, use of antibiotics during perioperative period, hospitalization time in intensive care unit, total hospitalization time, other comorbid system infections, frequency of dressing change for incision, and postoperative albumin content (All *P*>0.05), while there were great differences between them in sampling frequency of CSF, catheter retention time, urokinase perfusion, intubation, and subcutaneous tunnel (All *P*<0.05) (**Table 1**).

Multivariate analysis of risk factors of postoperative infection

Multivariate logistic regression was carried out to risk factors related to postoperative infection, and it came out that sampling frequency of CSF, catheter retention time, urokinase perfusion, intubation, and subcutaneous tunnel were independent risk factors for postoperative infection (**Tables 2** and **3**).

Comparison of NSE, LDH and ADA levels between the two groups

The NSE level in the infection group was significantly higher than that in the normal group (14.43±2.13 μg/L vs. 5.24±1.47 μg/L, *P*<0.05) (**Figure 1**). The LDH level in the infection group was significantly higher than that in the normal group (25.54±2.65 U/L vs. 17.35±1.58 U/L, *P*<0.05) (**Figure 2**). The ADA level in the infection group was also significantly higher than that in the normal group (4.25±1.32 IU/L vs. 2.57±2.78 IU/L, *P*<0.05) (**Figure 3**).

Relationship between NSE, LDH, and ADA levels in CSF and secondary infection after ventricular external drainage

Elevated levels of NSE, LDH and ADA in CSF may be associated with secondary infection after ventricular external drainage (P<0.05), as shown in **Tables 4**-**6**.

Discussion

In this study, we selected 60 patients with traumatic brain injury who received ventricle drainage in our hospital, and divided them into an infection group and a normal group according to their postoperative infection. First of all, we carried out univariate analysis and multivariate analysis on relevant factors that may cause secondary infection after ventricular drainage, finding that the sampling frequency of CSF, catheter retention time, urokinase perfusion, intubation, and subcutaneous tunnel could be adopted as independent risk factors for ventricular drainage infection. Some related studies also pointed out that the high infection rate related to ventricle drainage may be linked to CSF drainage time and frequent CSF sampling [11]. The results of this study showed that the use of urokinase in operation would increase the risk of infection, and the absent of subcutaneous tunnel would also increase the risk. One similar study regarded the intraventricular instillation of urokinase as a risk factor for infection, and concluded that extended subcutaneous tunnel technology would not affect the daily risk of infection [12]. Moreover, one study pointed out that urokinase may be a new inflammatory biomarker, and its elevated level may also be related to the increased risk of cardiovascular diseases [13]. Therefore, we suspected that the infusion of urokinase during treatment would increase the risk of infection when the infusion increased the level of urokinase to a level above the critical value. Therefore, it is suggested that appropriate dosage should be selected during treatment. One study found that catheter-related infection was also an important complication of ventricle drainage, and the relationship between detention time of inserted catheter and infection rate was the

Table 1. General data of the patients [n (%)] ($\bar{x} \pm sd$)

Group	The infection group (n=32)	The normal group (n=28)	χ^2/t value	*P*-value
Sex			0.837	0.360
Male	23 (71.87)	17 (60.71)		
Female	9 (28.13)	11 (39.29)		
Age (Y)			0.765	0.381
<25	15 (46.87)	10 (35.71)		
≥25	17 (53.13)	18 (64.29)		
BMI (kg/m^2)			0.004	0.944
<22	18 (56.25)	16 (57.14)		
≥22	14 (43.75)	12 (42.86)		
Height (cm)	167.48±5.25	166.37±5.29	0.814	0.418
Nationality			0.820	0.365
Han nationality	27 (84.38)	21 (75.00)		
Minority nationality	5 (15.62)	7 (25.00)		
Marital status			0.051	0.821
Married	22 (68.75)	20 (71.43)		
Unmarried	10 (31.25)	8 (28.57)		
Place of residence			0.001	0.966
Urban area	25 (78.13)	22 (78.57)		
Rural area	7 (21.87)	6 (21.43)		
Education background			0.357	0.550
≥ Senior high school	23 (71.88)	22 (78.57)		
< Senior high school	9 (28.12)	6 (21.43)		
Diabetes mellitus history			0.030	0.861
Yes	13 (40.63)	12 (42.86)		
No	19 (59.37)	16 (57.14)		
Hypertension history			0.033	0.854
Yes	11 (34.38)	9 (32.14)		
No	21 (65.62)	19 (67.86)		
Smoking history			0.150	0.697
Yes	25 (78.13)	23 (82.14)		
No	7 (21.87)	5 (17.86)		
Drinking history			1.006	0.315
Yes	19 (59.38)	13 (46.43)		
No	13 (40.62)	15 (53.57)		

Table 2. Main study factors and variable assignment

Study factors	Assignment description
Sampling frequency of CSF	<3 times/week =0; ≥3 times/week =1
Catheter retention time	<7 d=0; ≥7 d=1
Urokinase perfusion	No =0; Yes =1
Intubation	Unilateral =0; Bilateral =1
Subcutaneous tunnel	Yes =0, No =1

strongest, so it was suggested that drainage should be removed as early as possible during the operation [14]. Furthermore, one other study revealed that the risk of CSF infection could not be reduced by replacing the catheter regularly every five days, and it indicated that unilateral ventricle drainage could be adopted [15]. We found that most of the factors related to the catheter may cause infection, and speculated that bacteria would invade during the use of catheter. One study revealed that detention time of inserted catheter would increase the infection rate, and gram-negative

Table 3. Multivariate logistic analysis of risk factors of postoperative infection

Factor	β	SE	Wald	*P*-value	Exp (β)	95% CI
Sampling frequency of CSF	1.486	0.533	10.343	<0.001	3.134	2.464-5.264
Catheter retention time	1.902	0.697	6.375	0.005	2.365	1.342-3.574
Urokinase perfusion	1.214	2.892	6.596	0.016	2.769	1.363-5.257
Intubation	0.175	5.688	6.132	0.025	1.248	1.024-1.965
Subcutaneous tunnel	0.613	0.315	8.713	<0.001	1.864	1.224-3.147

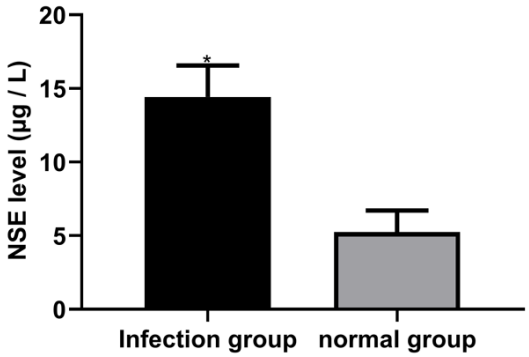

Figure 1. Comparison of NSE level between the two groups. The results showed that the NSE level in the infection group was significantly higher than that in the normal group (*P*<0.05). Note: *indicates that in comparison with the normal group, P<0.05.

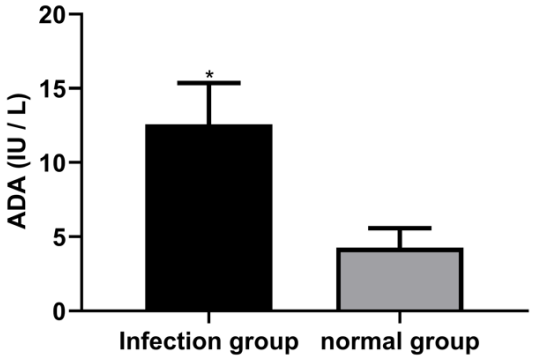

Figure 3. Comparison of ADA level between the two groups. The results showed that the ADA level in the infection group was significantly higher than that in the normal group (*P*<0.05). Note: *indicates that in comparison with the normal group, P<0.05.

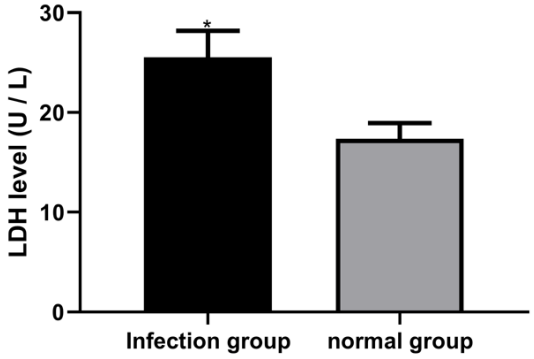

Figure 2. Comparison of LDH level between the two groups. The results showed that the LDH level in the infection group was significantly higher than that in the normal group (*P*<0.05). Note: *indicates that in comparison with the normal group, P<0.05.

microorganism was the most common pathogen [16], and one other study concluded that bacterial invasion during drainage tube insertion may be related to ventricular drainage infection [17]. Based on the above, it can be concluded that we can control catheter-related variables to reduce the infection rate, such as shortening the detention time of inserted catheter or reducing the number of catheters used, and high sampling frequency of CSF, long catheter retention time, application of urokinase perfusion, and bilateral ventricular drainage may all be risk factors for high infection rate.

CSF examination plays a certain role in the diagnosis of infection in severe diseases [18], so we have tested and compared relevant indices in this study. NSE is a neuronal form of glycolytic enzyme enolase, first discovered in brain tissue extract [19], and is also one of biochemical markers in CSF [20]. LDH is a tetramer enzyme with certain value in determining destructive neuropathy [21, 22]. ADA is an important enzyme in purine metabolism [23], and it, as a marker of cellular immunity, is found to have increased activity in diseases contributing to dial-down mediated immune responses [24]. In this study, we found that the NSE, LDH, and ADA levels in CSF of the infection group were significantly higher than those of the normal group, which implied that the levels of NSE, LDH and ADA are increased during postoperative infection. Moreover, one study revealed that the NSE level in the CSF of patients with bacterial meningitis was significantly higher than that of patients with other central nervous

Table 4. Relationship between NSE and secondary infection after external ventricular drainage

	Case	NSE level		χ^2	*P* value
		Low	High		
Sex				1.758	0.184
Male	40	17 (42.50)	23 (57.50)		
Female	20	5 (25.00)	15 (75.00)		
Age (years)				0.155	0.693
<25	25	13 (52.00)	12 (48.00)		
≥25	35	20 (57.14)	15 (42.86)		
BMI (kg/m^2)				0.938	0.332
<22	34	16 (47.06)	18 (52.94)		
≥22	26	9 (34.62)	17 (65.38)		
CSF sampling frequency				16.061	<0.001
<3 times/week	36	25 (69.44)	11 (30.56)		
≥3 times/week	24	4 (16.67)	20 (83.33)		
Catheter retention time				34.571	<0.001
<7 d	24	21 (87.50)	3 (12.50)		
≥7 d	36	4 (11.11)	32 (88.89)		
Urokinase perfusion				16.291	<0.001
Yes	38	29 (76.32)	9 (23.68)		
No	22	5 (22.73)	17 (77.27)		
Intubation				13.031	0.000
Unilateral	27	20 (74.07)	7 (25.93)		
Bilateral	33	9 (27.27)	24 (72.73)		
Subcutaneous tunnel				12.701	0.000
Yes	21	16 (76.19)	5 (23.81)		
No	39	11 (28.21)	28 (71.79)		

Table 5. Relationship between LDH and secondary infection after external ventricular drainage

	Case	LDH level		χ^2	*P* value
		Low	High		
Sex				0.034	0.853
Male	40	23 (57.50)	17 (42.50)		
Female	20	12 (60.00)	8 (40.00)		
Age (years)				0.230	0.631
<25	25	12 (48.00)	13 (52.00)		
≥25	35	19 (54.29)	16 (45.71)		
BMI (kg/m^2)				1.451	0.228
<22	34	21 (61.76)	13 (38.24)		
≥22	26	12 (46.15)	14 (53.85)		
CSF sampling frequency				11.391	0.000
<3 times/week	36	25 (69.44)	11 (30.56)		
≥3 times/week	24	6 (25.00)	18 (75.00)		
Catheter retention time				10.001	0.001
<7 d	24	18 (75.00)	6 (25.00)		
≥7 d	36	12 (33.33)	24 (66.67)		
Urokinase perfusion				9.408	0.002
Yes	38	29 (76.32)	9 (23.68)		
No	22	8 (36.36)	14 (63.64)		

Intubation				14.621	0.000
Unilateral	27	17 (62.96)	10 (37.04)		
Bilateral	33	5 (15.15)	28 (84.85)		
Subcutaneous tunnel				14.201	0.000
Yes	21	16 (76.19)	5 (23.81)		
No	39	10 (25.64)	29 (74.36)		

Table 6. Relationship between ADA and secondary infection after external ventricular drainage

	Case	ADA level		χ^2	*P* value
		Low	High		
Sex				3.394	0.065
Male	40	26 (65.00)	14 (35.00)		
Female	20	8 (40.00)	12 (60.00)		
Age (years)				3.126	0.077
<25	25	15 (60.00)	10 (40.00)		
≥25	35	17 (48.57)	18 (51.43)		
BMI (kg/m^2)				1.827	0.176
<22	34	22 (64.71)	12 (35.29)		
≥22	26	11 (42.31)	15 (57.69)		
CSF sampling frequency				12.321	0.000
<3 times/week	36	27 (75.00)	9 (25.00)		
≥3 times/week	24	7 (29.17)	17 (70.83)		
Catheter retention time				10.001	0.001
<7 d	24	18 (75.00)	6 (25.00)		
≥7 d	36	12 (33.33)	24 (66.67)		
Urokinase perfusion				16.811	<0.001
Yes	38	32 (84.21)	6 (15.79)		
No	22	7 (31.82)	15 (68.18)		
Intubation				16.261	<0.001
Unilateral	27	23 (85.19)	4 (14.81)		
Bilateral	33	11 (33.33)	22 (66.67)		
Subcutaneous tunnel				6.128	0.013
Yes	21	14 (66.67)	7 (33.33)		
No	39	13 (33.33)	26 (66.67)		

system disease, and it concluded that the further increase of NSE level in CSF may give rise to complications or sequelae of the central nervous system [25]. One other study also pointed out that NSE could affect neuron damage, and ventricle drainage could lead to a significant increase in CSF concentration [26]. Furthermore, there was a study indicating that the activity of LDH was significantly increased in patients with meningeal diffusion caused by bacterial meningitis, solid tumors or hematological malignancies [27], and there was also a study stating that determination of LDH in CSF was a useful auxiliary method for determination of other CSF parameters in diagnosis of central nervous system infection [28]. Those studies all implied that the NSE, LDH, and ADA levels in CSF of patients with ventricular drainage infection are increased significantly, and they had diagnostic value. In addition, we found that the increased levels of NSE, LDH and ADA in CSF may be closely related to the secondary infection after ventricular external drainage, suggesting that the levels of NSE, LDH and ADA may be important monitoring indicators in ventricular external drainage, which can provide important information for the timely detection of secondary infection.

However, there are still some deficiencies in this study. For example, we have not studied the prognosis of the patients, and we have also not explored the prognostic values of NSE, LDH, and ADA in ventricle drainage infection. We will address those shortcomings in the future and update our conclusion.

To sum up, high sampling frequency of CSF, long catheter retention time, application of urokinase perfusion, and bilateral ventricular drainage may all be risk factors for high infection rate of ventricle drainage, and the NSE, LDH, and ADA levels in CSF of infection patients are increased.

Disclosure of conflict of interest

None.

Address correspondence to: Bohe Li, Department of Neurosurgery, Yichun People's Hospital, No. 1061, Jinxiu Avenue, Yiyang New District, Yichun 336600, Jiangxi, China. Tel: +86-13807959754; E-mail: tt3l8i@163.com

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