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Analysis of changes in the volume of edema around brain contusions and the influencing factors

A single-center, retrospective, observational study

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Abstract

Traumatic brain injury (TBI), a common neurosurgical condition, has well-known treatment guidelines. However, the mechanisms underlying the varying severity of brain edema secondary to TBI are largely unknown, leading to controversial treatments.

This study seeks to measure edema volumes around brain contusions in different regions, analyze factors related to differences in edema volume and provide a theoretical basis for brain edema treatment.

Data from 113 brain contusion patients treated at the Department of Neurosurgery of Fuzhou General Hospital from January 2017 to November 2019 were analyzed retrospectively. Based on computed tomography (CT) data, the patients were divided into the venous group (brain contusion in regions with large cortical veins, n = 47) and the nonvenous group (brain contusions in other regions, n = 66). Here, 3D Slicer software was used to calculate the brain contusion volume on the first CT obtained after injury and the brain contusion volume and its surrounding edema on the 5th day after injury. The brain contusion volume to surrounding edema volume ratio was calculated, and the number of patients who showed brain contusion progression requiring surgery was determined. Hematocrit (Hct), fibrinogen (Fg), and D-dimer levels within 6 hours and on the 5th day after admission were also compared.

Patients in the venous group had a significantly increased percentage of area with edema around the brain contusion compared with patients in the nonvenous group ($P < .05$), and the 2 groups showed no significant difference in the number of patients with brain contusion progression or surgical treatment ($P > .05$) or Hct, Fg, or D-dimer (D-D) levels. For all patients, Hct, Fg, and D-D levels within 6 hours after admission were significantly different from those on the 5th day ($P < .05$ for all).

Cortical venous obstruction may be the most important factor influencing edema around brain contusions. The Fg level decreased slightly, and the D-D level increased to its peak rapidly after mild-moderate TBI. This change was followed by a gradual increase in the former and a gradual decrease in the latter.

Abbreviations: BBB = blood-brain barrier, CT = computed tomography, CTV = computed tomography venography, D-D = D-dimer, Fg = fibrinogen, GCS = Glasgow Coma Scale, Hct = hematocrit, HPC = Hemorrhagic progression of contusions, TBI = traumatic brain injury.

Keywords: 3D slicer software, angiogenesis, brain contusion, brain edema volume, D-dimer, fibrinogen, venous return

1. Introduction

According to the World Health Organization, traumatic brain injury (TBI) will be the leading cause of death and disability in children and young adults by 2020. Traumatic brain contusion, which is also known as traumatic intraparenchymal hemorrhage, is a type of TBI that can cause lifelong cognitive disorder and both physical and mental disability.[1] Traumatic intraparenchymal hemorrhage results from direct and indirect mechanisms. The

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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indirect or secondary injury involves the initiation of an acute inflammatory response, including blood–brain barrier (BBB) destruction, brain edema, peripheral blood cell infiltration, innate immunoreactive cell activation, massive immune mediator (eg, interleukin and chemokine) release, and immune cell exudation.[2] Brain edema and increased intracranial pressure are correlated with poor prognosis in TBI. Brain edema is the main cause of inpatient death, and its potential mechanisms vary greatly due to the nature of the primary injury (eg, etiology, speed, strength, severity, and bleeding pattern), patient characteristics (eg, age, sex, heredity, and comorbidities), and other accompanying conditions (eg, hypoxia, hypotension, hyperpyrexia, and epilepsy).[3,4] Brain edema is divided into 3 categories: osmotic, vasogenic, and cytotoxic. Different categories of edema can occur simultaneously. In hours to days after TBI, various signaling molecules and metabolic disorders can block the BBB and induce brain edema. In the early stage of TBI, vasogenic and cytotoxic brain edema are the most common, and changes in brain edema depend on the injury mechanism, the elapsed time, the molecular processes involved, intracranial injury patterns, and individual differences. Although these differences provide a basis for the development and management of targeted therapy, the pathophysiological mechanisms of brain edema remain unclear.[5,6] Brain microcirculation dysfunction is a major pathophysiological change after TBI that has been universally recognized as the main link to secondary injuries, such as brain edema, as well as an important factor affecting neurological functional recovery.[7] Currently, studies on secondary injury and intracranial veins after TBI are very rare. We thus aimed to investigate the severity of edema around brain contusions in different regions and to provide a theoretical basis for treating edema after brain contusion.

2. Materials and methods

2.1. Subjects

A total of 113 patients with TBI were selected from the Department of Neurosurgery of Fuzhou General Hospital from January 2017 to November 2019, including 67 males and 46 females with an average age of 43.08 ± 12.88 years. The injury mechanism included traffic accidents (n = 75), crashes (n = 25), high falls (n = 10), and crushing (n = 3). The site of the brain contusion included the lateral fissure vein (n = 16), Labbé vein (n = 25), Trolard vein (n = 6), frontal lobe (n = 32), occipital lobe (n = 17), cerebellum (n = 3), and white matter (n = 14). The inclusion criteria were as follows: (1) Glasgow Coma Scale (GCS) score of 10 to 15 on admission; (2) head trauma history and local brain contusion confirmed by brain computed tomography (CT) on admission with a contusion diameter in gray and white matter of greater than 1 cm; (3) relationship between brain contusion and cortical veins confirmed by brain CT venography or magnetic resonance imaging; and (4) stable vital signs and age from 16 to 60 years old. The exclusion criteria were as follows: (1) apparent surgical indications[8]; (2) depressed fractures affecting venous return; (3) history of cerebrovascular disease, brain tumor, cerebral hemorrhage, or cerebral infarction; (4) multiple brain contusions, multiple injuries, or combined injury; (5) severe heart, lung or kidney disease or hematological disease; (6) long-term use of anticoagulant or antiplatelet drugs; (7) history of TBI or craniocerebral surgery; and (8) incomplete data. This study was conducted according to the principles expressed in the Declaration of Helsinki (www.wma.net/en/30publications/10policies/b3/index.html) and was approved by the Ethics Committee of Fuzhou General Hospital.

Patients were excluded from the comparison of data within 6 hours and on the 5th day if (1) they showed brain contusion progression with surgical indications and underwent surgery, (2) they developed persistent hyponatremia during the treatment period, or (3) they had incident conditions that met the exclusion criteria.

2.2. Methods

The clinical and imaging data (including GCS score, age, sex, trauma type, images, and hematocrit (Hct), fibrinogen (Fg), and D-dimer (D-D) levels) on admission were collected retrospectively. Forty-seven patients with brain contusions in regions with large cortical veins (including the lateral fissure vein, Labbé vein, and Trolard vein) were selected as the venous group, and 66 patients with brain contusions in other regions were selected as the nonvenous group. After admission, patients were required to have absolute bed rest with the head of the bed raised 30°. Mannitol was administered for dehydration along with analgesia and other symptomatic treatments. Routes of defecation and urination were kept unobstructed, and changes in the patient's consciousness and pupils were closely observed. Brain CT (Dutch Philips Brilliance 256-slice spiral CT) images were reexamined at the 6th hour, 1st day, 3rd day, and 5th day after admission if no notable changes were observed in the patient's consciousness or pupils. The brain CT data were imported into 3D Slicer software to calculate the volume of brain contusion and edema. In addition, Hct, Fg, and D-D levels within 6 hours and on the 5th day after injury were recorded, and these indexes were not analyzed if brain contusion progression with surgical indications occurred.

Software operation, instruments, and reagents: here, 3D Slicer software, which serves as a medical image processor and 3D visualization open-source software, was used to measure the volume of the brain contusion and hematoma and the surrounding brain edema. The main steps were as follows: (1) import the patient's original CT images in DICOM format; (2) run the Editor module and select the appropriate threshold range (50–100 HU and 20–33 HU) under the 2-dimensional window to completely color the brain contusion and hematoma as well as the surrounding brain edema, and then automatically identify and mark the brain contusion and hematoma and the surrounding brain edema (Figs. 1 and 2). Other equipment included a BC-5500 automatic hematology analyzer from Shenzhen Mindray Company, a CA-7000 automatic coagulation analyzer (Sysmex, Japan), and D-D assay kits, calibrators, and control materials from Siemens Healthcare Diagnostics INNOVANCE@D-dimer. Patients' venous blood samples were tested within 2 hours, and all operations were performed strictly according to the operating instructions of the reagent and instrument.

2.3. Statistical analysis

SPSS 23.0 software was used for statistical analysis. Measurement data are expressed as $x \pm s$. The t test was used to compare the means of 2 groups in a completely random design; categorical variables are expressed as percentages. The χ^2 test was used to perform comparisons between groups. $P < .05$ was considered statistically significant.

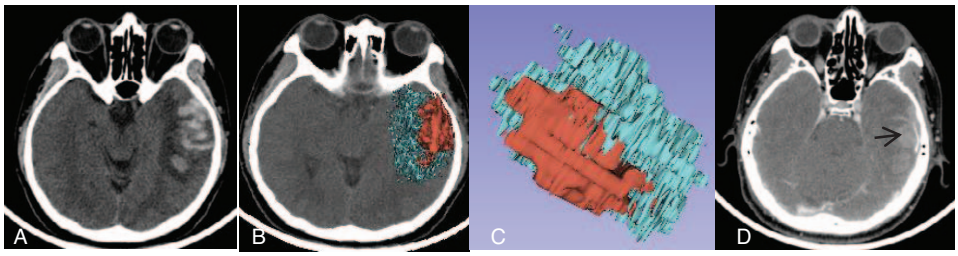

Figure 1. 3D Slicer software reconstruction of the volume of a brain contusion and the surrounding edema in a patient in the venous group. A. Brain contusion in the left Labbé vein. B. Coloring of the brain contusion and surrounding edema. C. 3D reconstruction produced by 3D Slicer software. D. CTV showing the Labbé vein (black arrow) located in the brain contusion. CTV = computed tomography venography.

3. Results

3.1. General data

A total of 113 patients were included. The 47 patients in the venous group (29 males and 18 females) had an average age of 43.17 ± 12.97 years; the 66 patients in the nonvenous group (40 males and 26 females) had an average age of 43.02 ± 12.92 years (Table 1).

3.2. Edema around brain contusions

Here, 3D Slicer software was used to calculate the volume of the brain contusion and hematoma and the surrounding brain edema (Figs. 1 and 2). Within 6 hours after injury, the GCS score, brain contusion, and hematoma volume, and Hct, Fg, and D-D levels showed no significant differences (Table 1). On the 5th day after the injury, the volume of the surrounding brain edema in the venous group was greater than that in the nonvenous group ($P = .002$, Table 2), and no differences in Hct, Fg, or D-D levels were noted between the 2 groups (Table 2). Fg and D-D levels within 6 hours after injury were significantly different from those on the 5th day, whereas Hct levels showed no significant differences (Table 3).

3.3. Cases of progression

The number of cases of progression in the venous group and the nonvenous group was 12 (25.53%) and 15 (22.73%), respectively, and the number of cases with surgical indications in the 2 groups was 7 (14.89%) and 11 (16.67%), respectively. The difference was not statistically significant ($P > .05$) (Table 2).

4. Discussion

Brain edema and intracranial hypertension are the main causes of death and disability in TBI. In the short term after TBI, the parenchyma cells of the central nervous system are activated, and injured brain tissue further releases bradykinin, fatty acids, free radicals, 5-hydroxytryptamine, prostaglandin, and nitric oxide to mediate opening of the BBB, leading to increased vascular permeability, the exudation of macromolecular substances from vessels, and finally vasogenic edema.[9] This type of edema is mainly characterized as the interstitial edema of brain tissue, which is often accompanied by cerebral infarction. Progressive brain edema increases the brain capacity and intracranial pressure and decreases cerebral blood flow. Veenith et al[10] used O15- and 18-FFMISO-labeled positron emission tomography-CT to observe the ischemic brain capacity and hypoxic brain capacity of normal subjects and patients with TBI, respectively. The results showed that patients with TBI exhibited an increased oxygen diffusion gradient in the anoxic brain tissue, indicating that under the condition of normal macrovascular blood flow, cerebral hypoxia after TBI results from microvascular ischemia, which is correlated with extensive microvascular collapse, perivascular edema, and microthrombosis after injury. The extent of edema in the venous group was significantly greater than that in the nonvenous group, indicating that venous obstruction may be an essential factor involved in the severity of local brain edema after TBI. Additionally, numerous studies have demonstrated that angiogenesis may contribute to recovery after stroke, TBI, and spinal cord injury.[11] Angiogenesis refers to the process of new blood vessels forming through blastogenesis based on the original blood vessels. Adults generally have extremely stable vasculature in the central nervous system under physio-

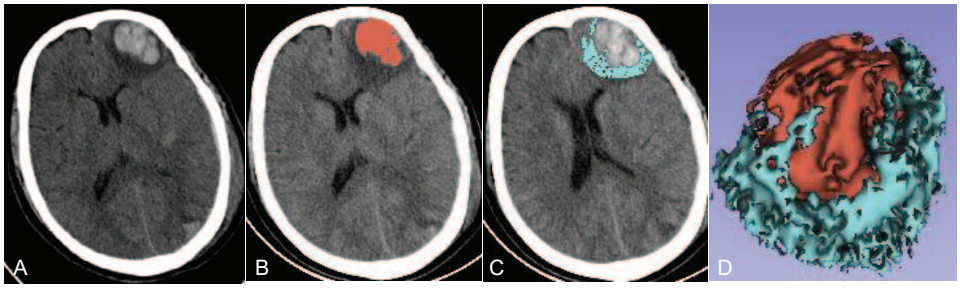

Figure 2. 3D Slicer reconstruction of the volume of the left frontal lobe contusion and the surrounding edema in a patient in the nonvenous group. A. Left frontal lobe contusion with intracerebral hematoma. B. Reconstruction and coloring of the hematoma in dark red. C. Reconstruction and coloring of the surrounding edema in blue. D. 3D reconstruction of the hematoma and edema.

Table 1

Clinical patient data from both groups.

Clinical data	Venous group	Nonvenous group	t/χ^2	P
Sex (male/female, n)	29/18	40/26	0.14	.91
Age (years)	43.17 ± 12.97	43.02 ± 12.92	0.63	.95
GCS score within 6 hours after injury	12.28 ± 1.67	12.62 ± 1.60	−1.11	.27
Brain contusion volume on first CT after injury (mL)	7.54 ± 3.29	8.8 ± 4.28	−1.69	.09
Hct (40%–50%)	37.6 ± 4.15	37.51 ± 3.52	0.12	.91
Fg (2–4 g/L)	2.7 ± 0.79	2.69 ± 0.68	0.11	.91
D-D (<0.5 mg/L)	4.83 ± 2.52	5.07 ± 2.4	−0.51	.72

CT = computed tomography, D-D = D-dimer, Fg = fibrinogen, GCS = Glasgow Coma Scale, Hct = hematocrit.

Table 2

Clinical patient data from both groups on the 5th day after injury.

Clinical data	Venous group	Nonvenous group	t/χ^2	P
Patients with progression (n)	12 (47)	15 (66)	0.12	.73
Patients who underwent surgery due to progression (n)	7 (47)	11 (66)	0.06	.80
GCS score on the 5th day after injury	12.38 ± 1.73	12.73 ± 1.55	−1.11	.27
Brain contusion volume (mL)	8.38 ± 3.65	9.21 ± 4.08	−1.12	.27
Surrounding edema volume (mL)	16.62 ± 6.55	14.09 ± 5.36	2.25	.03
Edema/contusion (%)	73.64 ± 5.25	59.5 ± 10.91	3.69	.002
Hct	37.67 ± 3.38	37.83 ± 3.04	−0.27	.79
Fg	4.28 ± 1.21	4.2 ± 1.09	0.35	.73
D-D	3.79 ± 1.7	4.26 ± 1.47	−1.58	.87

D-D = D-dimer, Fg = fibrinogen, GCS = Glasgow Coma Scale, Hct = hematocrit.

logical conditions. However, when affected by external factors, such as brain trauma, angiogenesis appears to be extremely active.[12,13] Vascular remodeling in adults consists of angiogenesis mediated by mature endothelial cells and endothelial progenitor cells. Angiogenesis may play a vital role in functional recovery after TBI,[14,15] which further confirms that venous obstruction intensely affects brain edema severity.

Sillesen et al[16] found that in both TBI and cerebral hemorrhage, platelet activation and dysfunction appeared 3 minutes after TBI in a fluid percussion injury model, and the corresponding coagulation and sympathoadrenal and complement responses appeared almost simultaneously. However, endothelial dysfunction, inflammation, and thrombosis occurred successively. The following factors affect microcirculation dysfunction: (1) decreased blood flow in brain microcirculation; (2) microvessel constriction instead of large vessel constriction outside the brain parenchyma; and (3) microthrombosis.[17,18] Stein and Smith[19] found that microthrombosis appeared 2 to 3 hours after TBI and resulted in 60% microvascular occlusion at 24 hours, mostly in the periphery of the ipsilateral trauma area. Therefore, secondary TBI largely consists of changes in the brain microcirculation due to microthrombosis, which has also been confirmed by autopsy.[20] According to the differences in edema between the 2 groups, the extent of edema in the venous group after brain contusion was significantly greater than that in the nonvenous group, which further indicates that venous obstruction is a key factor of brain edema formation. Hct is a determinant of blood viscosity; a higher Hct level indicates a higher blood viscosity, and vice versa.[21,22] Hemorheological studies on TBI have shown that decreased Hct is not considered harmful and can even improve the local microcirculation and optimize hemorheology. However, blood viscosity maintenance may be an essential factor in microvascular perfusion through producing shear stress, maintaining the oxygen supply, and activating compensatory mechanisms. Therefore, Hct can be treated as a laboratory index for evaluating TBI.[23] Hct affects blood viscosity after TBI, which subsequently aggravates secondary brain injury. Studies have shown that Hct differed between patients with mild and severe TBI at different times. Patients with severe TBI showed greater Hct levels than those with mild TBI, and the Hct level significantly negatively correlated with the GCS score over a specific range. All cases in this study consisted of simple TBI, and most of the patients had mild-moderate TBI. Hct minimally changed within 6 hours and on the 5th day after admission, and the change was not statistically significant. The serum Fg level is an important factor affecting blood viscosity. Fg facilitates blood cell aggregation and is an important indicator of increased red blood cell aggregation. Brain tissue contains abundant thrombin, which is massively released into the blood after TBI, stimulating the exogenous coagulation system. Fg conjugates to form fibrin, and the corresponding fibrinolysis is activated to degrade fibrin and maintain a dynamic balance; therefore, the D-D concentration

Table 3

Comparison of indexes in patients from both groups obtained within 6 hours and on the 5th day after injury.

Clinical indexes (n = 95)	Within 6 hours	On the 5th day	F/χ^2	P
Hct	37.67 ± 3.85	37.55 ± 3.28	0.23	.27
Fg	2.66 ± 0.75	4.25 ± 1.21	−10.93	.00
D-D	4.29 ± 2.06	3.83 ± 1.48	1.8	.01

D-D = D-dimer, Fg = fibrinogen, Hct = hematocrit.

increases.[24] D-D is a fibrin degradation product that is produced by the orderly degradation of a blood clot by fibrinolysis. It is a biomarker of fibrin formation and degradation and can be detected in whole blood or plasma. D-D concentrations are very low in healthy individuals but are increased in patients with thrombosis. The D-D level is used in determining the optimal duration of anticoagulant therapy in patients with venous thrombosis. These levels are also used to diagnose and monitor disseminated intravascular coagulation and identify patients at high risk of venous thrombosis.[25] In this study, the Fg level within 6 hours after admission was in the lower limit of normal, and the D-D level significantly increased. On the 5th day, the Fg level was slightly greater than the normal value, and the D-D level was significantly less than that within 6 hours after admission, which is consistent with the patterns of coagulation in mild-to-moderate TBI.[26]

Hemorrhagic progression of contusions (HPC) is an important predictor of adverse outcomes in TBI with an incidence ranging from 18% to 51%. Subarachnoid hemorrhage, subdural hematoma, and skull fracture are the main risk factors. Furthermore, the criteria for defining HPC are controversial. In our study, we defined HPC as an increase of greater than 30% in the lesion volume compared with that on initial CT and an absolute increase of ≥10 mL in the total brain contusion and bleeding volume on CT reexamination.[27] Patients in both groups showed HPC, including 25.53% in the venous group and 22.73% in the nonvenous group, and the difference was not statistically significant. The proportion of HPC cases with the development of surgical indications was 14.89% and 16.67% in the venous and nonvenous groups, respectively.

Our study was a retrospective single-center study with some limitations, such as small sample size and a cohort consisting mainly of mild-moderate TBI cases, which cannot represent severe and severe TBI. Most importantly, it is not possible to accurately measure the degree of venous obstruction in the corresponding area to analyze the association between the degree of edema and venous obstruction.

Prospective multicenter studies with large sample sizes are required to further analyze the key factors of edema around brain contusions.

To conclude, the prognosis of TBI depends on the severity of both the primary injury and secondary injury. Brain edema is an inevitable injury secondary to TBI and is induced by numerous factors; among them, the venous obstruction may be the determinant of brain edema severity.

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