

Original Article

Clinical value of continuous invasive intracranial pressure monitoring with combined hypothermia in the treatment of severe cerebrovascular diseases

Bin Ge¹, Gaolin Wang², Xin Liu¹

¹Department of Neurology, The People's Hospital of Pingyi County, Linyi, Shandong Province, China; ²Department of Neurology, The Second People's Hospital of Liaocheng, Liaocheng, Shandong Province, China

Received June 25, 2018; Accepted August 16, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: Objective: To explore the application effect of continuous invasive intracranial pressure monitoring with combined hypothermia in the treatment of severe cerebrovascular diseases. Methods: A total of 98 patients with severe cerebrovascular diseases admitted to The People's Hospital of Pingyi County from January 2014 to December 2017 were randomly divided into observation group and control group, with 49 cases in each group. Patients in observation group were performed with continuous invasive intracranial pressure monitoring, while the control group was given conventional intermittent intracranial pressure monitoring. Both groups were given routine treatment of severe cerebrovascular diseases, including monitoring of vital signs, fluid infusion to maintain adequate water intake, maintenance of internal environment, stability of respiratory and circulation system. The intracranial pressure, Glasgow Coma Scale (GCS) score, prognosis, complications, serum inflammatory factors IL-8 and IL-6 were observed in the two groups after treatment. Results: The intracranial pressure, levels of IL-6 and IL-8 as well as the mortality and occurrence of complications were all lower in observation group than in control group after treatment (all $P < 0.05$). The GCS scores in observation group were higher than those in control group on the 1st, 3rd, 5th and 7th day of treatment, and the differences were statistically significant at the 5th and 7th day (both $P < 0.05$), also, the favorable recovery rate in observation group was higher than that in control group. Conclusion: Timely and accurate evaluation of condition and better therapeutic effects can be achieved in patients with severe cerebrovascular diseases when treated by combination of hypothermia and continuous invasive intracranial pressure monitoring.

Keywords: Continuous invasive, intracranial pressure monitoring, severe cerebrovascular disease, inflammatory response, prognosis

Introduction

The stenosis and occlusion of the cerebral arterial system caused by various reasons are called cerebral apoplexy, which lead to cerebral ischemia and anoxia (cerebral infarction) or vascular rupture induced cerebral hemorrhage. Both of the above are severe causes of death or disability of patients [1]. Large volume of cerebral hemorrhage in key site (such as the brain stem, cerebellum), cerebral infarction combining with dyskinesia or aphasia, accompanied by or without major organ dysfunction, are named severe cerebrovascular diseases [2]. They can greatly affect patients' health condition, which lead to physical disability or even threat to life. Studies showed that severe cere-

brovascular diseases would lead to 12 million of death and 20 million of disability worldwide in 2030 [3, 4]. The mortality of cerebrovascular diseases in China is increasing year by year, which is the first disease-cause of death of the residents [5, 6]. The treatment of severe cerebrovascular diseases can not only save patients' lives but also to some extent reduce harm of cerebrovascular diseases to human health.

Whether it is ischemic stroke or cerebral hemorrhage, protection of brain cells at the first time is the key for treatment and an important measure for saving patients' lives [7]. Mild hypothermia has been applied for clinical brain protection since 1950s. According to the tem-

Invasive intracranial pressure monitoring with hypothermia treatment

Table 1. Comparison of general information between two groups

Category	Observation group (n=49)	Control group (n=49)	t/X ²	P
Stroke/cerebral hemorrhage	28/21	25/24	0.088	0.767
Gender (male/female)	23/26	27/22	0.367	0.544
Age (year)	68.92±9.44	69.19±9.37	0.106	0.916
Diabetes	16	18	0.0450	0.832
Hypertension	32	34	0.0464	0.829

perature, it is divided into three categories: mild hypothermia, moderate hypothermia and profound hypothermia; mild hypothermia is widely used clinically, that is, the temperature of patients is controlled at 33-35°C through cooling measures, aiming at reducing the energy metabolism of the brain tissues, restricting brain hematoma and edema as well as inhibiting inflammatory response, so as to achieve the purpose of brain protection [8].

Elevated intracranial pressure is a shared tissue change of all kinds of severe cerebrovascular diseases, which can lead to secondary damage of brain tissues. Therefore, it is of important clinical significance to monitor intracranial pressure during treatment [9]. At present, the routine assessment of intracranial pressure is to observe the clinical manifestations and the results of auxiliary examinations of patients, which cannot achieve a real-time monitoring of intracranial pressure changes, but continuous intracranial pressure monitoring can solve the problem above [10]. However, there is a lack of prospective randomized trials of using continuous intracranial pressure monitoring for the guidance of clinical treatment to confirm its clinical effects. Therefore, this study adopted the continuous intracranial pressure monitoring to guide the treatment of severe cerebrovascular diseases, evaluate the clinical therapeutic effect and the changes of inflammation as well as provide a theoretical basis for further researches.

Materials and methods

Subjects

We prospectively selected 98 cases (50 cases of ischemic stroke, 48 cases of cerebral hemorrhage) with severe cerebrovascular diseases admitted to the Department of Neurology of The People's Hospital of Pingyi County from

January 2014 to December 2017 as research subjects, and they were randomly divided into observation group and control group according to their admission numerical order, with 49 cases in each group. Informed consents were obtained from all patients, and this study was approved by the Ethics Committee of The People's Hospital of Pingyi County.

Inclusion criteria: patients aged 20-75 years; patients diagnosed as acute cerebral infarction or cerebral hemorrhage by head CT and MRI and confirmed as severe cerebrovascular diseases according to clinical manifestation (coma); Glasgow Coma Scale (GCS) score <8 points and onset time <12 hours. Exclusion criteria: patients with other major organs (heart, liver or kidney) dysfunction; pregnant or lactating women; patients with speech dysfunction and could not provide normal communication; patients with blood system disease or coagulation dysfunction; patients appeared fixed, dilated pupils; GSC score >8 points.

Therapeutic method

Dehydration, prevention of infection, reduction of intracranial pressure and nutrition for brain cells combined with mild hypothermia treatment were given for both groups. The specific measures were as follows: the ice cap and ice blanket were placed on patients' head for cooling, and their oral temperature was maintained at 33-35°C. Within the two weeks of treatment, the detection of vital signs (blood pressure, heart rate and blood oxygen saturation) were enhanced in two groups during mild hypothermia treatment.

Intracranial pressure monitoring

Codman intracranial pressure monitor (Johnson & Johnson, USA) was used to monitor the intracranial pressure in observation group. Percutaneous skull drilling and anterior horn puncture of the lateral ventricle were performed for implantation (until a stable condition of patients). According to the changes of intracranial pressure, the dosage of mannitol was adjusted reasonably (see the next part). In con-

Invasive intracranial pressure monitoring with hypothermia treatment

Table 2. Intracranial pressure and Score of Glasgow Coma Scale after treatment

Index Group	Intracranial pressure			Score of Glasgow Coma Scale		
	Observation group	Control group	P	Observation group	Control group	P
Before treatment	30.18±1.32	30.20±1.29	0.940	5.61±1.79	5.70±1.63	0.795
1st day of treatment	27.19±1.44	28.24±1.30	<0.001	6.24±1.96	6.11±1.99	0.273
3rd day of treatment	20.27±1.10	24.69±1.33	<0.001	6.78±2.11	6.54±2.07	0.571
5th day of treatment	15.10±1.91	19.49±1.83	<0.001	9.30±2.34	7.99±2.59	<0.05
7th day of treatment	10.33±1.06	13.71±0.99	<0.001	12.04±2.96	10.11±2.41	<0.05
F		18.321			9.553	
P		<0.05			<0.05	

trol group, the changes of intracranial pressure were monitored by different methods. Their CT imaging was obtained at the start, 48 hours and one week of treatment, and their intracranial pressures were comprehensively assessed according to CT results and various sedative and life support treatments; brain edema was evaluated according to the results of head CT reexamination [11].

Mannitol usage

Mannitol was used for dehydration therapy according to the real-time values of intracranial pressure in observation group. Mannitol 5 g was used when the intracranial pressure was greater than 20 mmHg and lasted for more than 15 minutes, at the same time, 40 mg of furosemide was also used for dehydration. The control group was given mannitol based on experience and the results of auxiliary examinations, their dehydration therapy was also performed with furosemide.

Outcome measures

Main outcome measures: The intracranial pressure and GCS scores were observed on the 1st, 3rd, 5th and 7th day of treatment in the two groups, and the prognosis of the two groups (recovery, death, mild disability, severe disability and vegetative state) was recorded.

Methods of GCS assessment: The awareness level of patients in the two groups was recorded by the same medical worker on the 1st, 3rd, 5th and 7th day of treatment.

Secondary outcome measures: Two inflammatory factors IL-6 and IL-8 as well as time of using mannitol in the two groups were recorded for further evaluation. Venous blood of the patients

was collected before treatment and on the 7th day of treatment for centrifugation, and the supernate was used to detect the changes of serum IL-6 and IL-8 in the two groups by ELISA; meanwhile, the usage amount and time of mannitol in the two groups were also recorded.

Data processing

SPSS20.0 was used for data analysis. The measurement data of both groups presented normal distribution and homogeneity of variance, expressed as mean±standard deviation (mean±sd). Paired t test was used for comparison before and after treatment within groups, and independent sample t test was used for comparison between groups. Counting data were expressed by percentage, tested by χ^2 . Repeated measures analysis of variance was performed for repeated measurements. The difference was statistical significant when $P < 0.05$.

Results

General data

There was no statistical difference between the two groups in disease type, age, sex, smoking history, diabetes and hypertension history (all $P > 0.05$). Therefore, the two groups were comparable. See **Table 1**.

Changes of intracranial pressure and GCS scores

After treatment, the intracranial pressure of both groups decreased gradually, and the differences between the two groups on the 1st, 3rd, 5th and 7th of treatment were statistically significant (all $P < 0.001$), while the GCS scores in both groups increased gradually, and the

Invasive intracranial pressure monitoring with hypothermia treatment

Table 3. Usage amount and time of mannitol in both groups

Group	Usage amount (g)	Usage time (d)
Observation group	450±70	11.48±6.31
Control group	800±75	16.97±7.13
t	23.881	4.056
P	<0.05	<0.05

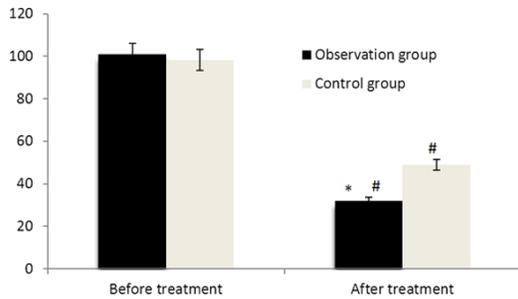


Figure 1. Content changes of serum IL-6 in two groups before and after treatment. Compared with before treatment, *P<0.05; Compared with control group, #P<0.05.

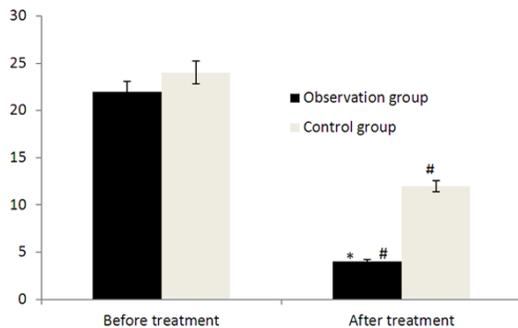


Figure 2. Content changes of serum IL-8 in two groups before and after treatment. Compared with before treatment, *P<0.05; Compared with control group, #P<0.05.

scores on the 5th and 7th day were significantly higher in observation group than in control group (both P<0.05). The results of repeated measures analysis of variance suggested statistically significant differences in intracranial pressures and GCS scores between the two groups (all P<0.05). See **Table 2**.

Usage amount and time of mannitol

The usage amount (450±70 g vs. 800±75 g, t=23.881, P<0.05) and time (11.48±6.31 d vs. 16.97±7.13 d, t=4.056, P<0.05) of mannitol

were significantly less in observation group than those in control group. See **Table 3**.

Content changes of serum inflammatory factors IL-6 and IL-8

There was no statistical change in IL-6 and IL-8 in the two groups before treatment, while both indicators decreased in the two groups after treatment (all P<0.05), and there were statistical differences between observation group and control group (both P<0.05). See **Figures 1 and 2**.

Prognosis

The mortality of patients in observation group was lower than that in control group (2/49 vs. 10/49, $\chi^2=5.017$, P=0.025), while the incidence of poor prognosis (death, mild disability, severe disability and vegetative state) was higher in control group than in observation group (9/49 vs. 22/49, P<0.05). See **Table 4**.

Discussion

Intracranial pressure refers to the pressure of the intracranial contents to the skull, and its change depends on the intracranial volume and components (brain tissues, blood and cerebrospinal fluid) as well as some lesions (tumor, edema) etc. [12]. It is the most common and harmful complication of all kinds of severe cerebrovascular diseases. As the main factor of secondary damage on the brain tissues, severity and duration of the intracranial pressure have a positive relationship with poor prognosis of patients [13, 14].

The main pathophysiological basis for the rise of intracranial pressure caused by ischemic stroke or cerebral hemorrhage is ischemia and anoxia of brain tissues. In the early stage of disease, cytotoxic brain edema is first appeared in the brain cells. If ischemia and anoxia can be timely and effectively corrected while providing brain protection measure (mild hypothermia) at this stage, cellular brain edema can be relieved or recovered. If time of ischemia and anoxia is longer than a few hours, damage on vascular endothelial cells and blood brain barrier can be caused. Consequently, vasogenic brain edema can occur. The edema of brain tissues affects the blood flow and aggravates the degree of cerebral ischemia and anoxia; a decrease of regional cerebral blood flow in turn aggravates

Invasive intracranial pressure monitoring with hypothermia treatment

Table 4. Comparison of mortality and poor prognosis between two groups (n, %)

Group	Poor prognosis			
	Death	Mild disability	Severe disability	Vegetative state
Observation group (n=49)	2 (4.08)	4 (8.17)	2 (4.08)	1 (2.04)
Control group (n=49)	10 (20.41)	7 (14.29)	3 (6.12)	2 (4.08)
χ^2	5.615			
P	0.018			

brain edema and eventually leads to a rise of intracranial pressure [15].

At present, there are two methods for monitoring intracranial pressure, invasive monitoring and non-invasive evaluation. The former is mainly based on the implantation of fluid system and transducer, which is the gold standard for the monitoring of intracranial pressure. In addition, it can achieve a drainage of cerebrospinal fluid in treatment [16]. Non-invasive evaluation is based on clinical signs and auxiliary examinations (such as CT or MRI). However, there is a dispute of clinical use of the two methods, that is, the use of invasive intracranial pressure monitoring may not change the final prognosis of patients, and there are also contrary opinions [17].

Mannitol is the most commonly used drug for the reduction of intracranial pressure; favorable effects makes it the first choice for reducing intracranial pressure [18]. The results of our study also showed that mannitol reduced intracranial pressure of patients in both groups, and the increased GCS scores confirmed its clinical effect. But the continuous monitoring group enjoyed more decrease in intracranial pressure and shorter usage time of mannitol when compared with control group, which may be related to more accurate usage of mannitol with the guidance of real-time intracranial pressure changes in observation group; besides, mild hypothermia provided brain protection. But large-amount and long-term use of mannitol can not improve the final outcome of the patients and may even lead to the risk of potential adverse reactions; it does show that accurate monitoring of intracranial pressure is a necessary auxiliary means for clinical use of mannitol [19, 20].

Latest researches have confirmed that inflammatory response is also an important factor in the development of severe cerebrovascular diseases, and studies have shown that the effective detection of serum inflammatory factors can reduce the mortality of patients with severe cerebrovascular diseases [21,

22]. Therefore, two common serum inflammatory factors IL-6 and IL-8 were detected in this study to evaluate the treatment effects in the two groups. Results showed that the clinical effect of observation group was better than that of control group in terms of serological indicators, indicating that effective continuous intracranial pressure monitoring combined with mild hypothermia could improve the effect of clinical treatment.

Clinical prognosis is the main way to check the effects of treatment, and results of this study showed that the mortality in observation group was lower than that in control group, with better clinical effects in observation group, which was consistent with the results of the latest research [17]. It can be seen that continuous monitoring of intracranial pressure can improve the prognosis of patients.

At present, the restriction of continuous intracranial pressure monitoring is complications caused by its operation, including bleeding and infection, but a meta-analysis of complications showed that the incidences were only 0.8% and 0.7% respectively, indicating that this monitoring method is safe and can be used in clinic [9, 23].

The average usage amount and time of mannitol in this study were within the recommended range, so the adverse reactions of the patients were not counted. The adverse reactions caused by the implantation of detection system is the focus of future researches. Besides, the sample size of this study is relatively small, so continuous intracranial pressure monitoring combined with mild hypothermia for the treatment of severe brain diseases need further confirmation by multi-center and large-scaled clinical trials.

Disclosure of conflict of interest

None.

Address correspondence to: Bin Ge, Department of Neurology, The People's Hospital of Pingyi County, No.7 Jinhua Road, Linyi 273399, Shandong Province, China. Tel: +86-0539-4689209; E-mail: gebin9423@163.com

References

- [1] Zhang X, Jing J, Zheng H, Jia Q, Zhao X, Liu L, Wang C, Meng X, Pan Y, Wang Y and Wang Y. Prognosis of intracerebral hemorrhage with newly diagnosed diabetes mellitus according to hemoglobin A1c criteria. *J Stroke Cerebrovasc Dis* 2018; 27: 1127-1133.
- [2] Rosenfeldt Z, Conklen K, Jones B, Ferrill D, Deshpande M and Siddiqui FM. Comparison of nicardipine with clevidipine in the management of hypertension in acute cerebrovascular diseases. *J Stroke Cerebrovasc Dis* 2018; 27: 2067-2073.
- [3] Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF and Coresh J. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA* 2014; 312: 259-268.
- [4] van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A and Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 2010; 9: 167-176.
- [5] Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M and Murray C. Global and regional burden of stroke during 1990-2010: findings from the global burden of disease study 2010. *Lancet* 2014; 383: 245-254.
- [6] Sun H, Zou X and Liu L. Epidemiological factors of stroke: a survey of the current status in china. *J Stroke* 2013; 15: 109-114.
- [7] Crossley S, Reid J, McLatchie R, Hayton J, Clark C, MacDougall M and Andrews PJ. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. *Crit Care* 2014; 18: R75.
- [8] Tang XN, Liu L and Yenari MA. Combination therapy with hypothermia for treatment of cerebral ischemia. *J Neurotrauma* 2009; 26: 325-331.
- [9] Tavakoli S, Peitz G, Ares W, Hafeez S and Grandhi R. Complications of invasive intracranial pressure monitoring devices in neurocritical care. *Neurosurg Focus* 2017; 43: E6.
- [10] Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW and Ghajar J. Guidelines for the management of severe traumatic brain injury, 4th edition. *Neurosurgery* 2017; 80: 6-15.
- [11] Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, Petroni G, Lujan S, Pridgeon J, Barber J, Machamer J, Chaddock K, Celix JM, Cherner M and Hendrix T. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012; 367: 2471-2481.
- [12] Kawoos U, McCarron RM, Auker CR and Chavko M. Advances in intracranial pressure monitoring and its significance in managing traumatic brain injury. *Int J Mol Sci* 2015; 16: 28979-28997.
- [13] Badri S, Chen J, Barber J, Temkin NR, Dikmen SS, Chesnut RM, Deem S, Yanez ND and Treggiari MM. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. *Intensive Care Med* 2012; 38: 1800-1809.
- [14] Ibrook J, Saindane AM. Imaging of intracranial pressure disorders. *Neurosurgery* 2017; 80: 341-354.
- [15] Chen YJ, Wallace BK, Yuen N. Blood-brain barrier KCa3.1 channels: evidence for a role in brain Na uptake and edema in ischemic stroke. *Stroke* 2015; 46: 237-44.
- [16] Harary M, Dolmans RGF and Gormley WB. Intracranial pressure monitoring-review and avenues for development. *Sensors (Basel)* 2018; 18.
- [17] Robba C, Cardim D, Tajsic T, Pietersen J, Bulman M, Donnelly J, Lavinio A, Gupta A, Menon DK, Hutchinson PJ and Czosnyka M. Ultrasound non-invasive measurement of intracranial pressure in neurointensive care: a prospective observational study. *PLoS Med* 2017; 14: e1002356.
- [18] Elliott CA, MacKenzie M and O'Kelly CJ. Mannitol dosing error during interfacility transfer for intracranial emergencies. *J Neurosurg* 2015; 123: 1166-1169.
- [19] Burgess S, Abu-Laban RB, Slavik RS, Vu EN and Zed PJ. A systematic review of randomized controlled trials comparing hypertonic sodium solutions and mannitol for traumatic brain injury: Implications for emergency department management. *Ann Pharmacother* 2016; 50: 291-300.

Invasive intracranial pressure monitoring with hypothermia treatment

- [20] Ropper AH. Hyperosmolar therapy for raised intracranial pressure. *N Engl J Med* 2012; 367: 1493-1502.
- [21] Buerki SE, Grandgirard D, Datta AN, Hackenberg A, Martin F, Schmitt-Mechelke T, Leib SL and Steinlin M. Inflammatory markers in pediatric stroke: an attempt to better understanding the pathophysiology. *Eur J Paediatr Neurol* 2016; 20: 252-260.
- [22] Dawes AJ, Sacks GD, Cryer HG, Gruen JP, Preston C, Gorospe D, Cohen M, McArthur DL, Russell MM, Maggard-Gibbons M and Ko CY. Intracranial pressure monitoring and inpatient mortality in severe traumatic brain injury: a propensity score-matched analysis. *J Trauma Acute Care Surg* 2015; 78: 492-501.
- [23] Poblete R, Zheng L, Raghavan R, Cen S, Amar A, Sanossian N, Mack W and Kim-Tenser M. Trends in ventriculostomy-associated infections and mortality in aneurysmal subarachnoid hemorrhage: data from the nationwide inpatient sample. *World Neurosurg* 2017; 99: 599-604.