HOSTED BY
ELSEVIER
Contents lists available at ScienceDirect
Journal of Acute Disease
journal homepage: www.jadweb.org

Original article http://dx.doi.org/10.1016/j.joad.2016.04.003

Clinical study on acute craniocerebral injury treated with mild hypothermia auxiliary therapy

Cheng Zhang*, Jian-Ming Li, De-Zhang Dou, Jun-Lin Hu

Department of Neurology, The Third People's Hospital of Zigong, Zigong, China

ARTICLE INFO

Article history:
Received 3 Mar 2016
Received in revised form 17 Mar 2016
Accepted 20 Apr 2016
Available online 10 Jun 2016

Keywords:
Craniocerebral injury
Mild hypothermia therapy
Intracranial pressure
Energy metabolism

ABSTRACT

Objective: To study the changes of the rest energy expenditure, intracranial pressure, brain function parameters and serum indexes of acute craniocerebral injury after treated with mild hypothermia auxiliary therapy.

Methods: Clinical data of 58 patients received emergency treatment for craniocerebral injury in our hospital from October 2009 to December 2014 were analyzed retrospectively. Among them, 27 cases treated with mild hypothermia therapy were included in the experiment group, while 31 cases without the therapy were considered as the control group. Their rest energy expenditure, intracranial pressure, brain function parameters and serum TNF-α, nitric oxide and myelin basic protein contents were determined.

Results: The intracranial pressure [(20.3 ± 2.9) *vs.* (25.8 ± 3.3) mmHg], [(17.8 ± 2.7) *vs.* (23.1 ± 3.6) mmHg], [(14.2 ± 2.4) *vs.* (20.6 ± 3.1) mmHg], [(11.3 ± 1.8) *vs.* (16.3 ± 2.6) mmHg] and rest energy expenditure [(6861 ± 994) *vs.* (14074 ± 2016) kJ/d], [(5946 ± 768) *vs.* (15525 ± 1936) kJ/d], [(5512 ± 873) *vs.* (5512 ± 873) kJ/d], [(6248 ± 906) *vs.* (14413 ± 2166) kJ/d] in patients of experiment group on the 1st, 2nd, 3rd and 4th days after treatment were all significantly lower than those of patients in the control group. After treated for 24 h, $P_{bt}O_2$ [(23.59 ± 4.97) *vs.* (15.68 ± 3.14) mmHg] and $S_{jv}O_2$ [(61.39 ± 9.79) *vs.* (46.76 ± 7.28) %] of the experiment group were distinctly higher than those of the control group, while its contents of TNF-α [(1.96 ± 0.29) *vs.* (3.39 ± 0.72) μg/L] and nitric oxide [(10.39 ± 2.16) *vs.* (24.42 ± 3.51) mg/L] and myelin basic protein [(2.19 ± 0.52) *vs.* (4.34 ± 0.78) μg/L] were all lower than those of the control group.

Conclusions: After treated with mild hypothermia auxiliary therapy, the metabolic rate and intracranial pressure of patients with craniocerebral injury decreased obviously, their cerebral blood flow perfusion were improved evidently and the release of adverse metabolic products were also reduced conspicuously, which was beneficial to the recovery of neurological functions.

1. Introduction

Craniocerebral injury is a common and dangerous disease. Trauma-caused intracranial hematoma, brain edema, increased ICP and cerebral hernia will lead to nerve function impairment. The disease is serious and rapid developed and also its disability rate and fatality rate are pretty high[1,2]. The main principles for treating sever craniocerebral injury are emergency rescue, correction of shock, craniotomies decompression and anti-infection[3,4]. Continuous increased intracranial pressure (ICP) is an important factor causing irreversible damage of neurological function for patients with craniocerebral trauma. Meanwhile, after the occurrence of trauma, the high metabolic state of craniocerebral tissues would consume more oxygen and influence the recovery of neurological function. It becomes an important issue that how to decrease ICP, maintain intracranial environmental stability and reduce brain metabolism and oxygen consumption reasonably and scientifically[5–7]. Mild hypothermia is a first aid measure for craniocerebral injury which was developed in recent years.

*Corresponding author: Cheng Zhang, Department of Neurology, The Third People's Hospital of Zigong, Zigong, China.
Tel.: +86 13990010657
E-mail: zhangchenghx@163.com

Foundation Project: Supported by the scientific research project of the Health Department in Sichuan Province (Grant No. 120349).
Peer review under responsibility of Hainan Medical College. The journal implements double-blind peer review practiced by specially invited international editorial board members.

The use of physical means for lowering the local temperature at 32–35 °C can inhibit the metabolism of the brain cells and oxygen consumption, reduce production of harmful substance produced in the traumatic acute phase, relieve brain edema, and decrease ICP[8,9]. In the following studies, the changes of the rest energy expenditure, ICP, brain function parameters and serum indexes of craniocerebral injury after treated with mild hypothermia auxiliary therapy were analyzed.

2. Materials and methods

2.1. Clinical materials

A total of 58 patients received emergency treatment for craniocerebral injury in our hospital from October 2009 to December 2014 were analyzed retrospectively. The inclusion criteria concluded: patients have a specific history of trauma; patients were sent to the emergency department within 3 h after trauma; patients' Glasgow Coma Scale (GCS) scores were lower than 8 when admitted to hospital; patients conform to the indications of decompressive craniectomy. Patients suffer serious trauma on thorax and abdomen, and complicate with arrhythmia, cardiovascular disease and diabetes were excluded. The causes of traumas of the 58 cases were described below: 39 cases were caused by traffic accidents, 14 cases by falling, and 5 cases by hitting. They were given water deprivation, hemostasis and anti-inflammation therapies as soon as they admitted to the Emergency Department, and surgery was prepared and inspected at the same time. After that, patients were treated with bone disc decompression surgery.

Among those 58 included cases, 27 of them were treated with mild hypothermia therapy. The specific methods were described as follows. Ice hats and ice blanket machines were use to lower the temperature. Ice bags were placed on the superficial areas of femoral and axillary artery to decrease the anal temperature at 32–35 °C within 8 h. Lyric cocktail, muscle relaxant, 100 mg atracurium, 50 mg chlorpromazine, and 50 mg promethazine were added together into 500 mL normal saline for intravenous infusion. The mild hypothermia would be maintained persistently for 24 h after the ICP returned to normal. After that, they were rewarmed. The ice hats were taken away firstly, and then ice blanket machines were removed 8 h later, meanwhile, the used of lyric cocktail was reduced gradually. The proper speed of rewarming should be 1 °C/6 h.

2.2. Study methods

The resting energy expenditure (REE) of patients was tested by the following methods. The 1st, 2nd, 3rd, 4th days before and after treatment, the oxygen consumption (V_{O_2}) and amount of carbon dioxide exhaled (V_{CO_2}) in unit time were determined by metabolic cart, REE (kJ/d) = $(3.9 \times V_{O_2} + 1.1 \times V_{CO_2}) \times 1.44 \times 4.18$. Brain function parameters were acquired by the following methods. Intellivue Mp30 system (Philip company) was used to monitor the ICP on the 1st, 2nd, 3rd, 4th days before and after treatment by brain hydraulic transmission method. After treated with mild hypothermia therapy for 24 h, brain tissue oxygen pressure ($P_{bt}O_2$) was detected by the cerebral oxygen brain temperature monitoring instrument, and the jugular vein bulb ($S_{jv}O_2$) was tested by Nova-H monitoring instrument. After treated with mild hypothermia therapy for 24 h, peripheral venous blood was collected and the contents of TNF-α, nitric oxide and myelin basic protein (MBP) were measured by ELISA kits.

2.3. Statistical methods

SPSS 19.0 was employed to input and analyze data. Measurement data were expressed by mean ± SD and tested by *t*-test. While enumeration data were presented by frequency and determined by *Chi*-square test. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. General data of patients with craniocerebral injury of the two groups

Among those 58 included cases, 27 of them were treated with mild hypothermia therapy. They were included in the experiment group which consisted of 19 males and 8 females aging from (38.1 ± 6.5) years with GCS scores of (6.2 ± 0.9), glutamic-pyruvic transaminase (ALT) [(38.5 ± 6.1) IU/L], glutamic oxal-acetic transaminase (AST) (45.2 ± 7.9) IU/L, serum creatinine (SCr) [(75.1 ± 10.8) μmol/L] and blood urea nitrogen (BUN) [(5.6 ± 0.9) mmol/L]. The rest of 31 cases who were not treated with mild hypothermia therapy were regarded as the control group which included 22 males and 9 females aging from (36.3 ± 6.9) years with GCS scores of (6.5 ± 0.8), ALT [(39.8 ± 6.4) IU/L], AST [(43.5 ± 7.5) IU/L], SCr [(76.3 ± 11.2) μmol/L] and BUN [(5.9 ± 0.8) mmol/L]. The age, gender, GCS score, ALT, AST, Scr and BUN showed no differences (Table 1).

Table 1
General clinical data of patients in the experiment group and the control group.

General clinical data	Experiment group (n = 27)	Control group (n = 31)	P
Gender (male/female)	19/8	22/9	>0.05
Age (year)	38.1 ± 6.5	36.3 ± 6.9	>0.05
GCS score	6.2 ± 0.9	6.5 ± 0.8	>0.05
ALT (IU/L)	38.5 ± 6.1	39.8 ± 6.4	>0.05
AST (IU/L)	45.2 ± 7.9	43.5 ± 7.5	>0.05
Scr (μmol/L)	75.1 ± 10.8	76.3 ± 11.2	>0.05
BUN (mmol/L)	5.6 ± 0.9	5.9 ± 0.8	>0.05

3.2. Changes of the ICP in patients of the two groups before and after treatment

Before treatment, the ICP [(28.9 ± 3.4) *vs.* (29.2 ± 4.1) mmHg] of patient in the experiment group had no significant differences as compare to that of the control group. The ICPs on the 1st, 2nd, 3rd and 4th days of patients in the experiment group were all obviously lower than those of in the control group (Table 2).

Table 2
Changes of the ICP in patients of the two groups before and after treatment (mmHg).

Time of treatment	Experiment group (n = 27)	Control group (n = 31)	P
Before treatment	28.9 ± 3.4	29.2 ± 4.1	>0.05
1 day after treatment	20.3 ± 2.9	25.8 ± 3.3	<0.05
2 days after treatment	17.8 ± 2.7	23.1 ± 3.6	<0.05
3 days after treatment	14.2 ± 2.4	20.6 ± 3.1	<0.05
3 days after treatment	11.3 ± 1.8	16.3 ± 2.6	<0.05

3.3. REE in patients of the two groups before and after treatment

Before treatment, the REE [(13347 ± 1935) *vs.* (13713 ± 1879) kJ/d] of patient in the experiment group had no significant differences as compare to that of the control group. The REE on the 1st, 2nd, 3rd and 4th days after treatment of patients in the experiment group were all significantly lower than those of patients in the control group (Table 3).

Table 3
Changes of REE in patients of two groups before and after treatment (kJ/d).

Time of treatment	Experiment group (n = 27)	Control group (n = 31)	P
Before treatment	13347 ± 1935	13713 ± 1879	> 0.05
1 day after treatment	6861 ± 994	14074 ± 2016	< 0.05
2 days after treatment	5946 ± 768	15525 ± 1936	< 0.05
3 days after treatment	5512 ± 873	14759 ± 1813	< 0.05
3 days after treatment	6248 ± 906	14413 ± 2166	< 0.05

3.4. The brain function parameters and serum indexes in patients of the two groups before and after treatment

After treated for 24 h, $P_{bt}O_2$ and $S_{jv}O_2$ of the experiment group were distinctly higher than those of the control group, while its contents of TNF-α and nitric oxide and MBP were all lower than those of the control group (Table 4).

Table 4
The brain function parameters and serum indexes in patients of the two groups before and after treatment.

Parameters	Experiment group (n = 27)	Control group (n = 31)	P
$P_{bt}O_2$ (mmHg)	23.59 ± 4.97	15.68 ± 3.14	< 0.05
$S_{jv}O_2$ (%)	61.39 ± 9.79	46.76 ± 7.28	< 0.05
TNF-α (μg/L)	1.96 ± 0.29	3.39 ± 0.72	< 0.05
Nitric oxide (mg/L)	10.39 ± 2.16	24.42 ± 3.51	< 0.05
MBP (μg/L)	2.19 ± 0.52	4.34 ± 0.78	< 0.05

4. Discussion

Craniocerebral injury is a kind of trauma with high disability rate and fatality rate, and about 22% patients with severe craniocerebral injury become severely disabled, in which 5% develop into the vegetative state and 40% die[10,11]. Craniocerebral tissues stay in a high metabolic state after suffering from external trauma. The oxygen consumption of brain tissues is massive and many adverse metabolic products are produced, which, on the one hand, injures cell functions, hinders the recovery of nerve functions, and causes cell-derived edema as well[12,13]. On the other hand, the accumulation of the local metabolites will change the vascular permeability and results in vascular edema[13–15]. Patients with craniocerebral injury commonly suffer from pathological states such as brain tissue edema and increased ICP, which would increase the risks of the development of the disease and the increase of cerebral hernia if it is not treated in time, and then cause the deterioration of nerve function and affect the outcome and prognosis of the disease. The clinical treatment measures for craniocerebral injury include debridement, correction of shock, craniotomies decompression and the dehydration of ICP, which can relieve the high ICP-caused nerve function injury. However, because the states of high brain tissue metabolism and oxygen consumption cannot be corrected in etiological consideration, and the adverse metabolic products are continuously produced, brain edema will persist for a long time. The prognosis of patients was poor, and the disease has high disability rate and fatality rate.

Mild hypothermia therapy is a newly developed way for treating craniocerebral trauma in recent years, which intends to decrease the basic metabolic rate and oxygen consumption of brain tissues and reduces the release of toxic byproducts so as to relieve edema and decreases ICP by maintaining the body temperature at 32–34 °C[16–18]. After trauma, the increase of the basic metabolic rate of brain tissues becomes a major important for brain tissue edema and high ICP. The value of mild hypothermia therapy is to reduce metabolic rate and oxygen consumption by decreasing the temperature of the local tissues and therefore alleviate cell-derived edema and vascular edema and decrease high ICP[16,19–20]. After treatment, the levels of REE and ICP were analyzed. It was found that the mean REE and ICP of the 1st, 2nd, 3rd and 4th days in patients of experimental group were all lower than those in the control group, which indicated that mild hypothermia therapy could reduce basic metabolic rate by decreasing body temperature so as to benefit for the decline of ICP level. Despite all this, since there were individual differences existing among individuals and the degrees of metabolism of patients were different, the stability range of the therapy should be designed in accordance with the individual differences, so as to ensure that the basic metabolic rate of those patients can be maintained in a stable range.

After trauma, the high metabolic rate and oxygen consumption of brain tissues will lead to hypoxia environment in local area. And along with the oppression of edema caused by external trauma, the blood perfusion of brain tissues will be affected and the brain tissue hypoxia will be aggravated as well[21–23]. The oxygen consumption of local brain tissues and blood perfusion condition were reflected by analyzing the $P_{bt}O_2$ and jugular venous saturation. The results were described as follows. The $P_{bt}O_2$ and $S_{jv}O_2$ of patients in experiment group were all higher than that in control group, which manifested that under mild hypothermia therapy the oxygen consumption of brain tissues was decreased significantly and the blood perfusion and oxygen supply conditions were improved obviously. Under a high-metabolic state, brain tissues will release multiple toxic metabolites and cause nerve injure. The levels of TNF-α and nitric oxide were proved to be related to brain tissue injure. The former causes injures mainly by inflammatory responses[24,25], while the latter causes injures primarily by the form of free radicals on local tissues[26,27]. In addition, when the neuron and gliocytes were injured, the compound of MBP increased, which put cells in an active state and influenced the recovery of nerve cells[28,29]. The analysis of the related serum biochemical indexes confirmed that the contents of serum TNF-α, nitric oxide and MBP in patients of experimental group were significantly lower than those in the control group, which illustrated that

with the treatment of mild hypothermia therapy the toxic metabolites released by brain tissues was reduced significantly. That was, apparently, good for the recovery of nerve functions.

To sum up, after treated with mild hypothermia auxiliary therapy, the metabolic rate and ICP of patients with craniocerebral injury was decreased obviously, and their cerebral blood flow perfusion was promoted evidently and the release of adverse metabolic products was also reduced conspicuously, which was beneficial to the recovery of neurological functions.

Conflict of interest statement

The authors report no conflict of interest.

References

[1] Gao J, Zheng Z. Development of prognostic models for patients with traumatic brain injury: a systematic review. *Int J Clin Exp Med* 2015; **8**(11): 19881-5.

[2] Wortzel HS, Granacher RP Jr. Mild traumatic brain injury update: forensic neuropsychiatric implications. *J Am Acad Psychiatry Law* 2015; **43**(4): 499-505.

[3] Ramsamy Y, Muckart DJ, Bruce JL, Hardcastle TC, Han KS, Mlisana KP. Empirical antimicrobial therapy for probable v. directed therapy for possible ventilator-associated pneumonia in critically injured patients. *S Afr Med J* 2016; **106**(2): 196-200.

[4] Hackenberg K, Unterberg A. [Traumatic brain injury]. *Nervenarzt* 2016; **87**(2): 203-16. German.

[5] Colantonio A. Sex, gender, and traumatic brain injury: a commentary. *Arch Phys Med Rehabil* 2016; **97**(Suppl 2): S1-4.

[6] Allen KA. Pathophysiology and treatment of severe traumatic brain injuries in children. *J Neurosci Nurs* 2016; **48**(1): 15-27.

[7] Lu XC, Shear DA, Deng-Bryant Y, Leung LY, Wei G, Chen Z, et al. Comprehensive evaluation of neuroprotection achieved by extended selective brain cooling therapy in a rat model of penetrating ballistic-like brain injury. *Ther Hypothermia Temp Manag* 2016; **6**(1): 30-9.

[8] Carter EL, Hutchinson PJ, Kolias AG, Menon DK. Predicting the outcome for individual patients with traumatic brain injury: a case-based review. *Br J Neurosurg* 2016; **30**(2): 227-32.

[9] Soon WC, Marcus H, Wilson M. Traumatic acute extradural haematoma-indications for surgery revisited. *Br J Neurosurg* 2016; **30**(2): 233-4.

[10] Sun Z, Zuo H, Yuan D, Sun Y, Zhang K, Cui Z, et al. Predictors of prognosis in patients with temporal lobe epilepsy after anterior temporal lobectomy. *Exp Ther Med* 2015; **10**(5): 1896-902.

[11] Ozyurt E, Goksu E, Cengiz M, Yilmaz M, Ramazanoglu A. Retrospective analysis of prognostic factors of severe traumatic brain injury in a university hospital in Turkey. *Turk Neurosurg* 2015; **25**(6): 877-82.

[12] Park KD, Lim OK, Yoo CJ, Kim YW, Lee S, Park Y, et al. Voxel-based statistical analysis of brain metabolism in patients with growth hormone deficiency after traumatic brain injury. *Brain Inj* 2016; **24**: 1-7.

[13] Patet C, Suys T, Carteron L, Oddo M. Cerebral lactate metabolism after traumatic brain injury. *Curr Neurol Neurosci Rep* 2016; **16**(4): 31.

[14] Amorini AM, Lazzarino G, Di Pietro V, Signoretti S, Lazzarino G, Belli A, et al. Metabolic, enzymatic and gene involvement in cerebral glucose dysmetabolism after traumatic brain injury. *Biochim Biophys Acta* 2016; **1862**(4): 679-87.

[15] Harish G, Mahadevan A, Pruthi N, Sreenivasamurthy SK, Puttamallesh VN, Keshava Prasad TS, et al. Characterization of traumatic brain injury in human brains reveals distinct cellular and molecular changes in contusion and pericontusion. *J Neurochem* 2015; **134**(1): 156-72.

[16] Andresen M, Gazmuri JT, Marín A, Regueira T, Rovegno M. Therapeutic hypothermia for acute brain injuries. *Scand J Trauma Resusc Emerg Med* 2015; **23**: 42.

[17] Ding L, Gao X, Yu S, Yang J. Effects of mild and moderate hypothemia therapy on expression of cerebral neuron apoptosis related proteins and glial fiber acidic protein after rat cardiopulmonary resuscitation. *Cell Biochem Biophys* 2014; **70**(3): 1519-25.

[18] Maekawa T, Yamashita S, Nagao S, Hayashi N, Ohashi Y, Brain-Hypothermia Study Group. Prolonged mild therapeutic hypothermia versus fever control with tight hemodynamic monitoring and slow rewarming in patients with severe traumatic brain injury: a randomized controlled trial. *J Neurotrauma* 2015; **32**(7): 422-9.

[19] O'Phelan KH, Merenda A, Denny KG, Zaila KE, Gonzalez C. Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury. *World J Crit Care Med* 2015; **4**(4): 296-301.

[20] Idris Z, Zenian MS, Muzaimi M, Hamid WZ. Better Glasgow outcome score, cerebral perfusion pressure and focal brain oxygenation in severely traumatized brain following direct regional brain hypothermia therapy: a prospective randomized study. *Asian J Neurosurg* 2014; **9**(3): 115-23.

[21] Mao XR, Kaufman DM, Crowder CM. Nicotinamide mononucleotide adenylyltransferase promotes hypoxic survival by activating the mitochondrial unfolded protein response. *Cell Death Dis* 2016; **25**(7): e2113.

[22] Croall I, Smith FE, Blamire AM. Magnetic resonance spectroscopy for traumatic brain injury. *Top Magn Reson Imaging* 2015; **24**(5): 267-74.

[23] Bossers SM, Schwarte LA, Loer SA, Twisk JW, Boer C, Schober P. Experience in prehospital endotracheal intubation significantly influences mortality of patients with severe traumatic brain injury: a systematic review and meta-analysis. *PLoS One* 2015; **10**(10): e0141034.

[24] Graber DJ, Costine BA, Hickey WF. Early inflammatory mediator gene expression in two models of traumatic brain injury: *ex vivo* cortical slice in mice and *in vivo* cortical impact in piglets. *J Neuroinflammation* 2015; **12**: 76.

[25] Baratz R, Tweedie D, Wang JY, Rubovitch V, Luo W, Hoffer BJ, et al. Transiently lowering tumor necrosis factor-α synthesis ameliorates neuronal cell loss and cognitive impairments induced by minimal traumatic brain injury in mice. *J Neuroinflammation* 2015; **12**: 45.

[26] Villalba N, Sonkusare SK, Longden TA, Tran TL, Sackheim AM, Nelson MT, et al. Traumatic brain injury disrupts cerebrovascular tone through endothelial inducible nitric oxide synthase expression and nitric oxide gain of function. *J Am Heart Assoc* 2014; **3**(6): e001474.

[27] Garry PS, Ezra M, Rowland MJ, Westbrook J, Pattinson KT. The role of the nitric oxide pathway in brain injury and its treatment-from bench to bedside. *Exp Neurol* 2015; **263**: 235-43.

[28] Su E, Bell MJ, Kochanek PM, Wisniewski SR, Bayir H, Clark RS, et al. Increased CSF concentrations of myelin basic protein after TBI in infants and children: absence of significant effect of therapeutic hypothermia. *Neurocrit Care* 2012; **17**(3): 401-7.

[29] Opara JA, Małecka E, Szczygiel J. Clinimetric measurement in traumatic brain injuries. *J Med Life* 2014; **7**(2): 124-7.