The Journal of International Medical Research
2006; 34: 58 – 64

Effects of Selective Brain Cooling in Patients with Severe Traumatic Brain Injury: a Preliminary Study

WG Liu[1], WS Qiu[1,2], Y Zhang[2], WM Wang[2], F Lu[2] and XF Yang[1]

[1]Department of Neurosurgery, The Second Affiliated Hospital, College of Medicine, Zhejiang University, and [2]Department of Neurosurgery, Hangzhou Second Hospital, School of Medicine, Hangzhou Normal College, Hangzhou, China

We prospectively investigated non-invasive selective brain cooling (SBC) in patients with severe traumatic brain injury. Sixty-six in-patients were randomized into three groups. In one group, brain temperature was maintained at 33 – 35 °C by cooling the head and neck (SBC); in a second group, mild systemic hypothermia (MSH; rectal temperature 33 – 35 °C) was produced with a cooling blanket; and a control group was not exposed to hypothermia. Natural re-warming began after 3 days. Mean intracranial pressure 24, 48 or 72 h after injury was significantly lower in the SBC group than in the control group. Mean serum superoxide dismutase levels on Days 3 and 7 after injury in the SBC and MSH groups were significantly higher than in the control group. The percentage of patients with a good neurological outcome 2 years after injury was 72.7%, 57.1% and 34.8% in the SBC, MSH and control groups, respectively. Complications were managed without severe sequelae. Non-invasive SBC was safe and effective.

KEY WORDS: Traumatic brain injury; Hypothermia; Intracranial pressure; Superoxide dismutase; Selective brain cooling

Introduction

Severe traumatic brain injury (TBI) is a major cause of permanent disability in adults after trauma in spite of recent advances in treatment.[1–4] Mild hypothermia (33 – 35 °C), one of the current therapies designed to combat the deleterious effects of TBI, helps to protect the brain and reduces mortality in severe TBI.[2–6] Since mild systemic hypothermia (MSH) leads to adverse side-effects such as severe secondary infections and shock during re-warming, selective brain cooling (SBC) has been investigated for rapid local hypothermia.[5,7] Despite its promise, the clinical benefits of SBC have rarely been investigated.[5] In order to evaluate the effects of SBC in patients with severe TBI, we conducted a randomized, controlled clinical trial of SBC, MSH and normothermia in patients with severe TBI, and the clinical effects were analysed prospectively.

Patients and methods

PATIENT GROUPS

This clinical study was designed as a randomized, controlled, double-blind trial. After informed consent had been obtained

from the patients' families, each patient was assigned to one of three groups according to a randomization table. Two groups received treatment to produce hypothermia (SBC or MSH); the third group was not exposed to hypothermia and constituted the control group. All the patients met the following criteria: a history of TBI, Glasgow Coma Scale score ≤ 8 at admission, and brain injury apparent on sequential computed tomography within 1 – 24 h (mean 8.6 h) of admission.

The research protocol was approved by the Clinical Research Ethics Committee of our university, and the principles of the Declaration of Helsinki were followed strictly.

TREATMENTS

All patients either underwent local decompression or were managed non-surgically, such as with dehydration.

In the SBC group, we began therapy directly on admission or after craniotomy, and applied it on each of three successive days for 0 – 6 h (average 4.5 h) according to the patient's condition. SBC was induced by fitting a cooling cap around the head, in which water at about 4 °C was circulating, and a neckband containing blue ice strips (BWB-10; BWKJ, Fujian, China) was placed around the neck. The cold water was cycled by a hypothermia machine (KN-01; EBM, Beijing, China), and fresh blue ice strips were placed in the interlayer of the neckband (using a strap with which the neckband could be loosened or tightened as needed) at intervals of 3 – 4 h according to the temperature of the patient and the thawing time of the ice strips. In this way, brain temperature could be reduced to 33 – 35 °C (within 2 h in most patients) and maintained in this temperature range. In patients who shivered, artificial hibernation mixture (20 ml normal saline + 100 mg chlorpromazine + 100 mg promethazine) was introduced intravenously at 2 – 10 ml/h.

In the MSH group, a cooling blanket and refrigerated ice-bags were used continuously to maintain rectal temperature at about 33 – 35 °C; the same artificial hibernation mixture as that used in the SBC group was used if necessary.

When hypothermia treatment terminated after 3 days, the temperature was expected to return to baseline spontaneously.

The normothermia control group received the same conventional treatment as the hypothermia groups, but they were not exposed to hypothermia.[6]

MONITORING PARAMETERS

The following parameters were monitored at admission or after operation:[6]

(i) Brain and rectal temperatures, using the KN-01 monitoring system (EBM, Beijing, China);
(ii) Intracranial pressure (ICP), using the SJN208l monitoring system (Gelan, Beijing, China);
(iii) Heart rate, breathing rate, blood pressure and arterial blood oxygen saturation, using multiple monitors (Model 90309; Space Labs, Redmond, WA, USA);
(iv) Blood superoxide dismutase (SOD), by radioimmunoassay;
(v) Complications, including pulmonary infection, digestive tract haemorrhage, thrombocytopenia (platelet count less than 100×10^9/l) and disturbance of electrolytes; and
(vi) The Glasgow Outcome Scale (GOS) score (1 = death, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, 5 = mild or no disability), evaluated at 2 years of follow-up after injury.

STATISTICAL ANALYSIS

The ICP and SOD levels are presented as mean ± SD, and were subjected to one-way

ANOVA (analysis of variance) if variances were equal; the Student–Newman–Keuls test was used to compare groups if differences within groups were significant. The rates of fatality and good recovery in the three groups were compared using the Pearson χ^2 test for multiple samples, as appropriate. Differences in outcome between groups were evaluated with the Cochran–Mantel–Haenszel test. Data were analysed using SAS® statistical software (version 8; SAS Institute, Cary, NC, USA). A *P*-value < 0.05 was considered to indicate a significant difference.

Results

The study population consisted of 66 adult in-patients with severe TBI admitted to our department during 2003 and 2004; 42 patients were male and 24 were female, and their ages ranged from 19 to 65 years (40.6 ± 10.3). There were 22 patients in the SBC group, 21 in the MSH group and 23 in the normothermic control group. The main characteristics of the patients, which did not differ significantly between groups, are shown in Table 1.

BRAIN AND RECTAL TEMPERATURES

During hypothermia, in the group exposed to SBC the brain surface temperature was maintained between 33 and 35 °C and rectal temperature between 36.5 and 37.5 °C; in the MSH group brain surface and rectal temperatures were about 35 and 37 °C, respectively. When hypothermia treatment was stopped in the SBC and MSH groups (after 3 days), brain temperature returned to baseline within 0.5 – 2.6 h and rectal temperature did so within 2.3 – 13.2 h. In the control group (normothermia), brain and rectal temperatures remained at about 37 °C throughout.

INTRACRANIAL PRESSURE

The ICP values of the groups receiving hypothermia were significantly lower 24, 48 and 72 h after injury than those of the control group ($P < 0.05$; Table 2). No significant differences were observed between the ICPs of the two hypothermia groups (SBC and MSH) at corresponding time points after initiation of hypothermia. The highest ICP was observed 48 h after injury in all three groups, which is consistent with previous studies.[6]

SERUM SOD LEVELS

As shown in Table 3, the serum SOD levels of the two groups receiving hypothermia had increased sharply on Days 3 and 7 after injury compared with levels before hypothermia. In the SBC group the increases were 45% and 76% on the 2 days, respectively, and in the MSH group they were 60% and 86%, respectively (linear correlations: Day 3, $r = 0.948$ in the SBC

TABLE 1:
Clinical characteristics of groups of patients treated for 3 days with selective brain cooling (SBC), mild systemic hypothermia (MSH) or normothermia (control) after severe traumatic brain injury

Group	No. of patients	Gender Male/female	Mean age (years)	Injury type Traffic accident/other	GCS 3 – 5/6 – 8	Surgery Yes/no
SBC	22	14/8	40.2	13/9	12/10	18/4
MSH	21	12/9	39.6	15/6	11/10	16/5
Control	23	16/7	42.3	16/7	14/9	17/6

GCS, Glasgow Coma Score.

TABLE 2:
Changes in intracranial pressure (mmHg) in groups of patients treated for 3 days with selective brain cooling (SBC), mild systemic hypothermia (MSH) or normothermia (control) after severe traumatic brain injury

Group	24 h after injury	48 h after injury	72 h after injury
SBC	27.38 ± 5.25[a]	29.18 ± 6.75[a]	26.70 ± 4.50[a]
MSH	27.08 ± 4.50	29.70 ± 3.08	26.48 ± 3.75
Control	32.63 ± 3.10	34.80 ± 6.00	31.81 ± 4.50

[a]$P < 0.05$ versus control group.
Values are mean ± SD.

TABLE 3:
Dynamic changes in serum superoxide dismutase (μg/l) levels at different intervals after severe traumatic brain injury in groups of patients treated for 3 days with selective brain cooling (SBC), mild systemic hypothermia (MSH) or normothermia (control)

Group	Day 1	Day 3	Day 7
SBC	387.1 ± 160.2	562.5 ± 98.8[a]	683.2 ± 236.2[a]
MSH	376.5 ± 159.4	602.4 ± 103.5[a]	701.2 ± 193.4[a]
Control	368.6 ± 171.4	446.6 ± 79.5	497.1 ± 101.2

[a]$P < 0.01$ versus control group.
Values are mean ± SD.
The normal reference range for superoxide dismutase is 235 – 535 μg/l.

group and 0.965 in the MSH group; Day 7, $r = 0.968$ in the SBC group and 0.906 in the MSH group, respectively). Although the SOD levels in the two hypothermia groups were not significantly different at corresponding time points after treatment, for each of these groups the difference with respect to the control (normothermia) group was highly significant ($P < 0.01$).

NEUROLOGICAL OUTCOMES

The GOS scores 2 years after injury indicated significant differences in overall neurological outcome between the three groups (Table 4). The frequency of mild or no disability did not differ significantly between the two hypothermia groups (SBC and MSH), but was significantly higher than in the control (normothermia) group ($P < 0.05$). Furthermore, the frequency of good neurological outcome (GOS score 4 or 5) in the SBC and MSH groups was significantly higher than that in the control group (72.7, 57.1 and 34.8%, respectively; $P < 0.05$) (Table 4). The mortality rates in the SBC and MSH groups were significantly lower than in the control group ($P < 0.05$).

COMPLICATIONS

No evidence of severe complications related to hypothermia was found. There were five cases (22.7%) of pneumonia in the SBC group, eight cases (38.1%) in the MSH group and eight cases (34.8%) in the control group. There was no significant difference between the platelet counts of the SBC and MSH

TABLE 4:
Clinical outcome at 2 years of follow-up in groups of patients treated for 3 days with selective brain cooling (SBC), mild systemic hypothermia (MSH) or normothermia (control) after severe traumatic brain injury

Group	No. of patients	Mild or no disability	Moderate disability	Severe disability	Vegetative state	Death
SBC	22	12 (54.5)[a]	4 (18.2)	1 (4.5)	0	5 (27.3)[a]
MSH	21	11 (52.4)	1 (4.8)	3 (14.3)	0	6 (28.6)
Control	23	6 (26.1)	2 (8.7)	3 (13.0)	0	12 (52.2)

[a]$P < 0.05$ versus control group.
Data are numbers (%) of patients. $\chi^2 = 6.0081$, $P < 0.05$ between groups.

groups, but thrombocytopenia occurred in 72.7% (16/22) and 66.7% (14/21) of patients in the SBC and MSH groups, respectively. Although thrombocytopenia was more common in the two hypothermia groups than in the control group (39.1%, nine of 23), all of the platelet counts during hypothermia returned to normal within 3 days after the termination of hypothermia. The rates of haemorrhage in the digestive tract and renal malfunction did not differ significantly among the groups. All complications were treated and improved without severe sequelae. There was no severe abnormality of heart rate, breathing rate, blood pressure, arterial blood gas analysis or blood electrolytes in any group.

Discussion

Hypothermia protects brain tissue after TBI, mainly by limiting ICP, preventing or alleviating secondary brain injury and thus improving cerebral perfusion pressure.[1 – 4] Hypothermia also has positive effects on primary brain injury by facilitating the restoration of membrane function and attenuating cytoskeletal damage and by other means.[8]

Generally speaking, there are two ways of inducing brain hypothermia: by systemic (whole-body) cooling and local (selective) cooling. Owing to the confirmed severe adverse complications, such as shock on rewarming, increased cardiac ischaemia perioperatively and a tendency to bleed even with a normal haemostatic test in patients receiving MSH,[9] SBC has been investigated and applied in clinical studies to maximize neuroprotection while minimizing systemic complications.[10]

There are different methods of achieving SBC. Hagioka *et al.*[11] reported that nasopharyngeal cooling with physiological saline (5%) enables the rapid and selective reduction of brain temperature. Noguchi *et al.*[12] concluded that producing SBC by perfusion of saline into the subdural space was effective and might be used in neurosurgery. Furuse *et al.*[13] showed that perfusion of the carotid artery was another way of producing SBC. Rapid induction of cooling by intravenous administration of cold crystalloid is another technique.[3,7,14] Recently, Ding *et al.*[14] described the production of SBC by regional cooling with local infusion of saline into ischaemic brain territory; in their *in vivo* study, pre-reperfusion infusion effectively induced hypothermia and ameliorated brain injury. It has been demonstrated that early head cooling is effective in preventing some of the earliest brain damage, even in the absence of profound systemic hypothermia.[15]

Although cooling can be induced more efficiently by an endovascular approach than by a surface approach, the placement of an effective central venous or jugular endovascular device requires additional techniques and operating time.[7] However, this approach may not be readily feasible in most clinical settings at present. Nasopharyngeal cooling or intraoperative cooling of the subdural space had a limited effect in lowering the brain temperature of adult patients.[1,3,5] Since surface cooling with a fluid-filled helmet is not a reliable way of reducing core temperature, we produced SBC by combining a cold-water cap with an ice strap around the neck. The results demonstrate that our non-invasive method of inducing SBC was effective. First, the brain temperature in the SBC group was lowered to 33 – 35 °C in less than 2 h, while rectal temperature remained at about 37 °C; thus, complications in other organs due to vasoconstriction during hypothermia may have been prevented. We decided that hypothermia should be applied as soon as possible, except in patients with contra-indications.[1 – 8,13,16] A possible advantage of SBC over MSH is more rapid local hypothermia, because the tissues with decreased perfusion as a result of physiological manipulation or local trauma may be more susceptible to local temperature changes.[10 – 15] Secondly, in the group receiving SBC the ICP was significantly lower (to a similar extent to that in the MSH group) than that in the normothermia control group at each time point. Since the ICP of the SBC group was much lower, this could theoretically improve the neurological prognosis. Thirdly, the serum levels of SOD in the SBC and MSH groups on Days 3 and 7 after injury were significantly higher than those in the normothermia control group. This implies that hypothermia could inhibit the generation of free radicals and could alleviate lipid peroxidation.[17] Statistically significant benefits were observed in survival and neurological outcome in patients treated with SBC and the mortality rate was lower than in previous studies.[18] Lastly, no confirmed evidence of a relationship between severe complications and therapeutic hypothermia was found.

The present study has some shortcomings. The group sizes were relatively small and the ICP values were above 20 mmHg. Therefore, there is a need for additional investigations in experimental and clinical brain injury to define the mechanism by which SBC produces its effects, and for a larger, randomized, controlled trial of SBC to establish a workable protocol in severe TBI.[1,9,16 – 20]

In conclusion, SBC, as applied in this preliminary study – an easy and non-invasive method of producing hypothermia – cannot only reduce elevated ICP and increase serum SOD levels, but can also improve the prognosis without severe complications in patients with severe TBI.

Conflicts of interest

No conflicts of interest were declared in relation to this article.

• Received for publication 1 August 2005 • Accepted subject to revision 12 August 2005
• Revised accepted 6 September 2005

References

1 Vincent JL, Berre J: Primer on medical management of severe brain injury. *Crit Care Med* 2005; **33:** 1392 – 1399.
2 Schwab S, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA: Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke* 2001; **32:** 2033 – 2035.
3 Sahuquillo J, Mena MP, Vilalta A, Poca MA: Moderate hypothermia in the management of severe traumatic brain injury: a good idea proved ineffective? *Curr Pharm Des* 2004; **10:** 2193 – 2204.
4 Battin MR, Penrice J, Gunn TR, Gunn AJ: Treatment of term infants with head cooling and mild systemic hypothermia (35.0 degrees C and 34.5 degrees C) after perinatal asphyxia. *Pediatrics* 2003; **111:** 244 – 251.
5 Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, *et al*: Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365:** 663 – 670.
6 Qiu WS, Liu WG, Shen H, Wang WM, Hang ZL, Zhang Y, *et al*: Therapeutic effect of mild hypothermia on severe traumatic head injury. *Chin J Traumatol* 2005; **8:** 27 – 32.
7 Wen YS, Huang MS, Lin MT, Lee CH: Rapid brain cooling by hypothermic retrograde jugular vein flush. *J Trauma* 2005; **58:** 577 – 581.
8 Haranishi Y, Kawata R, Fukuda S, Kiyoshima T, Morimoto Y, Matsumoto M, *et al*: Moderate hypothermia, but not calpain inhibitor 2, attenuates the proteolysis of microtubule-associated protein 2 in the hippocampus following traumatic brain injury in rats. *Eur J Anaesthesiol* 2005; **22:** 140 – 147.
9 Griffiths AP, Henderson M, Penn ND, Tindall H: Hematological, neurological and psychiatric complications of chronic hypothermia following surgery for craniopharyngioma. *Postgrad Med J* 1988; **64:** 617 – 620.
10 Wang H, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, *et al*: Rapid and selective cerebral hypothermia achieved using a cooling helmet. *J Neurosurg* 2004; **100:** 272 – 277.
11 Hagioka S, Takeda Y, Takata K, Morita K: Nasopharyngeal cooling selectively and rapidly decreases brain temperature and attenuates neuronal damage, even if initiated at the onset of cardiopulmonary resuscitation in rats. *Crit Care Med* 2003; **31:** 2502 – 2508.
12 Noguchi Y, Nishio S, Kawauchi M, Asari S, Ohmoto T: A new method of inducing selective brain hypothermia with saline perfusion into the subdural space: effects on transient cerebral ischemia in cats. *Acta Med Okayama* 2002; **56:** 279 – 286.
13 Furuse M, Ohta T, Ikenaga T, Liang YM, Isono N, Kuroiwa T, *et al*: Effects of intravascular perfusion of cooled crystalloid solution on cold-induced brain injury using an extracorporeal cooling-filtration system. *Acta Neurochir (Wien)* 2003; **145:** 983 – 993.
14 Ding Y, Li J, Luan X, Lai Q, McAllister JP, 2nd, Phillis JW, *et al*: Local saline infusion into ischemic territory induces regional brain cooling and neuroprotection in rats with transient middle cerebral artery occlusion. *Neurosurgery* 2004; **54:** 956 – 964.
15 Iwata O, Iwata S, Tamura M, Nakamura T, Sugiura M, Ogiso Y, *et al*: Early head cooling in newborn piglets is neuroprotective even in the absence of profound systemic hypothermia. *Pediatr Int* 2003; **45:** 522 – 529.
16 Polderman KH: Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence; Part 2: Practical aspects and side effects. *Intensive Care Med* 2004; **30:** 556 – 575, 759 – 769.
17 Hinerfeld D, Traini MD, Weinberger RP, Cochran B, Doctrow SR, Harry J, *et al*: Endogenous mitochondrial oxidative stress: neurodegeneration, proteomic analysis, specific respiratory chain defects, and efficacious antioxidant therapy in superoxide dismutase 2 null mice. *J Neurochem* 2004; **88:** 657 – 667.
18 Suzuki T, Bramlett HM, Dietrich WD: The importance of gender on the beneficial effects of posttraumatic hypothermia. *Exp Neurol* 2003; **184:** 1017 – 1026.
19 Iwata O, Thornton JS, Sellwood MW, Iwata S, Sakata Y, Noone MA, *et al*: Depth of delayed cooling alters neuroprotection pattern after hypoxia-ischemia. *Ann Neurol* 2005; **58:** 75 – 87.
20 Clifton GL: Is keeping cool still hot? An update on hypothermia in brain injury. *Curr Opin Crit Care* 2004; **10:** 116 – 119.

Address for correspondence
Dr WS Qiu
Department of Neurosurgery, The Second Affiliated Hospital, College of Medicine,
Zhejiang University, Hangzhou 310009, China.
E-mail: shihai954@163.com