Intensive Care Med (2002) 28:1563–1573
DOI 10.1007/s00134-002-1511-3

ORIGINAL

Kees H. Polderman
Rudi Tjong Tjin Joe
Saskia M. Peerdeman
William P. Vandertop
Armand R. J. Girbes

Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury

Received: 6 March 2002
Accepted: 4 September 2002
Published online: 4 October 2002

K.H. Polderman (✉) · A.R.J. Girbes
Department of Intensive Care,
VU University Medical Center
PO Box 7057, 1007 MB Amsterdam,
The Netherlands
e-mail: k.polderman@tip.nl
Tel.: +31-20-4443912
Fax: +31-20-6392125

R. Tjong Tjin Joe · S.M. Peerdeman
W.P. Vandertop
Department of Neurosurgery,
VU University Medical Center
PO Box 7057, 1007 MB Amsterdam,
The Netherlands

Abstract *Objective:* Therapeutic hypothermia may improve outcome in patients with severe head injury, but clinical studies have produced conflicting results. We hypothesised that the severe side effects of artificial cooling might have masked the positive effects in earlier studies, and we treated a large group of patients with severe head injury with hypothermia using a strict protocol to prevent the occurrence of cooling-induced side effects. *Design:* Prospective clinical trial. *Setting:* University teaching hospital.
Patients: Hundred thirty-six consecutive patients admitted to our hospital with severe head injury (Glasgow Coma Scale (GCS) ≤8).
Measurements and results: Patients included are the 136 patients with a GCS of 8 or less on admission in whom intracranial pressure (ICP) remained above 20 mmHg in spite of therapy according to a step-up protocol. Those who responded to the last step of our protocol (barbiturate coma) constituted the control group (n=72). Those who did not respond to barbiturate coma (n=64) were treated with moderate hypothermia (32–34°C). Average APACHE II scores were higher (28.9±14.4 vs 25.2±12.1, p<0.01) and average GCS at admission slightly lower (5.37±1.8 vs 5.9±2.1, p<0.05) in the hypothermia group, indicating greater severity of illness and more severe neurological injury. Predicted mortality was 86% for the hypothermia group versus 80% in controls (p<0.01). Actual mortality rates were significantly lower: 62% versus 72%; the difference in mortality between hypothermic patients and controls was significant (p<0.05). The number of patients with good neurological outcome was also higher in the hypothermia group: 15.7% versus 9.7% for hypothermic patients versus controls, respectively (p<0.02). These differences were explained almost entirely by the subgroup of patients with GCS of 5 or 6 at admission (mortality 52% vs 76%, p<0.01; good neurological outcome 29% vs 8%, p<0.01).
Conclusions: Artificial cooling can significantly improve survival and neurological outcome in patients with severe head injury when used in a protocol with great attention to the prevention of side effects. Because there is likely to have been bias against the hypothermia group in this study, the positive effects of hypothermia might even have been underestimated. In addition, our results confirm the value of therapeutic hypothermia in treating refractory intracranial hypertension.

Keywords Head injury · Artificial cooling · Outcome · Intracranial pressure · Side effects · Therapeutic hypothermia

Introduction

Over the past 20 years the outcome of patients with severe head injury has steadily improved due to a combination of various factors. These include more rapid transportation of patients to emergency departments, the advent of specialised trauma centres, improvements in methods of resuscitation, aggressive and early treatment of hypotension and hypoxia, early brain imaging, prompt surgical intervention and the guidance of treatment through monitoring and controlling of intracranial pressure (ICP) [1]. However, mortality remains high, as does the number of patients with severe neurological impairment following head injury. The main goal of therapy in these patients is the prevention of additional injury to the brain in the period following trauma.

Various in vitro and animal studies have demonstrated that mild hypothermia is effective in blocking deleterious chemical cascades and reverses pathophysiological changes such as cerebral thermo-pooling that can take place in the brain following neurological injury [2, 3]. In addition it may prevent re-perfusion injury and cellular damage induced by free radical reactions. On this basis, several clinical trials have been carried out to assess the effectiveness of artificial cooling in patients with severe head injury [4, 5, 6, 7, 8, 8, 10, 11, 12, 13, 14], various (usually cardiothoracic) surgical procedures [15, 16], post-anoxic coma following cardiopulmonary resuscitation [17, 18, 19, 20, 21, 22] and stroke [23, 24, 25]. The initial results in patients with head injury appeared highly promising [4, 5, 6, 7, 8, 9, 10], provided the artificial cooling was initiated shortly after admission [10, 12]. In contrast, a recently published multi-centre study observed no benefits resulting from therapeutic hypothermia and reported more 'days with complications' in patients treated with artificial cooling [14]. The findings of this study, however, may have been influenced by the fact that the side effects of artificial cooling were insufficiently taken into account, leading to a bias against the hypothermia group due to a higher prevalence of episodes of hypovolaemia, hypotension and electrolyte disorders in the hypothermia group [26].

We previously reported that artificial cooling is associated with significant side effects, including significant fluid loss through hypothermia-induced diuresis and electrolyte depletion [25]. This is important because even brief episodes of hypovolaemia can affect cerebral perfusion pressure (CPP) and cerebral blood flow and it has been shown that even very short episodes of decreased CPP can significantly affect neurological outcome [1, 27]. Electrolyte disorders are associated with various forms of cardiac arrhythmias, neuromuscular irritability, vasoconstriction and increased mortality in the ICU [28, 29, 30, 31] and may even negate any potential benefits of artificial cooling. Magnesium appears to be especially important in this regard [28, 29, 30, 32, 33, 34, 35]. We therefore studied the outcome of patients with severe head injury treated with moderate hypothermia, according to a strict protocol in which great attention was paid to the prevention of side effects.

Patients and methods

This study was conducted according to guidelines approved by the hospital ethics committee. All patients with a severe head injury (Glasgow Coma Scale score ≤8 on admission) admitted to our university teaching hospital, a tertiary neurosurgical referral centre, between July 1995 and July 2000 were treated according to a step-up protocol as described previously [32] and depicted schematically in Fig. 1.

A smaller number of patients had GCS higher than 8 at admission but subsequently suffered a deterioration in their neurological conditions; these patients were treated according to the same stepwise protocol and some of them were treated with artificial cooling according to this protocol. Data from these patients were pooled with data from the other patients; however, as this category of patients may represent a slightly different group (relatively high GCS at admission but deterioration shortly thereafter versus low GCS already present at admission), sub-analyses for the two categories of patients were also performed (shown in Table 4).

Standard treatment

A cranial probe (Camino, Integra LifeSciences, Plainsboro, N.J., USA) was inserted in every patient to measure ICP. The primary goals of therapy were stabilisation or improvement of the patient's neurological condition, maintenance of an ICP of 20 mmHg or less (normal value in healthy subjects: ≤15 mmHg) and a mean arterial pressure (MAP) 90 or more with vasoactive mediators (dopamine and norepinephrine) to maintain a cerebral perfusion pressure (CPP = MAP–ICP) of 70 mmHg or more. In patients with ICP higher than 20 mmHg initial treatment included appropriate sedation with the benzodiazepine midazolam (dosage: bolus of 10 mg, continuous dose of 14 (range 10–20) mg/h), the opiate fentanyl (dosage: bolus of 0.25 mg, continuous dose of 0.48 (range 0.35–0.70) mg/h), and propofol (dosage: bolus 20 mg, continuous dose 94 (range 80–110) mg/h), as well as treatment with muscle paralysers (vecuronium bromide, bolus 8 mg, continuous dose 10.4 (range 8–20) mg/h) and administration of mannitol (maximum dose: 100 ml 20% intravenously 8 times daily). Neurosurgical interventions were undertaken when necessary to evacuate subdural lesions or large intracerebral lesions if this was deemed appropriate. Arterial partial pressure of carbon dioxide ($PaCO_2$) concentrations were maintained at 34–40 mmHg; arterial partial pressure of oxygen (PaO_2) levels were maintained above 90 mmHg.

Study protocol

All patients in whom ICP remained higher than 20 mmHg in spite of the above measures were subsequently treated with barbiturates (pentobarbital bolus 100–200 mg, followed by continuous infusion of 100–300 mg/h) until burst suppression, monitored by electroencephalography (EEG). If the ICP responded to this treatment the patient was included in our *control* group. Response was defined as a significant decrease (=20% from baseline value) in ICP within 30 min and a decrease to and stabilisation at levels below 20 mmHg within 60 min after pentobarbital administration. All patients who did not meet these criteria (i.e., patients who failed to respond to barbiturate administration) were included in our *hypo-*

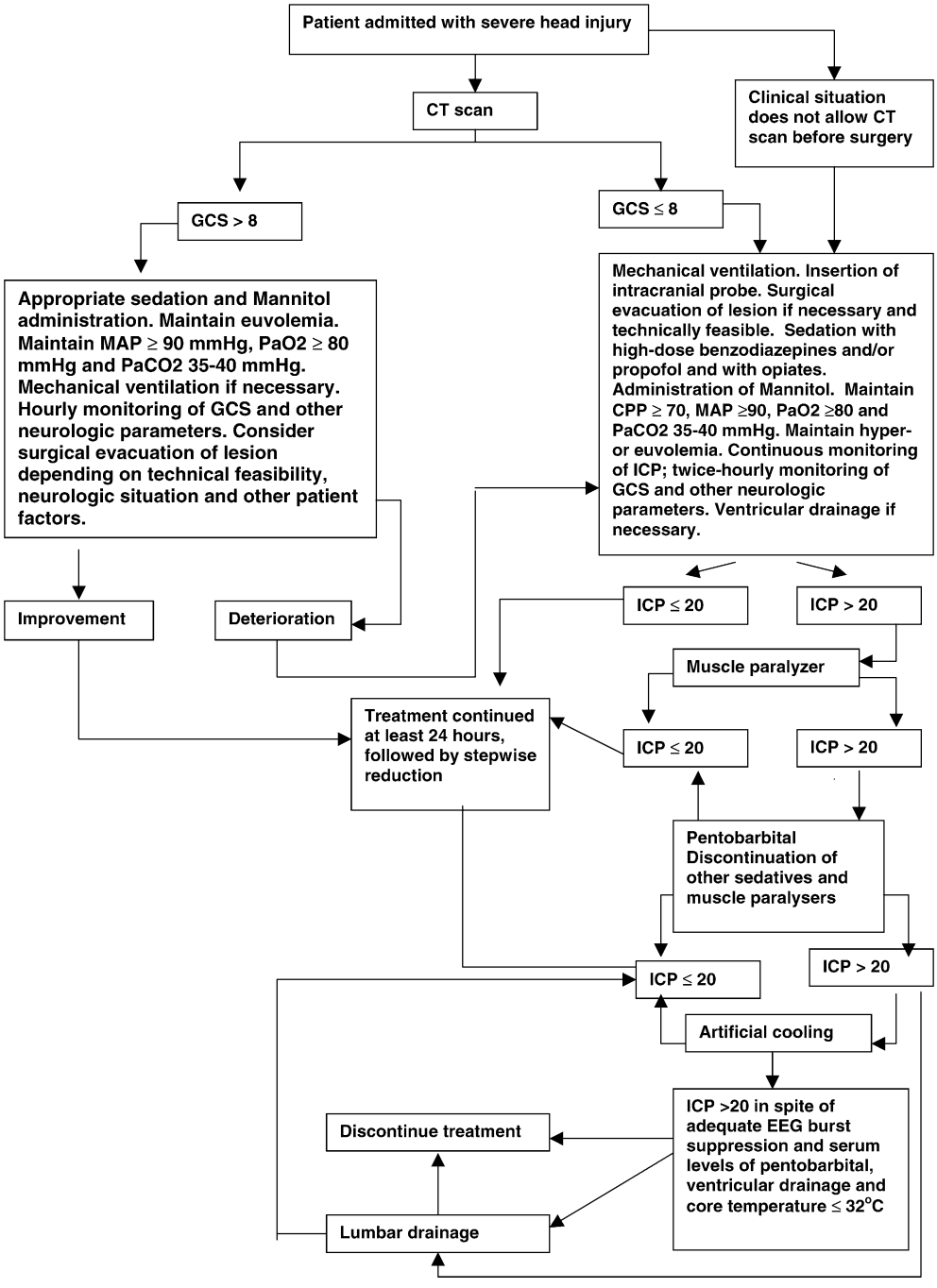

Fig. 1 Protocol for the treatment of patients with severe head injury (*CT* computed tomography, *GCS* Glasgow Coma Scale, *MAP* mean arterial pressure, PaO_2 arterial partial pressure of oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *EEG* electroencephalography)

thermia group. Barbiturate administration was continued in these patients. Previous sedation and muscle paralysis were discontinued in all patients when pentobarbital administration was initiated. Treatment with mannitol was continued in all patients.

Artificial cooling

Artificial cooling was initiated immediately when the above-mentioned steps had failed to control ICP, using water-circulating blankets (Blanketrol II hyper-hypothermia, Cincinnati Sub-Zero, Cincinnati, USA; blanket temperature 4°C). The aim was to lower the body temperature to 32°C as quickly as possible. Once the target core temperature had been achieved, temperatures were maintained by keeping the water-circulating blankets at or slightly below 32°C. If ICP remained at 20 mmHg or less for 24 h, the patient was slowly re-warmed (1°C per 12 h). If ICP rose above 20 mmHg, cooling was re-initiated until ICP decreased to below 20 mmHg.

Preventive measures

All patients (i.e., controls and hypothermia patients) were treated with large volumes of intravenous fluids, initiated at the start of

pentobarbital administration. Upon inclusion in our hypothermia group, patients received an additional dose of fluid (500–1000 ml of saline in 30 min) upon initiation of cooling. Central venous pressure and urine production were monitored continuously in all patients and fluid management was based on these parameters as well as changes in heart rate, wedge pressure in patients in whom a pulmonary artery catheter had been inserted, etc. Every effort was made to maintain CPP at 70 mmHg or higher using intravascular filling and vasoactive medication. Electrolyte levels were measured frequently (at 60min intervals or more frequently when necessary) using a rapid lab device installed in the ICU (RapidLab 855, Chiron Diagnostics, Emeryville, Calif.). This allowed us to correct any electrolyte disorders immediately. The goal of therapy was to maintain high-normal electrolyte levels [Mg ≥1.1 mmol/l, K ≥4.0, P ≥1.0 mmol/l, Ca (corrected for albumin) ≥2.3 mmol/l, free (ionised) Ca ≥1.2 mmol/l].

Table 1 Patient characteristics, clinical parameters, medication and outcome. Student's unpaired *t*-test used for statistical comparisons (*APACHE II* Acute Physiology And Chronic Health Evaluation II, *GCS* Glasgow Coma Scale)

Patient characteristics	Hypothermia group	Controls	*p* value
Number of patients	64	72	
Age (years)	39.2±24.2 (range 16–73)	34.2±29.6 (range 17–72)	<0.02
APACHE II score	28.9±14.4 (range 14–38)	25.2±12.1 (range 11–38)	<0.01
GCS at admission			
8 or higher	10	16	<0.01
7	6	10	NS
6	11	15	NS
5	14	10	0.09
4	10	11	NS
3	13	10	0.08
Computed tomography based assessment of severity of injury[a]			
Class I (no significant abnormalities visible on CT scan)	0	0	NS
Class II (small visible lesions, shift 0–5 mm, cisterns open)	14 (22%)	22 (31%)	NS
Class III (As class II but with compressed cisterns)	13 (20%)	14 (19%)	NS
Class IV (as class III but with shift >5 mm)	10 (16%)	12 (17%)	NS
Class V (surgically evacuated lesion)	15 (23%)	18 (2%)	NS
Class VI (large lesions (>25 cc) not surgically evacuated)	12 (19%)	6 (8%)	<0.05
Head injury as sole significant lesion	21 (33%)	27 (38%)	NS
Polytraumatised	43 (67%)	45 (62%)	NS
Craniotomy (apart from probe insertion)	58	61	NS
Average dose of dopamine (mg/h) before cooling	17.4±14	16.7±13	NS
Average dose of dopamine (mg/h) during cooling	19.2±12	15.8±12	<0.02
Average dose of nor-epinephrine (mg/h) before cooling	0.88±0.32	0.62±0.26	<0.01
Average dose of nor-epinephrine (mg/h)during cooling	1.01±0.24	0.61±0.22	
Number of patients treated with anti-arrhythmic medication	48	32	<0.01
Average amount of mannitol (ml) received in first 3 h of hospital admission (before cooling)	122	126	NS
Average amount of mannitol (ml) received in subsequent 6 h period	84	89	NS
Average amounts of electrolytes administered in first 6 h			
Magnesium (g)	4.2±1.4 (range 3.0–6.2)	1.8±0.5 (range 0–4.0)	<0.01
Potassium (mmol)	83±14 (range 56–130)	41±22 (range 12–60)	<0.01
Phosphorus (mmol)	7.8±2.2 (range 5.6–10.2)	1.4±2.4 mmol (range 0.0–6.8)	<0.01
Average amount of filling in first 6 h of admission (ml)	5389±1857	4135±964	<0.01
Core temperature (°C) before cooling (t=0)	37.5	37.2	NS
Core temperature (°C) during cooling	32.8	37.4	<0.01
Time (h) elapsed until temperature ≤34°C			
From start of cooling	2.8 (range 1.1–4.5)	– –	
From hospital admission	5.2 (range 1.3–17)	– –	

[a] Marshall classification [37]

Outcome

The primary outcome measure was the assessment of patients according to the five-category Glasgow Outcome Scale [36], which was conducted 6 months after hospital discharge by examiners who were unaware of the patients' treatment group assignments. Good recovery (GOS 5) and moderate disability (GOS 4) were designated as favourable outcomes; severe disability GOS 3), a vegetative state (GOS 2) and death (GOS 1) were designated as poor outcomes.

Statistical analysis

Data are expressed as means ± SD. Comparisons between patients treated with hypothermia and controls were carried out using chi-square tests or Fisher's exact test. Comparisons for some simple continuous variables were performed with two-sided *t*-tests. Analysis of variance for repeated measurements (ANOVA) was used for comparison of fluid and electrolyte administration and of serum electrolyte levels within groups (before and during artificial cooling and/or barbiturate administration). Student's *t*-test for unpaired results and, where necessary, Fisher's exact test were used for comparison between pooled measurements of electrolyte levels and amounts of electrolytes administered between hypothermia patients and controls. We considered p less than 0.05 to be statistically significant. Data from patients with GCS above 8 at admission but with a subsequent deterioration in neurological condition were analysed both separately and as pooled data.

Results

Patient inclusion and baseline characteristics

Baseline characteristics of the study patients are shown in Table 1. Most of the patients included in our study were men (group 1: 48/64, group 2: 51/72) and the most common cause of head injury was a motorcycle or car accident. Other causes included assault, bicycle accidents and falls from heights. Causes of injury were evenly matched in the hypothermia patients and controls, with no preponderance of any particular cause in either group (data not shown). Mean APACHE II scores, age and average ICP were slightly higher in the hypothermia group (Table 1). The two groups did not differ significantly in terms of numbers of patients with severe additional injuries, such as abdominal or chest injuries or pelvic fractures.

Mean GCS at admission was slightly lower in group 1, possibly reflecting more severe head injuries in this group; however, the CT-based classification of the severity of the injury (using the modified Marshall scale) [37] did not differ between the groups.

Barbiturates and artificial cooling

Hundred thirty-six patients met the study inclusion criteria and were treated with barbiturates. Within 30 min ICP decreased to below 20 mmHg in 52 patients; these were included in the control group. Barbiturate administration was continued in 29 patients in whom a decrease of 20% or more was observed. After 60 min, ICP had decreased below 20 mmHg in 20 of these 29 remaining patients, who were then also included in the control group (group 2, n=72). Patients who did not respond to barbiturate administration within 30 or 60 min, 55 and 9, respectively, were assigned to the hypothermia group (group 1, n=64). Core temperatures of 34°C or less were reached after an average period of 3.4 h (range 1.5–5.5 h). Temperatures were maintained at 34°C in five patients because of massive diuresis and resulting difficulties in maintaining euvolemia in these patients while their body temperatures were decreasing. This was deemed acceptable because, at 34°C, ICP had decreased to below 20 mmHg in four of these patients and to 23 mmHg in the fifth. Core temperatures of 32–33°C were reached in all the other 59 patients, on average within 4.1 h after initiation of cooling.

Hypothermia was continued until ICP was 20 mmHg or less for 24 h or more, after which the temperature was increased slowly (1°C/12 h). If ICP increased to 20 mmHg or more, the temperature was again decreased until ICP decreased to below 20 mmHg (protocol flow chart shown in Fig. 1). The average duration of hypothermia was 4.8 days (range 24 h–21 days).

Electrolytes and anti-arrhythmic medication

All patients were treated with high doses of electrolytes to prevent electrolyte disorders. The amounts required to achieve this aim were higher in group 1, especially during cooling; when target core temperatures were achieved the amounts of electrolytes required decreased and remained comparable in the two groups (Table 1). Anti-arrhythmic medications (mostly amiodarone; rarely sotalol, flecainide or lidocaine) were used to treat any form of arrhythmia occurring in our patients, except for isolated ventricular or supraventricular premature ventricular contractions (PVCs); when more than four of these occurred per minute anti-arrhythmic medication was also started. Anti-arrhythmic medication according to these criteria was required significantly more frequently in the hypothermia patients. Sodium levels were monitored frequently; levels remained normal in both groups (141±7.4 in group 1, 139.7±6.4 in group 2; p=NS).

Intracranial pressure and cerebral perfusion pressure

Upon inclusion in our study, the average ICP in the 136 patients was 38.4 mmHg (range 24–68). Due to the nature of our protocol, in which hypothermia was used as a last resort, patients in the hypothermia group had signifi-

Table 2 Effect on intracranial pressure (*ICP*), overall mortality and neurological outcome. Student's unpaired *t*-test used for statistical comparisons (*CPP* cerebral perfusion pressure, *GCS* Glasgow Coma Scale, *GOS* Glasgow Outcome Scale, *SDD* selective bowel decontamination)

Patient characteristics	Hypothermia group (*n*=64)	Controls (*n*=72)	*p* value
ICP before barbiturate administration	41±15	36±18	NS
ICP before cooling (mmHg	37±20	<20	<0.01
ICP during cooling (mmHg)	14±8	17±6.2	<0.05
Average time elapsed before normalisation of ICP from moment of injury (h)	5.1±3.3	3.7±2.6	<0.01
Average time (h) elapsed before normalisation of ICP from time of cranial probe insertion (h)	3.1±2.1	1.8±1.4	<0.01
Total amount of time (min) with CPP 60 mmHg in 6h period from moment of probe insertion	22±8	17±11	NS
Total amount of time (min) with CPP 70 mmHg in 6h period from moment of probe insertion	39±20	28±20	<0.01
Late complications			
Delayed intracranial haematomas	4.7% (*n*=3)	5.5% (*n*=4)	NS
Acute renal failure[a]	1.5% (*n*=1)	2.8% (*n*=2)	NS
Persistent renal failure	0.0%	0.0%	NS
Cardiac complications[b]	1.5% (*n*=1)	1.4% (*n*=1)	NS
Pulmonary complications[c]	9.4% (*n*=6)	12.5% (*n*=9)	NS
Deep venous thrombosis	1.5% (*n*=1)	0.0%	NS
ICU mortality	62.5% (*n*=40)	72.2% (*n*=52)	<0.05
Survivors with GCS ≥12 upon leaving the ICU	23.4% (*n*=15)	20.8% (*n*=15)	NS
Survivors with good or excellent neurological outcome (GOS 4 or 5) 6 months after hospital discharge	15.6% (*n*=10)	9.7% (*n*=7)	<0.02

[a] Defined as a rise in serum of creatinine ≥100 µmol/l
[b] Apart from brief and easily treatable arrhythmias with no significant haemodynamic effects
[c] Infections, pneumothorax and bleeding. The hypothermia group was treated with SDD

Table 3 Mortality and neurological outcome: subgroup analysis by Glasgow Coma Scale (*GCS*) at admission. Fisher's exact test used for statistical comparison (*GOS* Glasgow Outcome Scale)

GCS at admission	Hospital mortality			Good/excellent outcome (GOS 4 or 5)		
	Group 1 Hypothermia	Group 2 Barbiturates	*p* value	Group 1 Hypothermia	Group 2 Barbiturates	*p* value
≥7	9/16 (56%)	16/26 (61.5%)	NS	1/16 (5.9%)	3/26 (11.5%)	NS
5–6	13/25 (52%)	19/25 (76%)	<0.01	8/25(32.0%)	3/25 (12.0%)	<0.02
3–4	18/23 (78.3%)	17/21 (80.9%)	NS	1/23 (4.3%)	1/21 (4.8%)	NS
Total	40/64 (62.5%)	52/72 (72.2%)	<0.05	10/64 (15.6%)	7/72 (9.7%)	<0.02

cantly longer periods of time with high ICP. However, using inotropic medication and large volumes of fluid administration, we were able to maintain CPP above 70 mmHg in most patients after ICU admission, even while ICP levels were still (too) high (Tables 1 and 2). Artificial cooling was started in most patients (*n*=54) soon after admission. In a smaller number of patients in relatively good neurological condition and with high GCS at admission (Tables 3 and 4), barbiturate administration and/or cooling were initiated later, when their neurological condition deteriorated within 12 h of hospital admission, with GCS decreasing below 8 points. For this reason the time period elapsing between admission and initiation of cooling was somewhat longer in these patients. In other aspects they were comparable and the reaction of these patients' ICPs to artificial cooling was similar to the response in patients in whom cooling had been initiated earlier. The data shown in Tables 1, 2 and 3 reflect overall results (i.e., pooled data); Table 4 depicts separate data for the patients in whom cooling was started soon after admission and those in whom it was initiated somewhat later.

Intracranial pressure decreased markedly in all patients during cooling, to 14±8 mmHg (range 5–24). ICP values of 20 or less were achieved within 2 h in 39/64 patients, within 3 h in 55/64 patients and within 4 h in 62/64 patients. ICP levels remained above 20 but below 25 mmHg in two patients, one of whom was maintained at a slightly higher temperature because of severe side effects during the induction of hypothermia (described above). The amount of time from the moment of injury until ICP 20 mmHg or lower and the elapsed time from cranial probe insertion until ICP normalisation is presented in Table 3.

Table 4 Subgroup analysis: comparison of hypothermia patients cooled soon after admission and those in whom cooling was initiated later because of deterioration in Glasgow Coma Scale (*GCS*): mortality and outcome. Chi square test was used for statistical comparison

	Hypothermia					Barbiturates		
	Number	Time elapsed until rectal temperature ≤34°C		Outcome		Number	Outcome	
		From start of cooling	From hospital admission	Mortality	Good or excellent outcome		Mortality	Good or excellent outcome
Barbiturates and/or cooling initiated immediately after admission	54	2.8 h (range 1.1–4.5)	4.7 h (range 1.3–5.8)	61% (*n*=33)	17% (*n*=9)	56	75% (*n*=42)	13% (*n*=7)
Subgroup: patients with GCS of 7 at admission	6	3.2 h (range 1.7–4.5)	4.9 h (range 3.6–5.4)	33% (*n*=2)	0% (*n*=0)	10	60% (*n*=6)	30% (*n*=3)
Barbiturates and/or cooling initiated in later phase because of deterioration in clinical parameters and GCS	10	3.2 h (range 1.9–4.2)	10.8 h (range 3.8–17)	70% (*n*=7)	10% (*n*=1)	16	63% (*n*=10)	0% (*n*=0)
Overall	64	2.8 h (range 1.1–4.5)	5.2 h (range 1.3–17)	62.5% (*n*=40)	15.6% (*n*=10)	72	72% (*n*=52)	10% (*n*=7)

Haemodynamic parameters

Arrhythmias occurred in many hypothermia patients, but in most cases these were not serious. Most patients were treated with the above-mentioned anti-arrhythmic agents during the study period; five patients were treated with isoprenaline because of severe sinus bradycardia. All patients received dopamine and norepinephrine to maintain CPP at 70 mmHg or more (Table 1). We were able to keep the patients haemodynamically stable and therefore maintain CPP during cooling. Measurements of cardiac output (CO) carried out in 17 of our patients using a pulmonary artery catheter established a 28% decrease in CO compared to baseline when core temperatures of 33°C or below were achieved, as expected in view of the decrease in metabolism induced by cooling (data not shown).

Mortality and neurological outcome

These data are summarised in Tables 2 and 3. In the hypothermia group, hospital mortality was lower (62.5 vs 72.2%, $p<0.05$), and the number of patients with good neurological outcome higher (15.6 vs 9.7%, $p<0.02$) than in the control group. Average predicted mortality according to the APACHE II scores at ICU admission was 86% versus 80% ($p<0.01$). The mean stay in the ICU and in the hospital was similar in the two groups. The rates of late complications such as delayed post-traumatic intracranial haematomas, infections, deep venous thrombosis and pulmonary, renal and cardiac complications were similar in the two groups (Table 2). In particular, no bleeding complications related to hypothermia were observed.

The differences in outcome between the hypothermia group and controls are explained entirely by the subgroup of patients with GCS of 5 or 6 at admission. In this subgroup 12/25 patients (48%) in the hypothermia group survived, versus 6/25 (24%) in controls (24%) ($p<0.01$). Six months after hospital discharge, 8/26 hypothermia patients (30.7%) had a score on the Glasgow Outcome Scale of 4 or 5, as compared with 3/26 patients (7.7%) in controls ($p<0.02$). In contrast, patients with initial coma scores of 3 or 4 did not benefit from hypothermia (mortality 78.3 vs 80.9%, good neurological outcome 4.3 vs 4.8%). Patients with relatively good coma scores (≥7) upon admission also did not appear to benefit from hypothermia (mortality 60 vs 61.5%, good neurological outcome 5.9 vs 11.5%).

Discussion

In this study we observed clear benefits in survival and neurological outcome in patients with severe head injury and GCS of 5 or 6 at admission who were treated with artificial cooling according to a strict protocol in which great attention was paid to the prevention of side effects. Although overall mortality was high in both treatment groups, it was significantly lower than the predicted mortality according to APACHE II scores at admission, corrected for underlying disease using the appendix from the original APACHE II study [38]. Thus, although crude mortality rates were also high in the hypothermia group, this was to be expected on the basis of their severe injury and high APACHE II scores, and overall outcome was better than expected. In the subgroup of patients with GCS 5–6 the difference between predicted and actual outcome was significantly more pronounced.

Recently, two large studies have demonstrated that therapeutic hypothermia can improve outcome in patients with post-anoxic brain injury following cardiac arrest [21, 22]. However, this treatment remains highly controversial, especially in patients with severe traumatic head injury. In the 1990s a number of papers were published describing beneficial effects of artificial cooling as a means of controlling ICP [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13] and outcome [10]. In contrast, a recently published multi-centre trial by Clifton and associates reported no survival benefit and more "days with complications" in patients treated with hypothermia [14]. However, this particular study may have been influenced by the large number of participating hospitals, with resulting differences in treatment protocols, ICU procedures and various other factors. Moreover, treatment with hypothermia is associated with a number of potentially serious, but preventable, side effects including electrolyte depletion, arrhythmias, hypovolaemia and hypotensive episodes [26, 32]. These side effects appear to be caused in part by hypothermia-associated diuresis [26], as also observed in a previous study by our group [32].

These side effects are especially important in the brain-injured patient, in whom it is of vital importance to maintain euvolemia and "to squeeze [sufficient amounts of] blood through the swollen brain" [1]. It has been shown that even very brief episodes of mild hypotension and/or hypovolaemia can adversely affect outcome [27]. Therefore, in our opinion it is of the utmost importance that physicians using therapeutic hypothermia in any category of patients be aware of the risk of hypothermia-induced polyuria and take appropriate precautions and countermeasures [26, 32].

In addition, various animal experiments and clinical studies have demonstrated the important role of magnesium in the injured brain [33, 34, 39]. Thus, the induction of magnesium depletion by hypothermia is likely to have significant adverse effects on outcome in patients with severe head injury. Moreover, as demonstrated previously by our research group, patients with severe head injury often have hypomagnesemia and depletion of other electrolytes at admission [40]. Thus, potential beneficial effects of hypothermia are highly likely to be obscured by side effects if sufficient precautions are not taken to prevent these from occurring.

In our treatment protocol, great care was taken to avoid all the potentially harmful effects of hypothermia. Large amounts of electrolytes were given to all patients and great care was taken to prevent even the briefest episodes of hypovolaemia and hypotension. As shown in Tables 1 and 2 we were quite successful in achieving this objective. For the reasons set out above, we feel that this is a vital prerequisite to being able to assess the effects of artificial cooling adequately. We observed that fluid and electrolyte requirements were especially high in the initial phase of cooling, while body temperatures decreased. Fluid and electrolyte requirements decreased once the target temperatures had been reached.

As hypothermia-induced hypokalaemia is due to a combination of increased urinary loss and intracellular shift [32], there is a risk for hyperkalaemia during rewarming due to reversal of the intracellular shift, i.e. mobilisation of potassium from the cells. Thus potassium administration should be decreased in this phase and potassium levels should be monitored frequently. Our protocol prescribed slow re-warming and decrease in potassium administration during re-warming; we observed no cases of rebound hyperkalaemia in any of our patients.

The swift induction of hypothermia, pre-empting or correcting the resulting side effects while maintaining euvolemia and adequate CPP at all times, in combination with all the other forms of treatment simultaneously required in brain-injured patients, is a highly complex and difficult procedure. Thus it is hard to control all these variables in a multi-centre research setting. Variations in treatment protocol, monitoring, fluid infusions, surgical procedures, timing of probe insertion, vasoactive medication and other treatments between various centres are highly likely to occur. For this reason we feel that our single-centre results may more adequately reflect the potential benefits of artificial cooling than a multi-centre effort would.

It should be emphasised that artificial cooling, as an experimental form of treatment, was used only as an option of last resort in our protocol. Therefore only patients with refractory ICP elevation, in whom all other therapeutic options had been tried, were included in our protocol. Obviously this category of patients had an extremely poor prognosis and this explains the high overall mortality rate in our study group. However, predicted mortality according to the average APACHE II scores at ICU admission was significantly higher than

observed mortality (predicted: 86% vs 80%; observed: 62.5% vs 72.2% for groups 1 and 2, respectively). We also wish to underscore that the fact that hypothermia was used only as a measure of last resort in our protocol almost certainly induced substantial bias against the hypothermia group. The reason for this is that the control group was comprised of patients in whom earlier treatments (barbiturate coma and mannitol administration) were successful, while hypothermia was used only in patients who failed to respond to these treatments. Therefore, the average time period during which patients had elevated ICP was longer in group 1 than in group 2. This alone implies that any benefits in group 1 are likely to have been underestimated. In addition, the fact that ICP failed to respond to earlier steps in our protocol (including barbiturate administration) may in itself signify a more grave neurological situation in the patients in group 1. However, in spite of the gravity of our patients' neurological conditions *and* the inherent bias against the hypothermia group, we were still able to demonstrate clear benefits of artificial cooling. In our opinion this makes our observations extra poignant and underscores the potential benefits of this form of treatment.

In our study the benefits of hypothermia were limited to patients with GCS of 5 or 6 at admission. The general goal of therapy in all patients with severe head injury is to prevent secondary (additional) damage to the brain. It seems likely that the initial injury was so severe in patients with GCS of 3–4 at admission that they were unable to benefit from treatment ("beyond repair"). Our observations are in agreement with an earlier trial by Marion and associates [10], who also observed the best results in improving neurological outcome in patients with a GCS between 5 and 7 at admission, with no clear benefits in patients with GCS of 3–4.

The group of patients with GCS of 8 or higher at admission who were treated with hypothermia in our study also did not appear to benefit from this treatment. However, this group contained a substantial number of patients (10/16) whose neurological condition deteriorated during ICU stay; they developed refractory rises in ICP, were treated according to our protocol and finally were treated with hypothermia as an option of last resort. Indeed, this subgroup contained all patients in whom hypothermia was induced in a somewhat later phase of their stay. Although hypothermia was effective in controlling ICP in these patients, it seems likely that the events leading to the deterioration in their clinical situation and the concomitant rises in ICP also induced a situation where the patients' brain damage progressed to a level "beyond repair". Thus, although survival was relatively high in this group, good neurological outcome was rare, probably because irreversible brain damage had already occurred at the moment of inclusion in our study. Therefore we cannot rule out that artificial cooling might also be effective in patients with GCS of 7 or more at admission provided it is initiated soon after admission. For what it is worth, the only patient in this group with a good neurological outcome was one of those who had been treated with hypothermia.

Our observations show that therapeutic hypothermia can play an important part in decreasing ICP in patients with severe head injury and improve outcome at least in patients with GCS of 5–6 at admission. However, physicians using this mode of treatment should be aware of the various potentially deleterious side effects and take appropriate preventive measures. In our opinion, the lack of attention to these side effects (including hypomagnesemia, hypovolaemia, brief episodes of arrhythmias and hypotension) may explain the fact that some previous studies were unable to demonstrate the effectiveness of hypothermia.

The mechanism by which hypothermia can prevent brain damage has not yet been fully elucidated. It is likely that more than one mechanism plays a role. These may include decreased brain swelling and lowering of ICP and a decrease in the metabolic rate and oxygen demand in the brain (it has been shown that during moderate hypothermia cerebral metabolism is reduced 5–7% for each centigrade degree reduction in body temperature [41, 42]). Other potential mechanisms are the inhibition of deleterious chemical cascades in injured brain cells, decreases in unfavourable pathophysiological changes such as cerebral thermo-pooling occurring in the brain following neurological trauma, reductions in extracellular concentrations of free radicals and excitatory neurotransmitters such as glutamate, modulation of cytokine production (especially IL-10) and inhibition of leucocyte infiltration into injured brain areas [43, 44].

In most previous studies cooling was discontinued after an arbitrary period of time (usually 24–48 h). We maintained hypothermia for longer periods of time, slowly increasing body temperature after 24 h of ICP less than 20 mmHg and re-initiating artificial cooling if ICP rose above 20 mmHg during re-warming. In addition, we were able to induce hypothermia relatively quickly in our patients, with a shorter time interval than has been reported in most previous studies.

In conclusion, we observed that mortality was significantly lower and neurological outcome significantly better in patients treated with hypothermia and barbiturate coma compared to barbiturate coma alone. Moreover, the results of our study confirm that artificial cooling is a highly effective method to control high ICP in all categories of patients with severe head injury. When used in a strict protocol with great attention to the prevention of side effects, in a specialised neurosurgical centre, survival and neurological outcome can be improved by artificial cooling, at least in patients with GCS of 5 or 6 at admission. It is doubtful whether patients with GCS of 3–4 and persistent refractory high ICP will also benefit from

therapeutic hypothermia; it seems likely that brain damage resulting from the initial trauma is too great in these patients, although hypothermia is effective in controlling ICP even in this category of patients. We were unable to demonstrate long-term benefits from therapeutic hypothermia in patients undergoing neurological deterioration while in hospital (i.e., some time after the initial trauma), although (as in all other categories) hypothermia was effective in lowering ICP. The side effects of hypothermia, although potentially serious, are preventable and/or controllable, and thus should not deter us from using this form of treatment.

References

1. Ghajar J (2000) Traumatic brain injury. Lancet 356:923–929
2. Dempsey RJ, Combs DJ, Maley ME, Cowen DE, Roy MW, Donaldson DL (1987) Moderate hypothermia reduces postischemic edema development and leukotriene production. Neurosurgery 21:177–181
3. Busto R, Globus MY, Dietrich WD, Martinez E, Valdés I, Ginsberg MD (1989) Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904–910
4. Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC (1993) A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 10:263–271
5. Bernard OS (1996) Induced hypothermia in intensive care medicine. Anaesth Intensive Care 24:382–388
6. Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T (1993) Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 79:363–386
7. Tjong Tjin Joe R, Egeler SM, Vandertop WP, Girbes ARJ (1999) Hypothermia reduces intracranial pressure in patients with severe traumatic brain injury (abstract). Intensive Care Med 25 (Suppl 1):S95
8. Tateishi A, Soejima Y, Taira Y, Nakashima K, Fujisawa H, Tsuchida E, Maekawa T, Ito H (1998) Feasibility of the titration method of mild hypothermia in severely head-injured patients with intracranial hypertension. Neurosurgery 42:1065–1069
9. Milde LN (1992) Clinical use of mild hypothermia. J Neurosurg Anesthesiol 4:211–215
10. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST (1997) Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540–546
11. Hayashi N, Hirayama T, Udagawa A, Daimon W, Ohata M (1994) Systemic management of cerebral edema based on a new concept in severe head injury patients. Acta Neurochir Suppl (Wien) 60:541–543
12. Nakamura T, Nagao S, Kawai N, Honma Y, Kuyama H (1998) Significance of multimodal cerebral monitoring under moderate therapeutic hypothermia for severe head injury. Acta Neurochir Suppl (Wien) 71:85–87
13. Metz C, Holzschuh M, Bein T, Woertgen C, Frey A, Frey I, Taeger K, Brawanski A (1996) Moderate hypothermia in patients with severe head injury: cerebral and extracerebral effects. J Neurosurg 85:533–541
14. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Wagner FC, Marion DW, Luerssen TG, Chesnut RM, Schwartz M (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556–563
15. Veeragandham RS, Hamilton IN Jr, O'Connor C, Rizzo V, Najafi H (1998) Experience with antegrade bihemispheric cerebral perfusion in aortic arch operations. Ann Thorac Surg 66:493–499
16. Safi HJ, Letsou GV, Iliopoulos DC, Subramaniam MH, Miller CC 3rd, Hassoun H, Asimacopoulos PJ, Baldwin JC (1997) Impact of retrograde cerebral perfusion on ascending aortic and arch aneurysm repair. Ann Thorac Surg 63:1601–1607
17. Bernard SA, Jones BM, Horne MK (1997) Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 30:146–153
18. Sterz F, Safar P, Tisherman S, Radovsky A, Kuboyama K, Oku K (1991) Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 19:379–389
19. Sterz F, Zeiner A, Kurkciyan I, Janata K, Mullner M, Domanovits H, Safar P (1996) Mild resuscitative hypothermia and outcome after cardiopulmonary resuscitation. J Neurosurg Anesthesiol 8:88–96
20. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346:557–563
21. The Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549–556
22. Park CK, Jun SS, Kim MC, Kang JK (1998) Effects of systemic hypothermia and selective brain cooling on ischemic brain damage and swelling. Acta Neurochir Suppl (Wien) 71:225–228
23. Schwab S, Schwarz S, Aschoff A, Keller E, Hacke W (1998) Moderate hypothermia and brain temperature in patients with severe middle cerebral artery infarction. Acta Neurochir Suppl (Wien) 71:131–134
24. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W (1998) Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 29:2461–2466
25. Schwab S, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA (2001) Feasibility and safety of moderate hypothermia after massive hemispheric infarction. Stroke 32:2033–2035
26. Polderman KH, Girbes ARJ, Peerdeman SM, Vandertop WP (2001) Hypothermia (review). J Neurosurgery 94:853–855
27. Fearnside MR, Cook RJ, McDougall P, McNeil RJ (1993) The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of prehospital, clinical and CT variables. Br J Neurosurg 7:267–279
28. Nadler JL, Rude RK (1995) Disorders of magnesium metabolism. Endocrinol Metab Clin North Am 24:623–641
29. Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW (1993) Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med 21:203–209

30. Chernow B, Bamberger S, Stoiko M, Vadnais M, Mills S, Hoellerich V, Warshaw AL (1989) Hypomagnesemia in patients in postoperative intensive care. Chest 95:391–397
31. Bollaert PE, Levy B, Nace L, Laterre PF, Larcan A (1995) Haemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. Chest 107:1698–1701
32. Polderman KH, Peerdeman SM, Girbes ARJ (2001) Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurgery 94:697–705
33. McIntosh TK, Vink R, Yamakami I, Faden AI (1989) Magnesium protects against neurological deficit after brain injury. Brain Res 482:252–260
34. Vink R (1988) Decline in intracellular free Mg2+ is associated with irreversible tissue injury after brain trauma. J Biol Chem 263:757–761
35. Schmid-Elsaesser R, Hungerhuber E, Zausinger S, Baethmann A, Reulen HJ (1999) Combination drug therapy and mild hypothermia: a promising treatment strategy for reversible, focal cerebral ischemia. Stroke 30:1891–1899
36. Jennet B, Bond M (1975) Assessment of outcome after severe brain damage: a practical scale. Lancet i:480–484
37. Marshall LF, Marshall SB, Klauber MR, Van Berkum Clark M, Eisenberg H, Jane JA, Luerssen TG, Marmarou A, Foulkes MA (1992) The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma 9 (Suppl 1):S287–292
38. Knaus WA. Draper EA, Wagner DP, Zimmerman JE (1985) Apache II: a severity of disease classification system. Crit Care Med 13:818–829
39. Polderman KH, Bloemers F, Peerdeman SM, Girbes ARJ (2000) Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. Crit Care Med 28:2022–2025
40. Vink R, Cernak I (2000) Regulation of intracellular free magnesium in central nervous system injury. Front Biosci 5:656–665
41. Rosomoff HL, Holaday A (1954) Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 179:85–88
42. Stone GH, Donnelly C, Frobese AS (1956) The effect of lowered body temperature on the cerebral haemodynamics and metabolism of man. Surg Gynecol Obstet 103:313–317
43. Tisherman SA, Rodriguez A, Safar P (1999) Therapeutic hypothermia in traumatology. Surg Clin North Am 79:1269–1289
44. Milde LN (1992) Clinical use of mild hypothermia for brain protection: a dream revisited. J Neurosurg Anesthesiol 4:211–215