Experience with prolonged induced hypothermia in severe head injury

Stephen A Bernard, Bruce MacC Jones and Michael Buist

Background: Recent prospective controlled trials of induced moderate hypothermia (32–34°C) for relatively short periods (24–48 h) in patients with severe head injury have suggested improvement in intracranial pressure control and outcome. It is possible that increased benefit might be achieved if hypothermia was maintained for more periods longer than 48 h, but there is little in the literature on the effects of prolonged moderate hypothermia in adults with severe head injury. We used moderate induced hypothermia (30–33°C) in 43 patients with severe head injury for prolonged periods (mean 8 days, range 2–19 days).

Results: Although nosocomial pneumonia (defined in this study as both new chest radiograph changes and culture of a respiratory pathogen from tracheal aspirate) was quite common (45%), death from sepsis was rare (5%). Other findings included hypokalaemia on induction of hypothermia and a decreasing total white cell and platelet count over 10 days. There were no major cardiac arrhythmias. There was a satisfactory neurological outcome in 20 out of 43 patients (47%).

Conclusion: Moderate hypothermia may be induced for more prolonged periods, and is a relatively safe and feasible therapeutic option in the treatment of selected patients with severe traumatic brain injury. Thus, further prospective controlled trials using induced hypothermia for longer periods than 48 h are warranted.

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Introduction

Induced hypothermia (IH) was first used in clinical practice as an adjunct to the therapy of traumatic brain injury (TBI) over 50 years ago [1]. Between 1950 and 1960, several (uncontrolled) series were reported [2-5] in which IH was included in the management of patients with TBI. Although IH is still commonly used for neurological protection during cardiac surgery [6], the use of IH in TBI was largely abandoned after 1960 due to perceived problems of sepsis, cardiac arrhythmias and coagulopathy [7-9]. Recently, the first prospective controlled trials of IH in TBI were reported [10-12]. These have suggested benefit in intracranial pressure control and outcome when IH was used for 24-48h in the treatment of TBI. Further improvements in outcome may be possible if IH could be used for longer periods, but the effects of prolonged IH have not been well described in the literature. We used IH in 43 patients with severe TBI for periods longer than 48h and report the incidence of complications of prolonged IH in patients with severe TBI.

Methods

Dandenong Hospital is a 385-bed hospital situated in southeast Melbourne, Victoria, Australia. It services a

population of approximately 500000 people. The intensive care unit has seven beds and has an average of 500 admissions per year, 15% of which are because of major trauma (Injury Severity Score > 15). Of these, 30% suffer severe closed TBI, defined as a Glascow Coma Scale (GCS) score below 9 at any time after 6 h following injury.

All patients with severe TBI were treated with the following: controlled mechanical ventilation; moderate hypocapnea (partial pressure of carbon dioxide 30mmHg); avoidance of hypoxia (partial pressure of oxygen >100mmHg); moderate fluid restriction (15ml/kg per day dextrose/saline) once normal blood volume had been restored; normothermia (36–37°C rectal temperature); and sedation, when required, to control coughing. Mannitol (0.5g/kg) was given to patients when there was any clinical evidence of deterioration due to cerebral oedema. In addition, other therapies such as muscle relaxants, anticonvulsants and steroids were prescribed on an individual basis.

Monitoring included blood pressure, continuous electrocardiogram, central venous pressure, urine output and rectal temperature. Investigations such as arterial blood gas analysis, chest radiography and electrolyte analysis were performed at least daily. Arterial blood gases were analyzed immediately after collection in the intensive care unit. All arterial blood gas samples were temperature corrected to 37°C. Full blood examination, liver function tests, and specimens for sputum and urine microscopy and culture were collected three times per week. Central venous catheter tips were cultured after removal.

Computed tomography scans of the brain were performed on admission, at 24h and then as clinically indicated. Intracranial pressure monitoring, using an intraventricular catheter, was only occasionally used before 1996 and routinely since. Patients were nil-by-mouth for 4–5 days, after which enteral feeding was attempted. If this had not been established by 7 days, in general, total parental nutrition was instituted.

A group of 43 patients were selected to undergo IH to a rectal temperature of 33°C. This selection was made on an individual basis. In 20 out of 43 patients there was neurological deterioration, despite routine therapy. In 11 out of 43, there had been a failure to improve despite routine therapy. Usually, these patients had shown a significant, but transient improvement after mannitol administration. In 12 out of 43 patients, the decision to institute IH was made pre-emptively when clinical examination, computed tomography scan and/or operative findings suggested that cerebral oedema would be life threatening.

The induction of hypothermia was achieved with surface cooling using ice packs, applied around the head, neck, trunk, groin and axillae. Sedation and muscle relaxation were given as required to suppress shivering until the temperature reached 34°C, after which patients tended to become poikilothermic. Patients were maintained at 31–33°C, at which temperature minimal sedation was required, allowing accurate clinical assessment and immediate investigation and therapy of any neurological deterioration.

Patients were rewarmed when there had been a satisfactory improvement in their conscious state, when it was clear that IH had not helped (usually at 5–7 days) or when the patient had deteriorated and assessment for brain death was required. Rewarming was passive, and 1°C increase per day was allowed, with immediate recooling if there was clinical neurological deterioration.

Results

The admission GCS scores of the 43 patients studied are given in Table 1, clinical profiles in Table 2 and mechanisms of injury in Table 3. It can be seen from the Injury Severity Score that many of these patients had multisystem trauma. The outcomes of these patients are shown in Table 4. A total of 20 out of the 43 (47%) patients who

Table 1

Patient Glascow Coma Scale scores (lowest score after 6 h)

Glascow Coma Scale score	Numbers of patients
3	8
4	6
5	14
6	10
7	3
8	2

Table 2

Clinical profiles of 43 patients

Characteristic	Mean	Standard deviation	Range
Age (years)	22	9.7	9–53
APACHE-2 score	17	3.7	11-28
Injury Severity Score	32	8.0	25-59
Days cooled (<34°C)	8	4.3	2-19
Days ventilated	16	11	3-66
Days in ICU	18	13	3-85

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

underwent IH eventually made a good recovery, returning home after rehabilitation with minimal or mild disability. Three patients remained moderately disabled and five severely disabled. Three patients remained in a persistent vegetative state and were eventually discharged to a chronic care facility. One died at 3 months and another at 5 months after discharge; the third patient remains alive at 24 months. There were 12 other deaths in this group. Eight patients proceeded to brain death despite maximum therapy and required rewarming to 35°C for brain death certification. Two patients died of sepsis, both in the setting of nosocomial pneumonia. One patient developed a carotid-cavernous fistula and was transferred to another centre for further evaluation and management. She died several weeks later without neurological improvement. One patient died in the general ward of pneumonia 3 weeks following discharge from the intensive care unit.

Complications

Respiratory infection

The diagnostic criteria for nosocomial pneumonia are controversial [13]. Pneumonia was defined in this study as new chest radiograph opacities, together with a recognized respiratory pathogen cultured from a tracheal aspirate. There were new chest radiograph opacities seen in 22 out

Table 3

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Table 4

Glascow Ou	Itcome Coma	Score at	hospital	discharge	
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Outcome	Glascow Coma Scale outcome score
Good recovery (normal/near no	ormal) 20
Moderate disability	3
Severe disability	5
Vegetative	3
Deaths	12

of 43 (51%) patients and a sputum pathogen cultured in 28 out of 43 (65%) at some time during IH. Pneumonia, as defined above, occurred in 19 out of 43 (45%). This resolved without complication in 14 of these 43.

Sepsis syndrome

Sepsis syndrome may be defined as hypotension not due to hypovolaemia or cardiac failure in the setting of active infection, with or without positive blood culture [14]. A total of four out of 43 patients (9%) developed sepsis syndrome during IH, all with a focus of infection in the chest. Two of these had positive blood cultures (one for *Staphylococcus aureus* and one for *Pseudomonas aeruginosa*) and two had negative blood cultures. Two patients died despite physiotherapy, antibiotics and haemodynamic support, one with *P. aeruginosa* in the blood culture and one with negative blood cultures, but both with new chest radiograph changes. There were no central nervous system, urine or central venous catheter infections identified in the present study.

Cardiac arrhythmias

There were several patients with sinus bradycardia, but all maintained adequate blood pressure without specific therapy. Ventricular ectopy was occasionally seen in association with hypokalaemia. There were no life-threatening cardiac arrhythmias. Osbourne waves were often, but not always, seen on the 12-lead electrocardiogram.

Acid-base changes

All patients were mechanically ventilated to control the partial pressure of carbon dioxide at 30 mmHg, causing a mild respiratory alkalosis. When arterial blood gases were corrected for temperature, an apparent metabolic alkalosis developed in addition to the respiratory alkalosis. This was maintained while patients were hypothermic. Table 5 shows the pattern in the pH (mean±standard deviation) over the first 10 days of IH.

Electrolyte changes

Table 5 shows the potassium levels (mean \pm standard deviation) for the first 10 days of IH. Of note was the initial hypokalaemia (ie <3.5 mmol/l) in the first 24 h. Profoundly low potassium (1.2 mmol/l) was unexpectedly found in one patient when ventricular ectopy was noted. This resolved with vigorous intravenous potassium supplementation. No patient developed significant hyperkalaemia on rewarming.

Thrombocytopenia

There was a gradual decline in platelet numbers over a 10-day period, as shown in Table 5 (mean \pm standard deviation). Thirteen patients (30%) developed thrombocytopenia (a platelet count < 100 000/mm³) at some time during IH. Several of these patients had platelet supplements for surgical procedures, such as tracheostomy or central venous catheter change. No patient suffered a major bleeding complication.

Neutropenia

The total white cell count (mean±standard deviation) over the first 10 days is shown in Table 5. No patient developed neutropenia (total white cell count <1000/mm³). Differential counts were rarely requested, so it is not possible in the present study to identify the effects of IH on individual white cell types.

Gastrointestinal tract

A total of 23 out of 43 (53%) patients required total parenteral nutrition, having failed a trial of enteral feeding. A further eight patients tolerated enteral nutrition and 12 were not fed at all during IH.

Delayed wound healing/wound infection

One patient, who had undergone laparotomy on admission, suffered wound dehiscience on day 7 that required resuturing.

Pancreatitis

One patient developed abdominal tenderness and a diagnosis of pancreatitis was made on the basis of a rise in the serum amylase and exclusion of other causes. This settled without consequence.

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otassium (mmol/l)	3.9 土 0.4	3.5 ± 0.7	4.0 ± 0.7	4.0 土 0.4	3.8 ± 0.6	4.1 土 0.6	4.0 土 0.5	4.1 土 0.6	4.3 土 0.4	4.1 土 0.6	4.1 土 0.5
Platelets (×1000/mm³)	266 土 241	236 ± 177	216 ± 93	199 ± 90	234 ± 177	161 ± 68	188 土 142	170 ± 90	154 土 78*	155 土 78*	121 ± 94*
^r otal white cells ×1000/mm ³)	17.9 ± 6.2	15.4 ± 6.2	15.9 土 7.2	13.0 ± 5.7	13.6 ± 5.2	10.3 土 4.4	12.6 ± 6.2	11.3 ± 6.4	11.5 土 4.5	12.7 土 4.7	13.4 土 4.9
The day 0 column provide	s the test result	ts on day of indu	uction of hypoth	ermia. Values a	are * <i>P</i> •	< 0.05, versus	day 0.				

Discussion

There is evidence that cerebral ischaemia occurs after severe TBI [15] and therapy is directed towards the adequate supply of oxygen to meet cerebral metabolic demand, in order to avoid a 'secondary' injury [16]. Moderate hypothermia is theoretically attractive in this setting, because there is a 7% decrease in the cerebral metabolic rate for oxygen per 1°C decrease in temperature without a corresponding decrease in cerebral oxygen supply [17]. In addition, moderate hypothermia lowers intracranial pressure [10–12,18] and acts as an anticonvulsant [19].

The use of IH in severe TBI was first suggested by Fay in 1945 [2] when he observed dramatic improvement in a patient whose temperature was lowered from 38.3°C to 32.7°C. During the 1950s, there were further anecdotal reports of apparent improvement in outcome when IH was instituted in the setting of severe TBI [2–5]. There was little use of IH in adults with TBI during the 1960s and 1970s until recently, however.

Marion *et al* [10] compared 40 patients with severe TBI who underwent moderate IH (32–33°C for 24h) with 42 patients maintained at normothermia. In IH patients with a GCS score in the range 5–8, there were significant improvements in intracranial pressure and outcome, with differences in systemic complications.

Shiozaki *et al* [11] used IH in patients with severe TBI who had uncontrolled intracranial hypertension despite barbiturate therapy. Sixteen patients were randomized to moderate IH (34°C for 48 h) with 17 similar patients acting as control individuals. In the patients undergoing IH, the intracranial pressure decreased by a mean of 10.4 mmHg and cerebral perfusion pressure increased by a mean of 14.0 mmHg. In the normothermic group, 12 out of 17 patients showed progressive elevation of intracranial pressure, despite conventional reduction therapies. Eight patients (50%) in the IH group and three (18%) in the control group survived (P < 0.05), whereas five (31%) in the hypothermia group and 12 (71%) in the control group died of uncontrollable intracranial hypertension (P < 0.05).

In a third study, Clifton *et al* [12] randomized 22 patients with severe TBI to standard therapy, including normothermia, and 24 patients to similar therapy but including IH $(32-34^{\circ}C \text{ for } 48 \text{ h})$. There were no significant differences between the two groups at entry, but there was a trend towards improved outcome; there was a 16% increase in patients with good outcome in the hypothermic group at 3 months, but this was not significant.

expressed as means ± standard deviation.

There is evidence that IH carries an increased risk of complications. For example, in trauma patients hypothermia is associated with an increased mortality rate [20,21]. In both of these studies, hypothermia was not deliberately induced and was usually associated with vigourous resuscitation. In a study of IH in paediatric patients with anoxic brain injury after near drowning [8], IH increased the incidence of neutropenia and sepsis. A study of 200 patients undergoing major surgery [22] found that hypothermia increased the rate of wound infection and duration of hospital stay.

The major morbidity in the present patients was nosocomial pneumonia. The diagnosis of nosocomial pneumonia in patients undergoing mechanical ventilation may be difficult [13] and generally includes chest radiograph changes together with any two of fever, leucocytosis, hypoxaemia and culture of a repiratory pathogen obtained by bronchoalveolar lavage or protected brush. Thus, in the present series there may have been an over-diagnosis of pneumonia, because bronchoalveolar lavage or protected brush specimens were not routinely obtained. Other indicators of pulmonary infection, such as fever and neutrophilia, also were not included as markers of pulmonary infection. Pneumonia (defined in this study as new chest radiograph opacities, together with a recognized respiratory pathogen cultured from a tracheal aspirate) occurred in 20 out of 43 (47%), which is comparable to rates found in other series of patients with TBI [23]. With antibiotic therapy and physiotherapy, only two out of 43 (5%) patients died of sepsis secondary to pneumonia. Although four patients died after discharge from the intensive care unit, the deaths occurred several weeks after rewarming and appeared to be unrelated to hypothermia. Another study of IH (for 48h) in TBI [24] showed that there was no increase in pulmonary complications compared with concurrent control individuals.

There have also been reports that hypothermia may be associated with thrombocytopenia [25] and an increase in bleeding complications [26,27]. Thrombocytopenia developed in 13 out of 43 patients in our series, but there were no haemorrhagic complications. Another study that measured clotting times during IH for TBI [28] found no increase in bleeding complications. Neutropenia has been previously reported as a complication of IH [8,29] but this was not found in the present study.

The induction of hypothermia shifts potassium into cells [30,31] and may cause ventricular ectopy. Careful supplementation is required, because rebound hyperkalaemia during rewarming is a potential danger [32].

The present observations regarding arterial blood gases (temperature corrected) shows that an apparent metabolic alkalosis develops, in addition to the respiratory alkalosis caused by controlled hypocapnea. No patient in this series developed a metabolic acidosis, which may be seen in accidental hypothermia [33]. Although we did not routinely measure lactate levels, another study in patients with IH and severe TBI [34] found no increase in lactate levels compared with normothermic control individuals.

The combined effect of TBI, IH and sedation may lead to paralytic ileus and patients may require total parenteral nutrition. Because metabolic rate decreases by 7% for each 1°C decrease in body temperature [7], caloric intake may be prescribed accordingly. Hyperglycaemia may occur in hypothermic patients and insulin may be required [35]. Pancreatitis has been reported in accidental hypothermia [36] and this was observed in one patient in the present series, but resolved without complication.

The technique of induction and maintenance of hypothermia have been discussed elsewhere [37]. Rewarming after a significant period of IH should be slow, because rapid increases in temperature may be associated with increased cerebral oedema, and this neurological deterioration requires prompt recooling [38]. Two patients in the present series required IH for very prolonged periods (18 days and 19 days) because recooling was required.

In the present retrospective study, we are unable to conclude that IH improves outcome. There was patient bias in selection for hypothermia and it is difficult to determine the effects of changes in hyperventilation and fluid therapy that occurred during the course of the study. Nevertheless, we suggest that this study provides evidence that IH for more prolonged periods than 48h in adults with severe TBI appears to be feasible, provided there is prompt diagnosis and aggressive management of nosocomial pneumonia during maintenance of IH. Overall, sepsis does not appear to carry an unacceptable mortality. The platelet count needs to be regularly measured and, if low, supplemented for surgical procedures such as tracheostomy. The potassium level needs to be carefully monitored and corrected at induction of hypothermia. Because there is a theoretical benefit in the use of IH in TBI, and evidence of safety and efficacy of short-term (24-48h) IH in prospective controlled trials, we conclude that the use of moderate IH (30–33°C) for periods longer than 48h warrants further randomized prospective controlled trials in adults with severe TBI.

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