

## Traumatic Brain Injury: Treatment with Mild Prolonged Hypothermia

Alaa M Atia\* and Khaled A Abdel-Rahman

Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Egypt

\*Corresponding author: Alaa M Atia, Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Egypt, Tel: 0201223591937; E-mail: alaaguhina@yahoo.com

Received date: June 03, 2016; Accepted date: July 25, 2016; Published date: July 29, 2016

Copyright: © 2016 Atia AM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Introduction:** Hypothermia has been used as a method of brain protection in patients with traumatic brain injury (TBI) for many years. The protective effects of hypothermia are related to the inhibition of the excitatory amino acids (EAA) release including glutamate. The hypothermic decline of the cerebral metabolic rate of oxygen is also another mechanism of brain protection because it maintains the aerobic metabolism of the brain.

**Aim of the work:** To study the effect of mild hypothermia on the outcome and complications in severe head trauma.

**Patients and methods:** Ninety four patients (16-60 years old) with severe head trauma (Glasgow coma scale  $\leq$  8) were classified into hypothermic group (n=47) and normothermic group (n=47). The jugular venous bulb oxygen saturation, the jugular venous lactate, the Glasgow outcome scale at hospital discharge (GOS-HD), the length of ICU stay and other variables were measured and recorded.

**Results:** Mild hypothermia improved the jugular venous bulb oxygen saturation, decreased the jugular venous lactate, with no effect on (GOS-HD).

**Conclusion:** Prophylactic mild hypothermia lacks any effect on the outcome in patients with TBI, although there is improvement in the cerebral oxygenation and decrease the oxygen extraction and prevention of the anaerobic metabolism by decreasing the level of serum lactate. A subgroup of patients with intracranial hematoma may benefit from this type of treatment.

**Keywords:** Traumatic brain injury; Hypothermia

### Introduction

Hypothermia has been widely recognized as an effective cytoprotectant. It has been studied to improve outcome from myocardial infarction, organ transplantation, cardiopulmonary bypass, spinal cord injury, intestinal ischemia, and neonatal hypoxia-ischemia [1].

Traumatic brain injury (TBI) has been shown to cause marked elevation in glutamate concentrations, which is responsible through excitotoxicity for neuronal injury or death, making secondary injury as potentially lethal as primary injury [2].

Hypothermia's protective effect has long been thought to be due to preservation of metabolic stores, as cooling the brain leads to approximately 5% reduction in oxygen and glucose consumption per degree centigrade [3].

The aim of this work is to study the effect of mild hypothermia on the outcome and complications in severe head trauma.

### Patients and Methods

This study was carried out in the trauma ICU at Assiut University Hospital. The research protocol was approved by the Clinical Research Ethics Committee of our university. In this randomized controlled

clinical trial, we compared the effect of mild prolonged hypothermia versus normothermia in 94 adult patients with severe TBI with a score  $\leq$  8 on Glasgow coma scale (GCS).

We excluded patients with major systemic injuries, prolonged hypoxemia, sustained hypotension, previous C.N.S lesion, pregnancy and patients with hepatic, renal or diabetic diseases.

Patients met our entry criteria were assigned randomly into one of two groups: HT group (mild hypothermia group) or NT group (normothermia group) using computer generated random number table. An informed consent was obtained from patients guardians.

Patients of both groups were admitted within 6 hours to the trauma ICU. Arterial line, jugular venous bulb (JVB) and central venous catheters were inserted for all patients. Management of the patients were according to our institutional protocol for head injured patients including intubation and mechanical ventilation with sedation and relaxation for at least 48 hours, dehydrating measures, arterial CO<sub>2</sub> level (PaCO<sub>2</sub>) was kept around 35 mmHg, and serum glucose was controlled below 200 mg/dl.

Induction of cooling in HT group performed with both invasive and non-invasive techniques, invasive techniques included injection of intravascular cold saline 8°C at the rate of 30 ml/kg/hour and nasogastric lavage with iced saline. Non-invasive techniques included skin exposure, fans, application of ice packs, refrigerated cooling pads. Once the nasogastric temperature reached 34°C, invasive maneuvers

stopped and non-invasive were continued to maintain temperature between 34°C and 36°C for the next 72 hours. The invasive maneuvers may be used again if non-invasive failed to maintain the target temperature. After 72 hours of cooling, patients were passively rewarmed over a period of 6 hours to a temperature not more than 37.5°C by discontinuation of the above mentioned measures.

For patients in NT group, temperature was kept between 37°C and 37.5°C for the entire 3 days after trauma. Any drop in temperature below desired level in both groups was treated using warming blankets.

For measurement of JVB blood oxygenation, the internal jugular vein was cannulated in the cephalad direction, and the position of the catheter tip was confirmed by either a lateral or an antero-posterior (AP) neck radiograph. On the lateral film, the catheter tip must be above the disc of C1/C2 and as close to the skull base as possible. On AP view, a correctly placed tip should lie cranial to a line extending from the atlanto-occipital joint space and caudal to the lower margin of the orbit. The JVB samples were withdrawn at a rate of 0.5 ml/min to avoid extracranial contamination [4]. For estimation of the arterial-jugular oxygen content difference (AJDO<sub>2</sub>) we used the following equations:

$AJDO_2 \text{ (ml.dl}^{-1}\text{)} = \text{arterial oxygen content} - \text{jugular venous oxygen content}$

$AJDO_2 = (\text{Hb} \times 1.39 \times \text{SaO}_2 / 100 + 0.003 \times \text{PaO}_2) - (\text{Hb} \times 1.39 \times \text{SjO}_2 + 0.003 \times \text{PjO}_2)$ .

Where Hb, hemoglobin concentration (g.dl<sup>-1</sup>); SaO<sub>2</sub>, arterial oxygen saturation; SjO<sub>2</sub>, jugular venous oxygen saturation PaO<sub>2</sub>, arterial oxygen tension (mmHg); PjO<sub>2</sub>, jugular venous oxygen tension (mmHg); 1.39, the amount of oxygen that combines with Hb (mlgm<sup>-1</sup>); 0.003, the solubility of oxygen in blood (ml of oxygen per dL of blood per mmHg PaO<sub>2</sub>).

### Data collection

Patients' characteristics as age, sex, GCS on admission were recorded. Mean arterial blood pressure, heart rate, arterial pH, arterial oxygen tension and temperature were recorded every day for the first 3 days. JVB samples for ABG and JVB lactate were taken before hypothermia and after 24, 48, and 72 hours, arterial and JVB blood samples were used for estimating AJDO<sub>2</sub>.

Hemoglobin level, white blood cell count, prothrombin time, serum potassium, serum creatinine were recorded at the end of the third day.

At discharge from ICU: duration of mechanical ventilation, length of ICU stay and incidence of complications were recorded.

At hospital discharge: length of hospital stay and Glasgow outcome score [5] was recorded (Table 1).

1. Death	Severe injury or death without recovery of consciousness
2. Persistent vegetative state	Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions
3. Severe disability	Severe injury with permanent need for help with daily living
4. Moderate disability	No need for assistance in everyday life, employment is possible but may require special equipment.
5. Low disability	Light damage with minor neurological and psychological deficits.

**Table 1:** Glasgow outcome score.

### Statistical analysis

The Statistical Package for the Social Sciences software version 19 (SPSS) was used for statistical analysis;

Comparisons of nominal data were performed using chi-square test. Continuous data are presented showing the mean ± standard deviation.

Their comparison was performed using the Student's t-test and Mann-Whitney test as appropriate. Statistical significance was accepted at a probability level of less than 0.05

### Results

#### Patients' characteristics

Over a period of one year, we included 94 patients who met the eligibility criteria. They were randomly assigned to hypothermia and normothermic therapy. Baseline characteristics of the patients who were enrolled in the study are presented in Table 2.

There were no significant differences observed between both groups as regard age, sex, BMI, GCS on admission, and trauma severity score.

	HT group (n=47)	NT group (n=47)	p-value
Age (years)	40.74 ± 13.58	41.98 ± 13.28	0.657
Gender (male/female)	36/11	38/9	0.802
BMI	26.21 ± 5.09	26.91 ± 5.96	0.544
GCS on admission (median (range))	5 (5)	5 (6)	0.345
GCS from 3 to 5 (%)	26 (55.3)	23 (48.9)	
GCS from 6 to 8(%)	21 (44.7)	24 (51.1)	
Trauma severity score	30.79 ± 6.61	31.98 ± 7.15	0.403
DIAGNOSIS			
Diffuse Brain injury	29 (61.7)	27 (57.5)	
Intracranial Hematoma	18 (38.3)	20 (42.5)	
Data were represented as (mean ± SD) unless otherwise indicated. P-value<0.05 is considered significant			

**Table 2:** Patients' characteristics in the two studied groups.

### Laboratory data

We only observed a statistically significant prolongation in the prothrombin time in the HT group compared to NT group (Table 3).

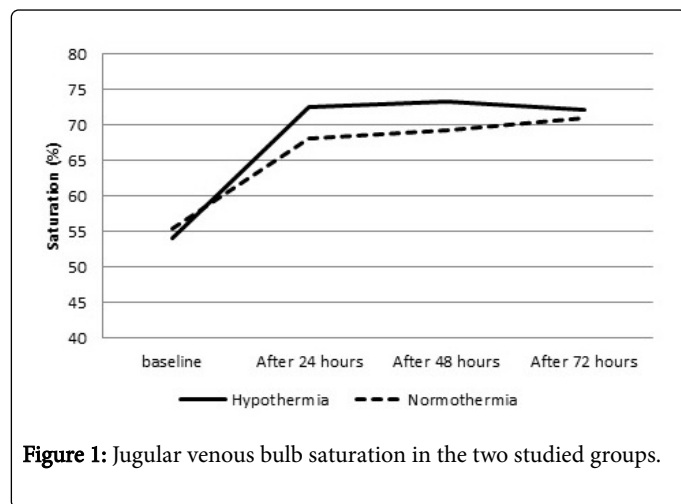
	HT group (n=47)	NT group (n=47)	p-value
Hemoglobin level	11.39 ± 2.21	10.96 ± 2.56	0.388
Platelet count	248.77 ± 61.48	262.40 ± 62.07	0.288
Prothrombin Time	12.99 ± 0.73	13.39 ± 0.92*	0.001
Creatinine level	86.66 ± 14.35	81.20 ± 14.58	0.071
Serum potassium	3.95 ± 1.16	4.29 ± 1.23	0.164
Blood glucose level	187.94 ± 27.56	177.91 ± 29.60	0.093

Data were represented as (mean ± SD), P- value<0.05 is considered significant

**Table 3:** Some laboratory data in both groups.

### Jugular venous bulb data

JVB O<sub>2</sub> saturation showed significant increase (p<0.001) at all studied times in both groups compared with baseline readings. JVB O<sub>2</sub> saturation was higher in HT group compared to NT group which is statistically significant (Figure 1).

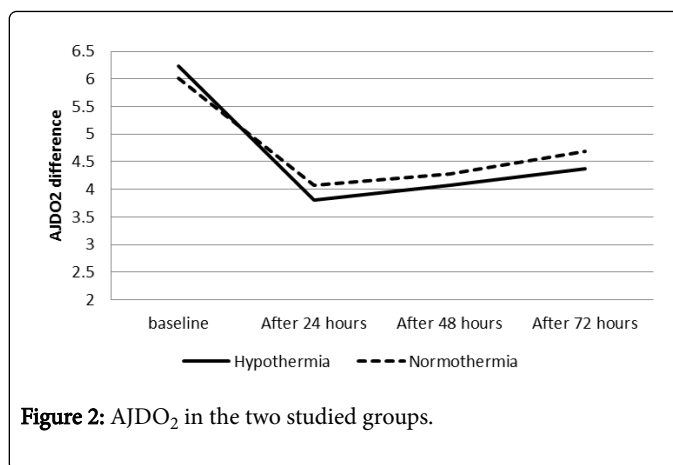


**Figure 1:** Jugular venous bulb saturation in the two studied groups.

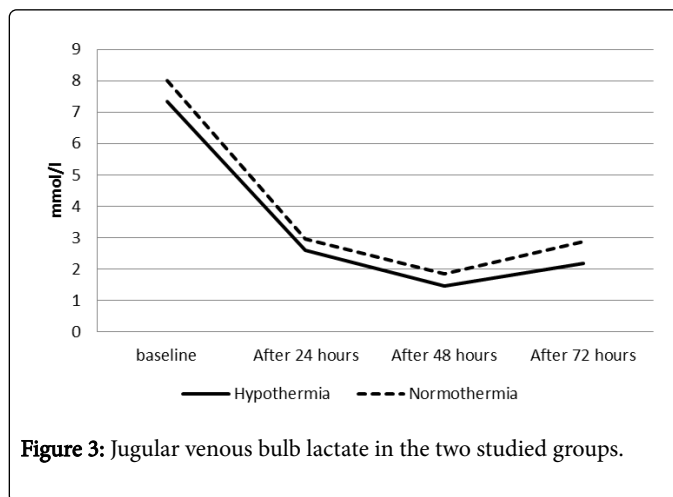
AJDO<sub>2</sub> difference (arterio-jugular oxygen difference): AJDO<sub>2</sub> difference also decreased significantly (p<0.001) at all studied times when comparing each group with the baseline readings.

AJDO<sub>2</sub> difference was lower in HT group compared to NT group which is statistically significant (Figure 2).

**JVB lactate:** Serum lactate level decreased significantly (p<0.001) at all studied times in HT group NT group when compared with baseline readings JVB lactate was lower in HT group compared to NT group which is statistically significant (Figure 3).



**Figure 2:** AJDO<sub>2</sub> in the two studied groups.



**Figure 3:** Jugular venous bulb lactate in the two studied groups.

### Study Outcomes

On the basis of GOS-HD we classified patients into those with favorable outcome and unfavorable outcome. Patients with favorable outcome include those with good recovery and moderate disability on GOS-HD. Patients with unfavorable outcome include patients with severe disability, vegetative state and death. Data for primary outcomes were available for all patients. Twenty three patients out of 47 patients (49%) in the HT group and 19 out of 47 patients (40%) in the NT group had a favorable outcome at hospital discharge with no significant difference between both groups(p-value=0.214). In a subgroup analysis, in patients with diffuse brain injury we found that 13 out of 29 (45%) of patients with diffuse brain injury in the HT group had a favorable outcome compared to 11 out of 27 (41%) in NT group with no significant difference between both groups (p-value=0.793). On the other hand for patients with intracranial hematoma 12 of 18 (67%) of patients in HT group had a favorable outcome compared to 8 out of 20 (40%) of patients in NT group, although it still statistically insignificant (p-value= 0.119) there is a strong trend toward favorable outcome in HT group in this type of injury and perhaps with larger sample size a significant level may be achieved.

In a subgroup analysis of the patients on the basis of GCS at time of admission, in patient with GCS (between 3 and 5), 46% of patients in HT group had favorable outcome compared to 35% in NT group. In patients with GCS on admission between 6 and 8, 62% on HT group

had favorable outcome compared to 48% in NT group. No statistically significant difference observed between both groups (Tables 4 and 5).

GOS-HD	All patients	
	HT group (n=47)	NT group (n=47)
Good recovery	10 (21)	9 (19)
Moderate disability	13 (28)	7 (15)
Severe disability	16 (34)	13 (28)
Vegetative state	5 (11)	10 (21)
Death	3 (6)	8 (17)

Data were represented as number (%), Favorable outcome include patients of good recovery and moderate disability categories, Unfavorable outcome includes patients of severe disability, vegetative state and death

**Table 4:** Glasgow outcome score in both groups.

Overall patients	HT group (n=47)	NT group (n=47)	P-value
Favorable outcome	25 (53)	19 (40)	0.214
Diffuse Brain injury	HT group (n=29)	NT group (n=27)	P-value
Favorable outcome	13 (45)	11 (41)	0.793
Intracranial hematoma	HT group (n=18)	NT group (n=20)	P-value
Favorable outcome	12 (67)	8 (40)	0.119
GCS (3-5)	HT group (n=26)	NT group (n=23)	P-value
Favorable outcome	12 (46)	8 (35)	0.562
GCS (4-8)	HT group (n=21)	NT group (n=24)	P-value
Favorable outcome	13 (62)	11 (48)	0.373

Data were represented as number (%), P-value <0.05 was considered statistically significant, Favorable outcome include patients of good recovery and moderate disability categories, Unfavorable outcome includes patients of severe disability, vegetative state and death.

**Table 5:** Overall and subgroup analysis of the outcome in both groups.

As regard duration of mechanical ventilation, length of ICU stay and length of hospital stay there were no significant differences between both groups.

As regard complications, there are minimal complications in both groups which can be just attributed to the hypothermia technique (Table 6).

	HT group (n=47)	NT group (n=47)	p-value
Duration of mechanical ventilation (Hours)	12 ± 6.75	14.25 ± 7.18	0.12
Length of ICU stay (days)	17.89 ± 9.51	20.87 ± 9.97	0.142
Length of hospital stay (days)	48.27 ± 22.92	51.36 ± 20.75	0.495
Complications			
Hypotension	5 (11)	2 (4)	0.435

Ventricular Tachycardia	2 (4)	0 (0)	0.485
Ventricular Fibrillation	3 (6)	1 (2)	0.617
ARDS	2 (4)	2 (4)	1
Pneumonia	14 (30)	10 (21)	0.478
Septic Shock	3 (6)	1 (2)	0.617
Seizures	2 (4)	5 (11)	0.435

Data were represented as mean± SD and number (%) p-value<0.05 was considered statistically significant

**Table 6:** Duration of mechanical ventilation, length of ICU and hospital stay and complications in both groups.

## Discussion

Hypothermia slows down metabolic processes and thereby inhibits deleterious biochemical events such as free radical production [6] and excitatory amino acid release including glutamate [7].

In the present study 94 patients with severe head trauma (GCS ≤ 8) were enrolled. We used the mild type of hypothermia (34-36°C) within 6 hours of patients' admission and lasting for 72 hours as a neuroprotective technique.

The results of our study showed that mild hypothermia was effective in decreasing the JVB lactate level, increasing the JVB oxygen saturation and decrease the AJDO<sub>2</sub> difference. No significant differences were found as regard the duration of mechanical ventilation, length of ICU and hospital stay. As regard neurological outcome, despite non-significant differences between both groups, there is a trend toward good outcome in HT group.

The value of hypothermia in improvement of neurological outcome was documented early by several studies [8-10]. These promising results were soon antagonized by many studies [11-14].

The increased intracranial pressure associated with rewarming may explain the bad neurological outcome. This conflict about the outcome may be due to several factors as the scale used to measure the outcome, the timing for measurement that outcome, the definition of good and bad outcome, the protocol for hypothermia may differ according to the time of initiation of hypothermia, the degree of hypothermia used, the duration of application of hypothermia, the time to reach the coldest temperature and the rate of rewarming. Patient factors include the type and severity of the trauma, and the associated injuries.

In our study we applied mild degree of hypothermia for 72 hours; better outcomes were obtained in many studies where hypothermia was applied for more than two days [15-17].

In our study a subgroup of patients with intracranial hematoma may benefit from mild prolonged hypothermia. This correlation between brain pathology and neurological outcome was documented in many studies with the favor of hematoma type over the diffuse brain injury [18,19]. The reperfusion injury occurred after decrease in the intracranial pressure is the pathophysiologic mechanism responsible for secondary brain injury in this type of patients [20] which is similar to the pathophysiologic mechanism of brain injury in cardiac arrest patients who has been successfully treated with hypothermia [21].

Adequacy of brain perfusion after TBI is one of factors that prevent secondary brain injury. AJDO<sub>2</sub> inversely correlated to the ratio of

cerebral blood flow and Oxygen metabolic rate [22]. In traumatic brain injury  $AJDO_2$  was measured for targeted therapies as for  $PaCO_2$  level [23] or mannitol therapy [24]. The profound episodes of desaturation were associated with poor neurological outcome [25].

Both groups in our study showed comparable rates of complications. Pneumonia was the most frequent complication occurred in our patients followed by cardiovascular complications as arrhythmias and hypotension.

Nearly all body organs are affected to a various degree by hypothermia and minimal organ affection may be hazardous in critically ill patients. Cardiovascular system will suffer from increased incidence of arrhythmia [26], increased venous pressure and systemic vascular resistance [27,28] and increased plasma level of catecholamines [29,30]. The diuretic effect of cooling may results in low electrolytes level. Magnesium ion depletion may play a role in increasing the brain injury following TBI [31,32].

A limitation of the study is the lack of blinding to the intervention, which is problematic in all trials of therapeutic hypothermia. However, because cooling to normothermia was permitted in the standard-care group, it is possible that there was masking of the intervention to patients and relatives in some cases. Outcome scoring was blinded.

## Conclusion

Prophylactic mild Hypothermia lacks any effect on the outcome in patients with TBI although there is improving in the cerebral oxygenation and decrease the oxygen extraction and preventing the anaerobic metabolism by decreasing the level of serum lactate. A subgroup of patients with intracranial hematoma may benefit from this type of treatment.

## References

1. Tang XN, Yenari MA (2010) Hypothermia as a cytoprotective strategy in ischemic tissue injury. *Ageing Res Rev* 9: 61-68.
2. Zipfel GJ1, Babcock DJ, Lee JM, Choi DW (2000) Neuronal apoptosis after CNS injury: the roles of glutamate and calcium. *J Neurotrauma* 17: 857-869.
3. Frietsch T, Krafft P, Piepgras A, Lenz C, Kuschinsky W, et al. (2000) Relationship between local cerebral blood flow and metabolism during mild and moderate hypothermia in rats. *The Journal of the American Society of Anesthesiologists* 92: 754-763.
4. Schell RM, Cole DJ (2000) Cerebral monitoring: jugular venous oximetry. *Anesth Analg* 90: 559-566.
5. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. *Lancet* 1: 480-484.
6. Dietrich WD, Busto R, Alonso O, Globus MYT, Ginsberg MD, et al. (1993) Intraischemic but not postischemic brain hypothermia protects chronically following global forebrain ischemia in rats. *Journal of Cerebral Blood Flow & Metabolism* 13: 541-549.
7. Kawai N, Okauchi V, Morisaki K, Nagao S (2000) Effects of delayed intraischemic and postischemic hypothermia on a focal model of transient cerebral ischemia in rats. *Stroke* 33: 1982-1989.
8. Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, et al. (1993) A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma* 10: 263-271.
9. Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM (1993) The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *J Neurosurg* 79: 354-362.
10. Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, et al. (1993) Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *Journal of neurosurgery* 79: 363-368.
11. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, et al. (2001) Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 344: 556-563.
12. Shiozaki T, Hayakata T, Taneda M, Nakajima Y, Hashiguchi N, et al. (2001) A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. *Journal of neurosurgery* 94: 50-54.
13. Shiozaki T1, Nakajima Y, Taneda M, Tasaki O, Inoue Y, et al. (2003) Efficacy of moderate hypothermia in patients with severe head injury and intracranial hypertension refractory to mild hypothermia. See comment in PubMed Commons below *J Neurosurg* 99: 47-51.
14. Chen L, Piao Y, Zeng F, Lu M, Kuang Y, et al. (2001) Moderate hypothermia therapy for patients with severe head injury. *Chinese journal of traumatology= Zhonghua chuang shang za zhi/Chinese Medical Association* 4: 164-167.
15. McIntyre LA, Fergusson DA, Hébert PC, Moher D, Hutchison JS (2003) Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA* 289: 2992-2999.
16. Jiang JY, Xu W, Li WP, Gao GY, Bao YH, et al. (2006) Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab* 26: 771-776.
17. Fox JL, Vu EN, Doyle-Waters M, Brubacher JR, Abu-Laban R, et al. (2010) Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review. *CJEM* 12: 355-364.
18. Smrcka M, Vidlák M, Máca K, Smrcka V, Gál R (2005) The influence of mild hypothermia on ICP, CPP and outcome in patients with primary and secondary brain injury. See comment in PubMed Commons below *Acta Neurochir Suppl* 95: 273-275.
19. Inamasu J, Saito R, Nakamura Y, Horiguchi T, Kuroshima Y, et al. (2006) Therapeutic hypothermia for severely head-injured patients with acute subdural haematoma. See comment in PubMed Commons below *J Clin Neurosci* 13: 733-737.
20. Kuroda, Y, Kusumoto K, Teasdale GM, Bullock R (1993) Local cerebral blood flow mapping before and after removal of acute subdural hematoma in the rat, in *Intracranial Pressure VIII* 253-256.
21. Janata A, Holzer M (2009) Hypothermia after cardiac arrest. *Prog Cardiovasc Dis* 52: 168-179.
22. Gibbs E, Lennox WG, Nims LF, Gibbs FA (1942) Arterial and cerebral venous blood arterial-venous differences in man. *Journal of Biological Chemistry* 144: 325-332.
23. Cruz J, Miner ME, Allen SJ, Alves WM, Gennarelli TA (1990) Continuous monitoring of cerebral oxygenation in acute brain injury: injection of mannitol during hyperventilation. *Journal of neurosurgery* 73: 725-730.
24. Cruz J (1993) Combined continuous monitoring of systemic and cerebral oxygenation in acute brain injury: preliminary observations. *Critical care medicine* 21: 1225-1232.
25. Gopinath SP, Robertson CS, Contant CF, Hayes C, Feldman Z, et al. (1994) Jugular venous desaturation and outcome after head injury. *J Neurol Neurosurg Psychiatry* 57: 717-723.
26. Polderman KH (2008) Induced hypothermia and fever control for prevention and treatment of neurological injuries. 371: 1955-1969.
27. Thoresen M, Whitelaw A (2000) Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. *Pediatrics* 106: 92-99.
28. Reuler JB (1978) Hypothermia: pathophysiology, clinical settings, and management. *Ann Intern Med* 89: 519-527.
29. Frank SM, Satitpunwaycha P, Bruce SR, Herscovitch P, Goldstein DS (2003) Increased myocardial perfusion and sympathoadrenal activation during mild core hypothermia in awake humans. *Clinical Science* 104: 503-508.
30. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, et al. (1995) The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia A randomized clinical trial. *The Journal of the American Society of Anesthesiologists* 82: 83-93.

- 
31. van den Bergh, WM, Group MS (2005) Magnesium sulfate in aneurysmal subarachnoid hemorrhage a randomized controlled trial. *Stroke* 36: 1011-1015.
32. Soliman HM, Mercan D, Lobo SS, Mélot C, Vincent JL (2003) Development of ionized hypomagnesemia is associated with higher mortality rates. *Crit Care Med* 31: 1082-1087.