Chapter

# Direct Brain Cooling in Treating Severe Traumatic Head Injury

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## Abstract

There are scientific evidences that hypothermia provides a strong neuroprotective effect on the brain following traumatic insults. In this chapter, we describe the pathophysiology of severe head injury with emphasis on benefits of hypothermia. To support these hypothetical or theoretical benefits, we describe our previous study with very encouraging findings done on severe head injuries, treated with direct focal brain cooling, and monitored with intracranial pressure, cerebral perfusion pressure, brain oxygenation, and brain temperature. This chapter ends with our current and still ongoing study in which one of its main objectives is to innovate a direct focal brain cooling machine. This chapter briefly explains the technical part of this cooling machine.

**Keywords:** hypothermia, trauma, brain oxygenation, brain temperature, intracranial pressure, severe head injury, focal brain cooling

## 1. Introduction

Severe traumatic brain injury (TBI) is one of the causes contributed to the major source of death and severe disability worldwide. In some countries, the increasing number of severe traumatic brain injury is alarming, bringing negative impact not just toward the individual itself, but also the society. Patients suffering from severe traumatic brain injury usually will end up with disability, as they most often are associated with extensive irreversible damages to the brain. This makes the management of severe TBI to be challenging and very often associate with disappointing outcomes. Thus, severe TBI has become a common issue or interest that requires appropriate attention from various levels in order to reduce the damage impacts often associated with it. Many clinical trials and researches were conducted to improve our understanding and knowledge, with various treatment protocols being updated from time to time [1, 2].

During the trauma impact itself, there will be energy transfer to the brain tissue causing direct neuronal damages, causing irreversible damages to the neuronal structures, and affecting the neurophysiological function of the central nervous system. From the initial impact, primary injuries occur due to the direct impact and the damage that are usually irreversible. Secondary injuries will be subsequently triggered by hypoxic-ischemic event, inflammatory cytokines, and free radicals,

which are released by the injured neuronal cells. Secondary injuries play an important role in determining posttraumatic recovery [3–5]. Secondary injuries will lead to breakdown of the cerebral blood brain barrier, leading to worsening cerebral edema and thus forming a vicious cycle toward further neuronal damages.

The management of severe TBI is aiming for restoration and maintenance of adequate brain perfusion to prevent hypoxia, surgical intervention for significant size of hematoma or edema, and prevention or prompt treatment of cerebral edema and raised intracranial pressure (ICP). However, clinical studies and analysis had proven that ICP and cerebral perfusion pressure (CPP) guided treatment alone, does not necessarily prevent hypoxic-ischemic damage to the brain [6]. Despite knowing that ICP remains the most important determinant factors of mortality outcome in severe head injury patients, brain hypoxia (defined as $PbtiO_2 < 10$ mmHg and for more than 15 minutes) is actually more important in determining the morbidity and patient functional outcome [7].

Many new strategies and alternative protocols are introduced to improve the management and outcome of severe TBI patients. Throughout the years, the definition of adequate cerebral resuscitation including the targeted ICP and CPP values are often debatable. Other treatment strategy such as $PbtiO_2$, plus ICP and CPP guided therapy showed promising result, with reduced hypoxic-ischemic damages to the brain and better patient functional outcome recovery.

Controlled systemic hypothermia treatment in managing severe head injury patient, is associated with neuroprotective effect to the injured brain tissue. Hypothermia significantly reduce metabolic rate and energy expenditure, attenuate excitatory amino acids and the synthesis of free radicals, suppresses excessive ischemia-induced and posttraumatic inflammatory reactions, and prevent blood-brain barrier disruption and brain edema. Furthermore, hyperthermia in head injury increases postischemic injury and is a significant predictor of poor outcome. Induced and controlled systemic hypothermia is used in patient with stroke, perinatal asphyxia, hypoxic encephalopathy following cardiovascular arrest with improved recovery, and functional outcome documented [8–11]. However, the pitfall of the treatment is that it is associated with alteration of the body core temperature and hence induced alteration in the systemic function and affecting the whole body hemostasis. Few possible adverse systemic complications that are associated with induced systemic hypothermia treatment include increase risk of infection and sepsis, pneumonia, poor wound healing and breakdown, cardiac arrhythmias, coagulopathy and electrolytes imbalances such as hypoglycemia and hypokalemia [12–18]. These systemic complications may outweigh the beneficial effect of the hypothermia treatment. Thus, treatment with induced and controlled systemic cooling therapy in head injury patient has become an interesting but controversial subject. Given so much controversy in inducing hypothermia for the injured brain, we sought to design a prospective, randomized pilot study to assess efficacy of new method in brain cooling called "direct regional or focal brain hypothermia." In this chapter, we present our experience with direct focal or regional brain cooling, obtained via direct irrigation of cold fluid onto the surface of severely injured brain of trauma patients who required decompressive craniectomy with Glasgow Coma Score (GCS) of 6–7, and the chapter ends with our current and still ongoing study in which, one of its main objectives is to innovate a direct focal brain cooling machine.

## 2. Role of hypothermia in head injury patient

There have been multiple mechanisms suggesting benefit of hypothermia in head injury patient. However, there is likely that no single factor can be used to explain

the neuroprotective effect of hypothermia. Understanding the combination of the factors may help us understand better the effect of hypothermia [3]. The proposed mechanisms are summarized below [12, 19, 20] and depicted as in **Figure 1**.

a. Hypothermia can inhibit the activation of caspase enzymes.

b. It prevents or mitigates mitochondrial dysfunction.

c. It decreases the metabolism as well as decreases the overload of excitatory neurotransmitters such as glutamate and free oxygen radicals.

d. It modifies the cellular disorders of intracellular ion concentrations.

e. It suppresses the inflammatory and immunological responses and epileptic activity.

f. It reduces the disruption in blood brain barrier (BBB), vascular permeability, and edema.

g. It improves the microcirculatory circuits and intra- and extracellular acidosis.

h. It corrects the hyperthermia after brain injury and influences the local secretion of various vasoactive mediators secreted by the endothelium.

i. It enhances expression of immediate early genes and cold shock proteins.

j. Hypothermia may also influence neurogenesis, gliogenesis, and angiogenesis.

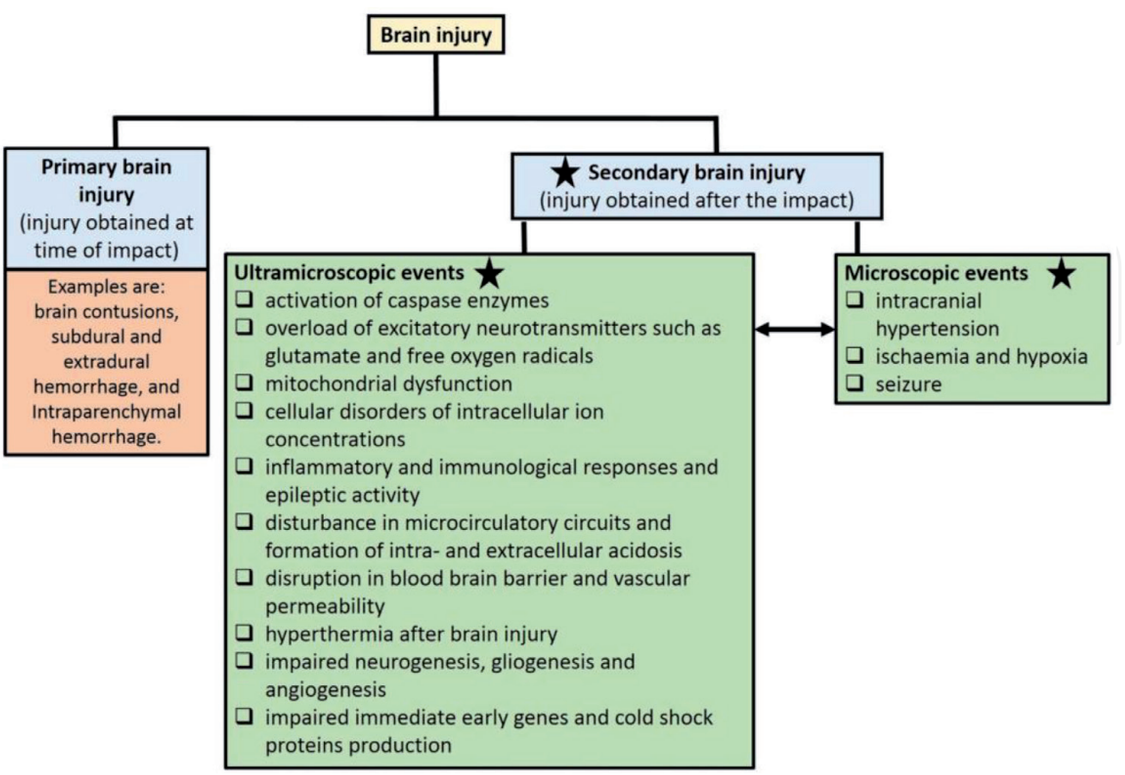


**Figure 1.**
*Effect of hypothermia on pathophysiology of brain injury. Therapeutic hypothermia works by reducing the detrimental consequence of secondary brain injury (black stars).*

## 3. Current evidences on the usage of direct brain cooling in treating severe head injury: animal studies

There are previously multiple papers that suggested targeted brain cooling as a reasonable treatment option to patient with severe traumatic brain injury [21–33]. Targeted brain cooling is a good alternative to systemic hypothermia, as systemic hypothermia has serious side effects such as circulatory constrain, increased risk of infection, electrolyte imbalance, and coagulopathy [15–18].

Jacek et al. [33] suggested in their animal study that selective brain hypothermia, which is applied via a cranial window after decompressive craniectomy seems to be reducing posttraumatic structural and functional damage. However, the study is actually limited by small rodent model and also short observational period. It is suggested that thermodynamic of brain of human rodent may differ as the size is significantly different. It may affect the penetration of the cooling effect in human brain, hence limiting the cooling effect to the superficial areas only.

## 4. Current evidences on the usage of direct brain cooling in treating severe head injury: our clinical study

Here, we describe our pilot study on direct focal hypothermia therapy in treating severe head injury with positive and very encouraging results that enable us to proceed with another innovative study to create a direct hypothermia machine, which will be used in our ongoing study.

### 4.1 Methodology

This is a randomized controlled trial study, which is designed to answer the research questions regarding the effect of direct focal brain cooling treatment in severe head injury patients. The study has been approved by the research and ethics committee and is sponsored by the Research University Grant. Patients were randomized into two treatment groups of A and B. Group B is the control group.

Group A (treatment group) consists of patients, who have therapy with direct focal brain cooling. All patients have intracranial pressure monitoring, Licox (focal brain oxygenation and temperature) probes inserted, and blood for immunological parameters. The immunological blood parameters are however taken only prior and after local cooling therapy to the brain. The overall monitoring and therapy period was for 48 hours.

The neurosurgical operations are standard operations, decompressive craniectomy covering frontal, parietal and temporal lobes; intracranial pressure probe insertion into the ventricle or parenchyma of the brain, and Licox probe into abnormal brain areas. The monitorings and therapies given after the surgery are the standard therapy for severe head injury patient (**Figure 2**). They include sedation with or without muscle paralysis agents, ventilator support, hypertonic saline or mannitol, draining of cerebrospinal fluid (CSF) for the persistent raise in intracranial pressure (ICP) of more than 20 mmHg and thiopentone coma therapy as a final step to treat persistently raised ICP.

Direct focal brain cooling method done through persistently irrigating the brain with cold Hartmann's solution in which the temperature of the infused fluid is divided into two subgroups as follow:

1. Deep cooling: temperature of 20–29°C.

2. Mild cooling: temperature of 30–36°C.

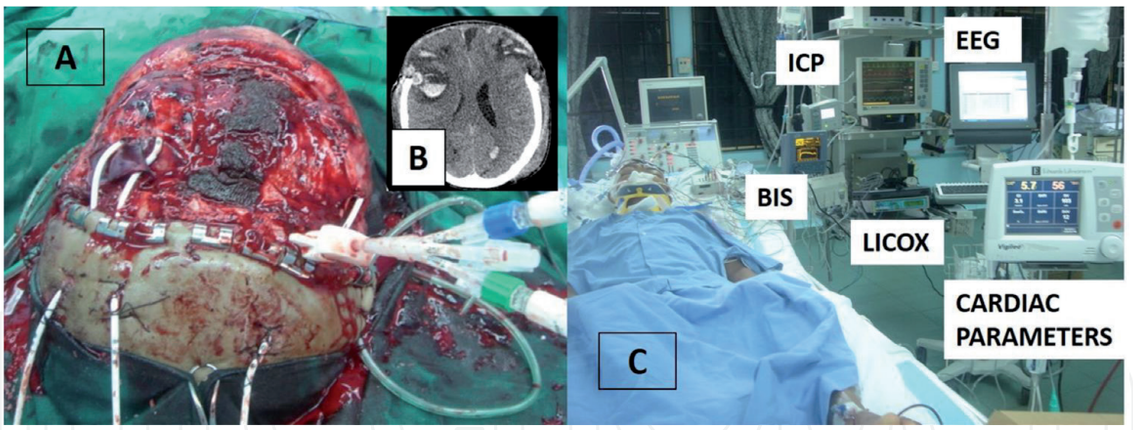


**Figure 2.**
*Direct brain cooling monitoring and therapy. (A) intraoperative bifrontal decompressive craniectomy with insertion of Licox and ICP probes; (B) inset image: Post-op CT scan; (C) neurointensive care management and monitorings with Licox, cardiac parameters, ICP, bispectral index (BIS) and electroencephalography (EEG).*

The Hartmann's solution was infused via Neurojaf external ventricular drainage (EVD) catheter, which was inserted superior to the dura flap and at the inner surface of the dura, acting like rains flushing through the surface of the swollen brain (multiple extra holes are made). The catheter is in contact with the surface of the brain. The infusion rate is 70 mls/hr. Due to the position of the head, the second draining tube will be inserted at the lower part of the craniectomy flap outside the dura (which is closed loosely) to drain the excess fluid with low suction pressure. The temperature of the infused Hartmann's solution is checked via the three-way connector draining the fluid out to the collection port for temperature assessment. If temperature reading is under or above the intended value, new solution with correct intended temperature will replace the previous one.

All patients will have CT scan done if the ICP shows persistently raised values despite of standard therapies given. This is important to exclude any new surgical lesion and to exclude the retention of infused solution as a cause of raised ICP. If

| | **No cooling** | **Mild cooling** | **Deep cooling** | **Total** |
|---|---|---|---|---|
| Total patients | 13 | 10 | 9 | 32 |
| Variables | No cooling | Mild cooling | Deep cooling | P value |
| Age (mean in years) [95% CI] | 45.5 [35.0–56.1] | 28.9 [17.3–40.5] | 26.7 [11.9–41.4] | 0.02 |
| Gender (number): | | | | |
| 1. Male | 10 | 8 | 9 | |
| 2. Female | 3 | 2 | 0 | 0.40 |
| GCS (median) | 6 | 7 | 7 | 0.38 |
| Injury Severity Score (mean) [95% CI] | 27.8 [21.2–34.5] | 24.0 [18.5–29.5] | 28.7 [21.3–36.0] | 0.56 |
| Marshall Score (median) | 4 | 4 | 3 | 0.33 |
| Patients with disseminated intravascular coagulopathy (DIVC) | 3 | 2 | 4 | 0.44 |

**Table 1.**
*Basic parameters comparison among three studied groups.*

the ICPs show normal values, the CT scan of the brain is done after 48 hours of therapy prior to removal of the EVD tube to document the location of the EVD tip. The measured outcomes are: (a) trend and values for monitored parameters (ICPs, CPPs, brain temperature and focal brain oxygenation), (b) Glasgow Outcome Score (GOS – good and poor GOS), and (c) immunological parameters.

## 4.2 Results

### *4.2.1 Social demographic data of patients included in the study*

There were 32 patients recruited in this study with 27 male patients and 5 female patients. The median age of patients recruited were 45.5 in no cooling group, whereas 28.9 and 26.7, respectively, for mild cooling and deep cooling groups. Median GCS for the patients recruited were 6–7. The highest injury severity score recruited was 36, whereas the lowest was 18.5. The median Marshall score for patient recruited were 3–4. Patients with disseminated intravascular coagulopathy for no cooling, mild cooling, and deep cooling were 3, 2, and 4 patients, respectively. The demographic data is shown in **Table 1**.

### *4.2.2 Effects of direct focal brain cooling on median ICP, CPP, brain oxygenation, and temperature*

The trend of the ICPs, CPPs, brain temperature, and focal brain oxygenation for all studied groups are shown in **Figure 3A–D**. During 48 hours of observation and monitoring, there is no significant statistical difference in overall 4 hourly mean ICPs, CPPs, and brain temperature amongst the no cooling, mild cooling, and deep cooling groups; but there is significant statistical difference in overall 4 hourly mean focal brain oxygenation according to repeated measure ANOVA (between groups analysis based on time) (depicted in **Tables 2** and **3**).

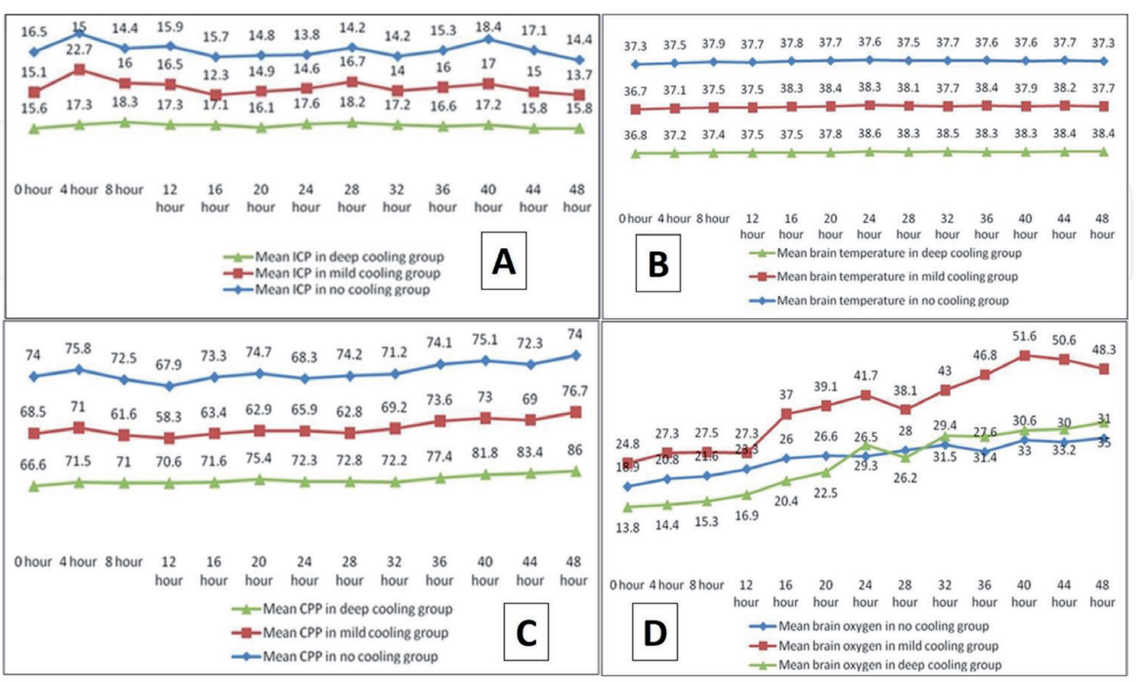


**Figure 3.**
*(A) Trend of ICPs in the first 48 hours after the treatment. (B) Trend of brain temperature observation for the first 48 hours after treatment. (C) Trend of CPPs in the first 48 hours after the treatment. (D) Trend of brain oxygen observation for the first 48 hours after treatment.*

**Table 2** shows day 1 of monitoring and treatment, mean brain oxygenation of mild cooling group has mostly fallen outside the 95% CI (confidence interval) of deep cooling group. Therefore, there is significant difference in mean brain oxygen between mild cooling and deep cooling; with mild cooling having significantly higher mean brain oxygen values. On day 2 of monitoring and treatment, mean brain oxygenation of no cooling group has mostly also fallen outside the 95% CI of mild cooling group. Therefore, there is significant difference in mean brain oxygen between no cooling and mild cooling. Likewise to day one findings, there is also a significant difference on day 2 in mean brain oxygen between mild cooling and deep cooling. Interestingly, in all group comparisons, mild brain cooling group has significantly higher mean brain oxygenation values as compared to either deep or no cooling group (depicted in **Table 3**).

*4.2.3 Effect of regional brain cooling on GOS at discharge and at 6 months*

There is no significant difference in GOS at time of discharge for both studied groups (no cooling vs. cooling groups). However, there is significant difference on good GOS in cooling group compared to no cooling group at 6 months follow-up (as shown in **Table 4** with $p < 0.007$). On stratifying the cooling group further into deep and mild cooling, it shows that there is significant difference in term of GOS score at 6 months with significant better outcomes noted in mild cooling as compared to no cooling group with $p < 0.013$. The deep cooling group at 6 months outcome, failed to have significant difference value when compared with either no or mild cooling groups. For this reason, direct and mild brain hypothermia

| Time (Day 1) | Treatment group | Mean brain oxygen | 95% confidence interval (CI) |
|---|---|---|---|
| 0 hour | No cooling | 18.94 | 8.29–29.60 |
| | Mild cooling | 28.27 | 15.54–41.01 |
| | Deep cooling | 13.82 | 1.91–25.73 |
| 4 hour | No cooling | 20.78 | 11.72–29.83 |
| | **Mild cooling** | 31.17 | ***20.35–41.99*** |
| | Deep cooling | 14.43 | 4.31–24.55 |
| 8 hour | No cooling | 21.55 | 12.40–30.70 |
| | **Mild cooling** | 31.39 | ***20.45–42.32*** |
| | Deep cooling | 15.33 | 5.10–25.56 |
| 12 hour | No cooling | 23.27 | 15.31–31.22 |
| | **Mild cooling** | 31.14 | ***21.64–40.65*** |
| | Deep cooling | 16.89 | 8.00–25.78 |
| 16 hours | No cooling | 25.96 | 16.30–35.62 |
| | **Mild cooling** | 36.93 | ***25.38–48.47*** |
| | Deep cooling | 20.36 | 9.56–31.16 |
| 20 hours | No cooling | 26.64 | 16.22–37.05 |
| | **Mild cooling** | 39.11 | ***26.67–51.56*** |
| | Deep cooling | 22.51 | 10.86–34.15 |

*Statistical analysis: Repeated Measure ANOVA (between groups analysis based on time).*

**Table 2.**
*Comparison of mean brain oxygen between three treatment groups based on 4 hourly observations (day 1).*

| Time (Day 2) | Treatment group | Mean brain oxygen | 95% confidence interval (CI) |
|---|---|---|---|
| 0 hour | No cooling | 28.00 | 16.98–39.03 |
| | Mild cooling | 48.73 | 31.89–65.58 |
| | Deep cooling | 28.91 | 14.32–43.49 |
| 4 hours | No cooling | 29.20 | 16.98–41.43 |
| | **Mild cooling** | 50.17 | ***31.50–68.84*** |
| | Deep cooling | 28.13 | 11.96–44.30 |
| 8 hours | No cooling | 28.96 | 17.57–40.35 |
| | **Mild cooling** | 52.27 | ***34.87–69.66*** |
| | Deep cooling | 34.39 | 19.33–49.46 |
| 12 hours | No cooling | 27.46 | 18.63–36.30 |
| | **Mild cooling** | 52.00 | ***38.51–65.49*** |
| | Deep cooling | 33.69 | 22.01–45.38 |
| 16 hours | No cooling | 30.63 | 21.34–39.92 |
| | **Mild cooling** | 51.60 | ***37.41–65.79*** |
| | Deep cooling | 35.17 | 22.88–47.45 |
| 20 hours | No cooling | 30.05 | 20.01–40.08 |
| | **Mild cooling** | 50.57 | ***35.24–65.90*** |
| | Deep cooling | 36.12 | 22.84–49.39 |

*Statistical analysis: Repeated Measure ANOVA (between groups analysis based on time).*

**Table 3.**
*Comparison of brain oxygen between three treatment groups based on 4 hourly observations (day 2).*

with coolant temperature of 30–36°C might truly be beneficial to the severely head injured patients. Having said that, obviously future studies are still needed to ascertain this finding with higher number of more homogenous recruited patients.

#### *4.2.4 Effects of regional brain cooling on immunological parameters*

There is no significant difference on immunological parameters upon comparing prior and after cooling therapy. Nonetheless, the postcooling immunological parameters seem to have lower values than the precooling ones (depicted in **Table 5**).

### 4.3 Discussion

This was a randomized controlled pilot study involving 32 patients, who were admitted to our hospital with severe head injury with GCS of 6 or 7. The aim was to study the effect of direct focal brain cooling therapy in severe head injury patients.

#### *4.3.1 Effect of direct focal brain cooling on brain oxygen level*

All the treatment groups were able to reach the desired mean brain oxygen level within the treatment period. Notwithstanding, the mean brain oxygen of mild cooling group was significantly higher as compared to the no- and deep cooling groups. It remained significantly higher throughout the treatment periods (24–48 hours) with the level of >50 mmHg. The mean brain oxygen of deep cooling group was the

| **Outcomes (GOS)** | **No cooling [13 patients]** | **Cooling group [19 patients]** | | **p value** |
|---|---|---|---|---|
| Poor GOS (GOS 1–3) | | | | |
| Good GOS (GOS 4–5) | | | | |
| Comparing 2 groups | | | | |
| GOS at discharge: | | | | |
| a. Poor GOS | 12 (92.3%) | 15 (78.9%) | | 0.307 |
| b. Good GOS | 1 (7.7%) | 4 (21.1%) | | |
| GOS at 6 months: | | | | |
| a. Poor GOS | 11 (84.6%) | 7 (36.8%) | | **0.007*** |
| b. Good GOS | 2 (15.4%) | 12 (63.2%) | | |
| ***Comparing 3 groups*** | ***No cooling [n (%)]*** | ***Mild cooling [n (%)]*** | ***Deep cooling [n (%)]*** | |
| ***GOS at 6 months:*** | | | | |
| a. Poor GOS | 11(84.6%) | 3 (30%) | 4 (44.4%) | 0.023* |
| b. Good GOS | 2 (15.4%) | 7 (70%) | 5 (55.6%) | |
| GOS at 6 months: | | | | |
| a. Poor GOS | 11 (84.6%) | 3 (30%) | | 0.013* |
| b. Good GOS | 2 (15.4%) | 7 (70%) | | |
| GOS at 6 months: | | | | |
| a. Poor GOS | 11 (84.6%) | | 4 (44.4%) | 0.074 |
| b. Good GOS | 2 (15.4%) | | 5 (55.6%) | |
| GOS at 6 months: | | | | |
| a. Poor GOS | | 3 (30%) | 4 (44.4%) | 0.650 |
| b. Good GOS | | 7 (70%) | 5 (55.6%) | |

**Statistically significant. Statistical analysis: Pearson Chi-squared test.*

**Table 4.**
*Effect of regional brain cooling on GOS at discharge and at 6 months; and effect of regional brain cooling on GOS only at 6 months, after stratifying the cooling group further into mild and deep cooling.*

lowest but still did not reach the critical ischemic state (10–15 mmHg). Despite of having the lowest brain oxygen level on day 1, the improvement in brain oxygen level in deep cooling group was accelerated and reached the desirable range after 16 hours of treatment (with mean brain oxygen of >20 mmHg).

Patients with severe head injury were at higher risk of developing cerebral ischemia particularly in the first 48 hours. Cerebral ischemia was defined by brain oxygen of <10 mmHg for more than 2 hours [34]. Low mean brain oxygen pressure often associated with poorer clinical outcome, while patients with good GOS often had good or normalized reading within 2 hours after the injury. Brain oxygen level is a good indicator of functional outcome in addition to ICP and CPP. Targeted therapy of ICP < 15 mmHg, CPP > 75 mmHg, and brain oxygen >25 mmHg often associated with good clinical outcomes. The clinical trials comparing the ICP-CPP guided therapy to ICP-CPP-brain oxygen guided therapy showed significant better functional outcome at 6 months and lower mortality rate in the latter group [34, 35]. This showed that ICP-CPP-brain oxygen guided therapy is beneficial in treating severe head injury patients as it can improve the patient outcomes.

| | Precooling (mean ± SD) | Postcooling (mean ± SD) | Wilcoxon signed Ranked test (p value) |
|---|---|---|---|
| T-cell markers (cells/mm$^3$) | | | |
| CD 3 | 776.8 (407.5) | 756.3 (339.9) | 0.86 |
| CD 4 | 443.1 (268.5) | 429.7 (210.0) | 0.64 |
| CD 8 | 328.1 (183.6) | 301.7 (135.7) | 0.96 |
| CD 19 | 284.4 (168.6) | 261.5 (126.6) | 0.62 |
| CD 16 and 56 | 172.4 (113.8) | 112.7 (80.8) | 0.05 |
| **Pro-inflammatory cytokines (pg/ml)** | | | |
| Interleukin-1 (IL-1) | 45.34 (130.7) | 5.7 (13.0) | 0.33 |
| Interleukin-6 (IL-6) | 278.5 (221.1) | 190.0 (208.4) | 0.44 |
| Tumor necrosis factor (TNF) | 34.5 (37.6) | 18.1 (14.2) | 0.41 |
| **Other immunological parameters** | | | |
| Total WBC | 13.6 (5.0) | 12.8 (4.0) | 0.16 |

**Table 5.**
*Effect of regional brain cooling (both mild and deep cooling groups combined together) on immunological parameters.*

### *4.3.2 Effect of direct focal brain cooling on ICP and CPP*

The mean ICP did not show any significant difference amongst the studied groups as shown in the results above. There was also no evidence of refractory intracranial hypertension throughout the treatment period in all three groups, indicating that the focal cooling therapy used in this study was safe and not associated with risk of intracranial hypertension. The results seemed to contradict the effect of hypothermia, which supposed to have better control on ICPs, and hence, leading to better CPPs and mean brain oxygenation. Previous clinical study on the effect of mild systemic hypothermia to the head injury patients clearly had established a significant reduction in ICPs following cooling therapy [36]. The mechanisms of reduction in ICP values were postulated to be due to reduced cerebral edema, following an improvement of:

1. the blood brain barrier [37],
2. vascular permeability of microvascular endothelial cells [38],
3. extravasation of hemoglobin [39],
4. membrane disintegration processes,
5. cytotoxic edema via decreased inflammatory reactions and free radical formation within the brain, and
6. ion homeostasis including calcium [40].

Reduction in ICP and improvement in CPP did not happen in our pilot study, perhaps, because decompressive craniectomy had been completed prior to direct hypothermia therapy. Hence, intracranial pressure and perfusion pressure effects might not be shown-up in this particular study. Nevertheless, future related study should be carried out with more homogenous patients to confirm this finding.

### *4.3.3 Effect of direct focal brain cooling on brain temperature*

There was no significant difference in brain temperature in all treatment groups as shown above in trend-results, thus showing that focal cooling did not seem to be effective in reducing focal brain temperature. This study was initially designed to reduce brain temperature; the mechanism of temperature reduction was thought to be achieved through two ways, which were direct cooling effect over the brain surface (via continuous irrigation of the cold Hartmann fluid) as well as through the indirect cooling effect (to the deeper part of the brain) via circulation and pulsation around the brain and cisterns. However, it seemed that the targeted effect was not achieved. This can be due to many factors including poor CSF circulation, and hence affecting the thermoregulation of the brain. It is worth mentioning that there is limitation of Licox probe as well. This device was specifically designed to detect the changes occurred around the area where it was inserted. Hence, it was unable to reflect accurately the whole brain temperature changes following head injury [41].

It was well documented in the literature that an injured brain might have significantly higher temperature compared to the core body temperature; ranging from 0.1°C to more than 2°C. The difference in the temperature gradient may be more significant in an injured brain as a result of destructive hyperactivity of the injured cells [42]. Numerous clinical studies have found that higher brain temperature is associated with adverse outcome and negative correlation with the prognosis of head injury patients. Hyperthermia increases the risk of ischemic area to become necrotic or apoptotic. In animal model, transient increase in core body temperature to 39–40°C led to 2.6-fold increase in the extent of neuronal injury in the hippocampus [43]. Since hyperthermia was an important independent factor of adverse neurological outcome and increase mortality in brain injury [44], accurate brain temperature reading was rather essential. For future reference, focal brain temperature reading with Licox may be combined with adjunct devices such as CT thermography as it can accurately measure the focal and whole brain temperature for better comparison during treatment.

### *4.3.4 Effect of direct focal brain cooling on the Glasgow Outcome Score (GOS)*

Patients GOS was the most important factor to determine the outcome of the focal brain cooling treatment in this study. This classification system was specifically designed to help clinicians to determine the patients response following the treatment by assessing their functional status at discharge and at 6 months after the injury; score 1 reflects mortality, score 2 and 3 reflect significant morbidity, while score 4 and 5 reflect ability to function normally or near normal. The outcomes were promising as significant difference was noted, whereby the proportion of patients who received direct focal brain cooling treatment showed better GOS score of 4 and 5 at 6 months follow-up when compared to the no cooling group. However, no significant difference was established in GOS at day of discharge. The outcome of patient in severe head injury is actually multifactorial and could not just be attributed to a single factor. The age, other associated injuries, and hemodynamic instability will all contribute to the outcomes of the patients. The obvious contributing factor in our study is the increment in focal brain oxygenation during cooling therapy and it is markedly obvious in mild cooling group who received cold-fluid of 30–36°C.

### *4.3.5 Effect of direct focal brain cooling on immune responses*

In this study, the T-cell markers, pro-inflammatory cytokines, and total white cell count show reduction in values after cooling therapy; nonetheless, no

significant statistical difference noted in each studied immune parameters. This may be due to our small sample size; therefore, future related study should consider to recruit more patients with better homogenous participants' population. Besides this drawback, another shortcoming is no level taken from non-cooling group for comparison, thus the true effect of regional brain cooling on immunological biomarkers cannot be truly ascertained. This initial result, however, might indicate that focal brain cooling treatment has little adverse effect onto immune responses, which often associated with induced systemic cooling. Following head injury, acute immunological responses to the trauma begin around 1 hour after the injury until several days. Pro inflammatory mediators such as tumor necrosis factors-alpha (TNF-α) and IL-1 are released from injured tissues and stimulate the migration of the leukocytes across the BBB. These lead to accumulation of the inflammatory cells in the injured brain within hours. Activation of the complement systems following head injury will stimulate the neutrophil and in later stages, also monocytes and macrophages. These initial stages are basically causing granulocytosis (up to 90%), increasing immunoglobulins (Ig)-E, slight increase or normal level of monocytes, B-lymphocytes as well as Ig-A, -G and -M. On the other hand, there is suppression of the other lymphocytes subsets particularly the CD3, CD4 and CD8 counts [45]. Some of these changes were found to be beneficial and associated with neuroprotective effects while some other inflammatory mediators were neurotoxic [46]. The CD3, CD4, and CD8 counts are normally suppressed after few hours following severe head injury. This level will remain low for the next 24–48 hours and generally normalized after 3 days. The CD8 count tends to normalize faster than the CD3 and CD4. Increased risk of infection had been attributed to the suppression of these cellular immunities. Besides these mechanisms in causing alterations in immune parameters, other possibilities should also be considered. Those possibilities include:

1. blood product transfusion pre-, intra-, or postoperatively,

2. possibility of neuroendocrine changes,

3. the duration of the surgery,

4. the incidence of pre- and intraoperative hypothermia, which were not documented, and

5. the severity of trauma with consideration of the extend of tissues damaged [47].

## 5. Current innovation in direct focal brain cooling: D-Brain Cooling Machine™

The internal cooling methods use central venous catheters to either infuse cold saline or directly to reduce the blood temperature by convection. By advancement in microelectronic industry, instrumentation system can be integrated on chip level that can miniaturize the system to micro dimension. One of the advancements is miniaturization of micro-controller that can be easier to interface with sensing instrumentation system. Thus in this project, simple and intelligent localized brain cooling instrument by using Programmable System on Chip (PSoC) is proposed. Advantages of this system are simple, can localize coolant area in brain and System on chip (SoC) based automation system. This project involves designing temperature chamber to place the sterile fluid that is connected with antibiotic piping directly to

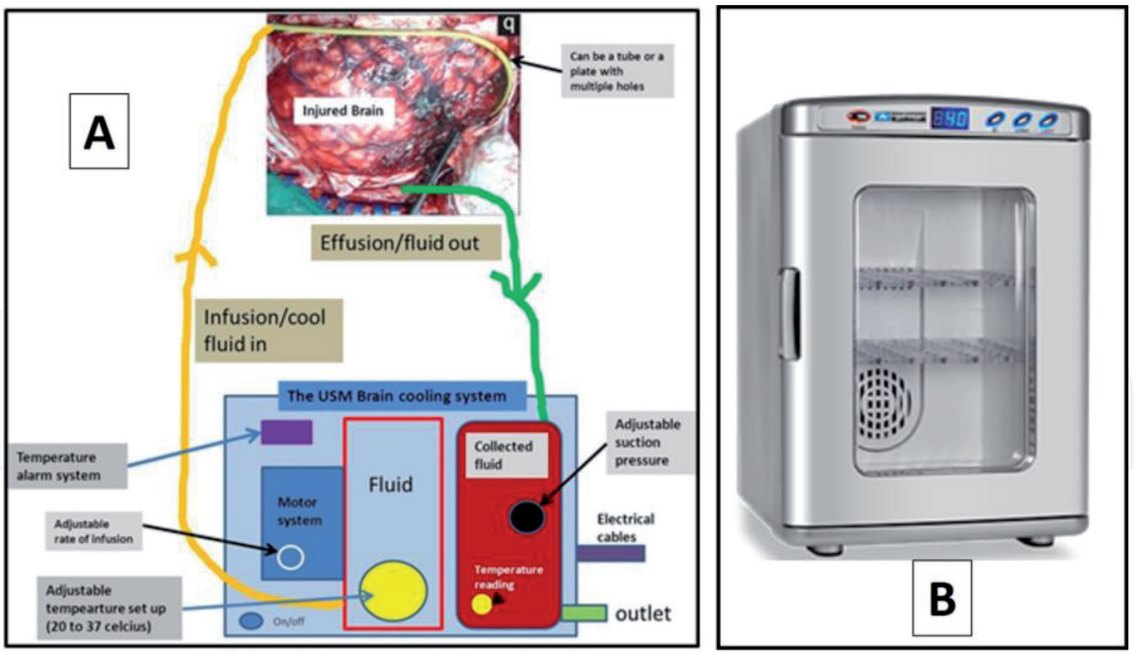


**Figure 4.**
*Direct brain cooling or D-brain cooling machine™. (A) Its principles; and (B) Illustration of final image of adjustable temperature chamber.*

the brain location. This chamber will be integrated with temperature controller, then, processed by PSoC microcontroller, as shown in **Figure 4A** and **B**. Subsequently, sensing and micro-controller will be interfaced to the system for temperature display. This direct brain cooling machine is known as D-Brain Cooling Machine™.

## 6. Conclusions

This chapter highlights the fascinating result of our pilot study on direct focal brain cooling therapy in severe head injury patients. The significant clinical outcome results seem in mild cooling group is thought to be due to an elevation in oxygenation level of injured and decompressed brain tissues. Thus, direct brain cooling therapy seems as a promising treatment in severe head injuries, and should be considered by neurosurgeon and neurointensivist as an adjunctive method to decompressive craniectomy. Therefore, combination of both therapies may help many diffused and severely injured brains secondary to neurotrauma in gaining better clinical outcomes. Base on this initial and encouraging results, there is ongoing study by our group on direct focal brain cooling therapy in severely head injured patients by using newly invented cooling machine named D-Brain cooling machine™ therapy.

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## Conflict of interest

None declared.

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