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EDITORS CHOICE

Better Glasgow outcome score, cerebral perfusion pressure and focal brain oxygenation in severely traumatized brain following direct regional brain hypothermia therapy: A prospective randomized study

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ABSTRACT

Background: Induced hypothermia for treatment of traumatic brain injury is controversial. Since many pathways involved in the pathophysiology of secondary brain injury are temperature dependent, regional brain hypothermia is thought capable to mitigate those processes. The objectives of this study are to assess the therapeutic effects and complications of regional brain cooling in severe head injury with Glasgow coma scale (GCS) 6-7.

Materials and Methods: A prospective randomized controlled pilot study involving patients with severe traumatic brain injury with GCS 6 and 7 who required decompressive craniectomy. Patients were randomized into two groups: Cooling and no cooling. For the cooling group, analysis was made by dividing the group into mild and deep cooling. Brain was cooled by irrigating the brain continuously with cold Hartmann solution for 24-48 h. Main outcome assessments were a dichotomized Glasgow outcome score (GOS) at 6 months posttrauma.

Results: A total of 32 patients were recruited. The cooling-treated patients did better than no cooling. There were 63.2% of patients in cooling group attained good GOS at 6 months compared to only 15.4% in noncooling group ($P = 0.007$). Interestingly, the analysis at 6 months post-trauma disclosed mild-cooling-treated patients did better than no cooling (70% vs. 15.4% attained good GOS, $P = 0.013$) and apparently, the deep-cooling-treated patients failed to be better than either no cooling ($P = 0.074$) or mild cooling group ($P = 0.650$).

Conclusion: Data from this pilot study imply direct regional brain hypothermia appears safe, feasible and maybe beneficial in treating severely head-injured patients.

Key words: Brain oxygenation, brain temperature, head injury, hypothermia, trauma

Introduction

Despite current standards of treatment and care for the severely head injured patients, the desirable outcome for this patient group is hampered by the high morbidity and mortality rates. Conventional treatment routinely involves surgical evacuation of significant hematomas, efforts to restore and maintain adequate brain perfusion and prompt management of cerebral edema and raised intracranial pressure (ICP). Other treatment modality, in particular systemic hypothermia, had shown promising beneficial effect, though results appeared inconsistent in numerous trials.[1-7] Notwithstanding, induced hypothermia had also been reported in the management of stroke, hypoxic encephalopathy and seizures.[8-11]

The therapeutic basis of inducing hypothermia is supported by a neuroprotective effect on the brain following trauma or ischemic insults. Several mechanisms thought to underlie this effect which include the reduction in the metabolic rate and energy expenditure, attenuation in excitatory amino acids release and free radicals synthesis, suppression of excessive

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ischemia-induced and post-traumatic inflammatory reactions, and prevention of blood-brain barrier disruption and brain edema.[12,13] Despite our greater understanding in the scientific basis of brain hypothermia, an optimal method of brain cooling remains an issue that needs to be vigorously studied. It is apparent that method of inducing hypothermia does influence the effectiveness of delivering the cooling effect onto the injured brain. Methodically, brain cooling can be divided into peripheral and core cooling.[14] In our opinion, the direct cooling effect on the injured brain via both methods could still remain suboptimal, and frequently limited by complications. Such complications include pneumonia, systemic infections and cardiac arrhythmias in a systemic body cooling, and focal soft tissue injuries over the head in a helmet cooling.[14-16] 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 brain hypothermia." In this article, we present our preliminary experience with direct focal or regional brain cooling, obtained via direct irrigation of cold fluid onto the surface of severely injured brain for trauma patients who require decompressive craniectomy with a Glasgow coma scale (GCS) of 6-7.

Materials and Methods

Study design

This was a randomized controlled trial, designed to assess the effect of direct regional brain cooling treatment in severely head injured patients. The study has been approved by our local research and ethics committee (USMKK/PPP/JEPem [225.3 (13)]). Patients referred to the Department of Neurosciences from January 1, 2010 to January 1, 2012 and fulfilled the criteria were recruited into the trial. The sample size was calculated using two proportions formula with alpha of 0.05 and power of 80% with expected total sample size of 36 patients.

Subject criteria

All patients with traumatic brain injury were screened prior to recruitment. The inclusion criteria were: (a) Age 12 and above; (b) severe head injury with GCS 6-7; (c) require decompressive craniectomy; (d) able to be followed-up after 6 months being discharged from the hospital and (e) consented by next of kins or guardians. Patients with the following criteria were excluded: (a) Penetrating brain injury; (b) significant drop in blood pressure (systolic blood pressure of <90 or diastolic blood pressure of <60 mmHg) and/or significant hypoxia prior to admission; (c) bilateral fixed and dilated pupils; (d) severe injury to other organ systems which may lead to marked morbidity or even mortality; (e) concomitant traumatic spinal cord injury; (f) known pre-morbid immune or neurological diseases; (g) severe head injury with only extradural hematoma, and (h) known pre-morbid condition prior to the accident, including history of seizures. All recruited patients were then randomized to either group A (cooling group) or B (no cooling or standard treatment group).

Randomization and therapy

Potential patients were identified and screened by the principal investigators who are also the treating surgeons (Z.I and M.S.Z). They explained the randomization process, surgical procedures and cooling method, required neuromonitorings, imaging and follow-up to all potential candidates' legal representative in details. Once they agreed to participate, informed consent was obtained, and the patient was randomized to one of the two-treatment arms: Cooling versus no cooling. Sealed envelopes, initially blinded to both consenting individuals (on patients' behalf) and clinicians containing either paper A (for cooling group) and B (for no cooling or standard treatment group) were randomly chosen. Group A consisted of patients who had therapy with direct regional brain cooling and group B consisted of patients who did not have direct regional brain cooling therapy. There was no blinding done after assignment to interventions. All recruited patients received monitoring for ICP, brain oxygen and brain temperature using ICP and Licox probes (GMS, Kiel-Mielkendorf, Germany). ICP probe was inserted into the ventricle or brain parenchyma whilst Licox probe for brain oxygen and temperature was placed into the damaged brain areas. In addition, the cooling group (group A) had bloods taken for immunological parameters pre- and post-cooling therapy. The studied immunological parameters were CD3, CD4, CD8, CD19, CD16, and 56, interleukins (IL-1), IL-6, tumor necrosis factor (TNF) and total white blood cells count. The duration for monitoring and period of cooling therapy was for at least 24 h, although in case-by-case basis, longer therapy and monitoring was considered for persistently raised ICP without obvious surgical lesion on repeated computed tomography (CT) images. The body temperature was also monitored during the treatment period.

The recruited patients had CT brain prior to surgery and were categorized into different grade of severity of brain or whole body injury based on: (a) GCS; (b) Marshall score and (c) injury severity score (ISS). The unilateral decompressive craniectomy was the standard operation indicated for pathology causing midline shift, while bifrontal decompression was done for diffused pathology that causing cerebral swelling. The monitoring [Figure 1a] and therapies given after the surgery were the standard therapy for severely injured brain patients which include the following: (a) On ventilator support; (b) sedated with or without muscle paralysis agents; (c) draining of cerebrospinal fluid and/or hypertonic saline or mannitol therapy for persistently raised ICP of >20 mmHg; and (d) thiopentone coma therapy as a final step to treat postoperative refractory intracranial hypertension. For the cooling group (group A), direct regional brain cooling therapy was given after decompressive craniectomy [Figure 1b] by persistent irrigation of the swollen brain with a cold Hartmann's solution. The temperature range of initial infused fluid was used as the basis to analyze and to further divide Group A into two groups: (1) Deep cooling at a temperature of

20-29°C and (2) mild cooling at a temperature of 30-36°C. The cold infusion was achieved via neurojaf external ventricular drainage (EVD) with multiple side-holes catheter, which was inserted superior to the dura flap and at the inner surface of the dura, sprinkled onto the surface of the swollen brain. The catheter was in contact with the surface of the brain. The 500 ml of Hartmann's solution infusion rate was scheduled within 7 h (70 ml/h). Owing to patients' head position setting in the Intensive Care Unit, a second larger draining tube was inserted at the lower part of the craniectomy flap outside the dura, which was loosely closed to drain the excess fluid with a low suction pressure. The temperature of the infused Hartmann's solution was regularly monitored through the three way connector draining the fluid out to the collection port for temperature assessment. If the drained solution's temperature was under or above the intended value (s), the preceding infusion was replaced by a new solution with the correct intended temperature. An immediate CT scan of the brain was indicated if patients' ICP showed persistently raised values despite standard therapies being given. This was to exclude any new surgical lesions and/or the retention of infused solution as a cause of raised ICP. However, if the ICP hold within normal values, the CT scan was repeated after 48 h of therapy.

Outcome measures

The assessment of outcomes was performed through a dichotomized Glasgow outcome score (GOS) at discharge and mainly at 6 months after trauma as: (a) Good neurological outcome group (GOS 4 and 5), and (b) poor neurological outcome group (GOS 1, 2 and 3).

Statistical analysis

Data entry and analysis was done using Statistical Package for Social Sciences (SPSS; IBM, Chicago, Illinois USA) version 18.0. The level of statistical significant was set at 0.05 in a two-tailed fashion. In the descriptive analysis, the frequency, percentages, mean, median and confidence interval (CI) were reported for numerical variables. For inferential statistical analysis, the following tests were used for each objective: (a) Pearson Chi-squared test was used to compare the dichotomized GOS (good and poor) at discharge and at 6 months post-therapy for the studied groups, (b) general linear model for repeated measures ANOVA was used to calculate and depict the trends for ICP, cerebral perfusion pressure (CPP), brain oxygenation and brain-body temperature and their gradients, (c) trends and Wilcoxon signed rank test for comparison of immunological parameters, before and after cooling therapy, (d) Spearman rank correlation coefficient was used in correlation analysis between studied parameters with outcome scores and (e) Kruskal Wallis test comparing the studied groups for complication.

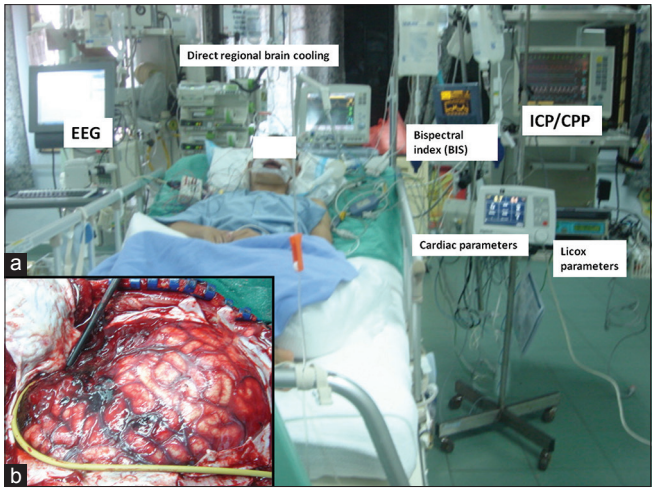

Figure 1: (a) Neurointensive care monitoring and therapy for patients in this study. (b) External ventricular drainage with multiple side-holes for surface irrigation of the brain with cold solution

Results

Demographic and clinical characteristics

A total of 32 patients were recruited into the 2 years study period from 1st January 2010 to 1st January 2012, aged between 14 and 74 years old. Of these, five patients aged more than 60 years old (19.2%). There were 27 (84.4%) males and 5 (15.6%) females. Patients were randomized into 2 groups; cooling group consisted of 19 patients (59.4%) and no cooling group consisted of 13 patients (40.6%). Finally, further stratification of cooling group based on the temperature of infused solution created 3 analyzable groups; mild cooling consisted of 10 patients (31.3%), deep cooling of 9 patients (28.1%) and no cooling of 13 patients (40.6%). The mean ages of the recruited patients were 28.9, 26.7 and 45.5 years old for the mild cooling, deep cooling and no cooling groups, respectively. Fifteen patients were admitted with GCS of 6 (46.9%) and 17 patients with GCS of 7 (53.1%). Among these, 28 patients (87.5%) underwent unilateral decompresive craniectomy, while four patients had bifrontal decompressive craniectomy (12.5%). Table 1 illustrates those parameters where all groups were

Table 1: Basic parameters comparison among the 3 studied groups

Variables	No cooling	Mild cooling	Deep cooling	*P*
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				
Male	10	8	9	0.40
Female (number)	3	2	0	
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 DIVC	3	2	4	0.44

CI – Confidence interval; DIVC – Disseminated intravascular coagulation; GCS – Glasgow coma scale

comparable with non-statistical difference shown for gender, GCS, ISS, Marshall score and clotting profiles. Age was the only basic parameters that differed among the three studied groups ($P = 0.02$). Even though the highest mean age was found in the control group, the 95% CIs (95% CI) for all three groups were still within the age of <60 years old.

Effect of regional brain cooling on Glasgow outcome score

There was a strong significant difference at 6 months post-trauma outcomes with $P = 0.007$ between the two studied groups: Cooling versus no cooling [Table 2]. There were 63.2% of patients (12 patients) in cooling group attained good GOS at 6 months compared with only 15.4% in non-cooling group (2 patients). There was no significant difference between the two groups when outcomes analysis was made at time of discharge. Further analysis at 6 months post-trauma was made after stratifying the cooling group into 2: Mild and deep cooling. Table 3 disclosed presence of significant difference among the three analyzed groups at 6 months post-trauma ($P = 0.023$). When comparison was only made between 2 groups (no cooling vs mild cooling; no cooling vs deep cooling and mild cooling vs deep cooling), it seems that the mild-cooling-treated patients fared better than no cooling (70% of mild cooling attained good GOS compared with only 15.4% attained good GOS in no cooling group, $P = 0.013$); and apparently, the deep-cooling-treated patients failed to be better than either no cooling ($P = 0.074$) or mild cooling group ($P = 0.650$).

Table 2: Effect of regional brain cooling on GOS at discharge and at 6 months

Outcomes (GOS)	No cooling (13 patients) (%)	Cooling group (19 patients) (%)	*P* value
GOS at discharge			
Poor GOS	12 (92.3)	15 (78.9)	0.307[a]
Good GOS	1 (7.7)	4 (21.1)	
GOS at 6 months			
Poor GOS	11 (84.6)	7 (36.8)	0.007[a]
Good GOS	2 (15.4)	12 (63.2)	

[a]Pearson Chi-squared test. GOS – Glasgow outcome score

Table 3: Effect of regional brain cooling on GOS at 6 months after stratifying the cooling group into mild and deep cooling

	n (%)			*P* value
	No cooling	Mild cooling	Deep cooling	
Outcomes (GOS): Comparing three groups				
GOS at 6 months				
Poor GOS	11 (84.6)	3 (30)	4 (44.4)	0.023[a]
Good GOS	2 (15.4)	7 (70)	5 (55.6)	
Outcomes (GOS): Comparing two groups				
GOS at 6 months				
Poor GOS	11 (84.6)	3 (30)		0.013[a]
Good GOS	2 (15.4)	7 (70)		
GOS at 6 months				
Poor GOS	11 (84.6)		4 (44.4)	0.074[a]
Good GOS	2 (15.4)		5 (55.6)	
GOS at 6 months				
Poor GOS		3 (30)	4 (44.4)	0.650[a]
Good GOS		7 (70)	5 (55.6)	

[a]Pearson Chi-squared test. GOS – Glasgow outcome score

Effect of regional brain cooling on trends of intracranial pressure, cerebral perfusion pressure, brain oxygenation, brain and body temperature and brain-body temperature gradient

All recruited patients did have ICP monitored but there were one patient in deep cooling, two patients in mild cooling and three patients in no cooling groups did not have neuromonitoring for focal brain oxygenation ($PtiO_2$) and temperature due to unavailability at certain time of the study period (26 patients did have those two specific neuromonitorings). Cooling the severely injured brain which had underwent decompressive craniectomy did not reduce the ICP further, but instead shown marked improvements in CPP and Licox $PtiO_2$ after 12 h of cooling. Figure 2 discloses mean ICP values and patterns for the three studied groups. All ICP readings stayed below 25 mmHg, and marked fluctuations were noted in cooling groups. Figures 3 and 4 reveal mean values and trends for CPP and Licox $PtiO_2$, respectively. Mild cooling group had ascending trends of CPP with mean values above 60 mmHg but <75 mmHg together with $PtiO_2$ mean values of above 40 mmHg after 12 h of cooling therapy. Interestingly, the deep cooling group did have similar ascending trends for CPP and $PtiO_2$ but their mean values after 12 h of cooling therapy were above 75 mmHg and <30 mmHg, respectively. Figure 5 gives additional information on brain-body (axillary) temperature gradient and types of cooling therapy. Patients in mild cooling group appeared to have a larger difference in brain-body (axillary) temperature gradient. Figure 6 shows, even during brain cooling therapy for severely injured brain, the brain temperature is still higher than body (axillary) temperature.

Effect of regional brain cooling on immunological biomarkers

Due to inadequate volume of blood taken for immunological analysis for either before or after cooling therapy, immunological data of three patients in mild cooling and one patient in deep cooling were excluded from the analysis. Trend analysis of seven patients in mild cooling and eight patients in deep cooling showed obvious decrements in values for both, T cell markers and pro-inflammatory cytokines after cooling therapy. Intriguingly, markers for pro-inflammatory cytokines (IL-1, IL-6 and TNF) did show more marked decrement than markers for T-cell [Table 4]. Despite of marked decrement in most

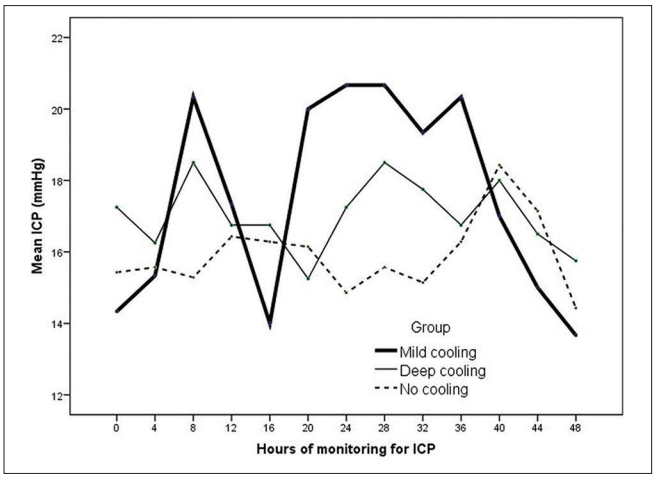

Figure 2: Trends of mean intracranial pressures for three different groups within 48 h of monitoring and therapy

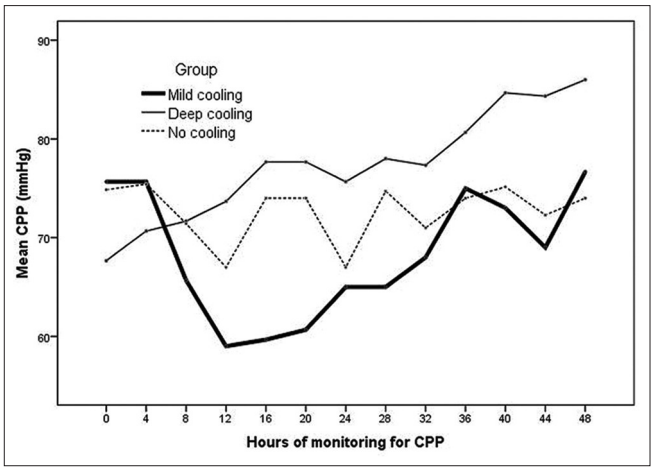

Figure 3: Trends of mean cerebral perfusion pressures for three different groups within 48 h of monitoring and therapy

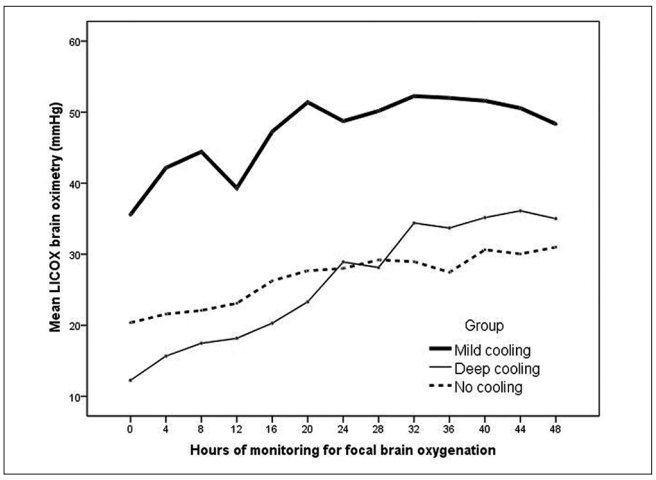

Figure 4: Trends of mean focal brain oxygenation for three different groups within 48 h of monitoring and therapy

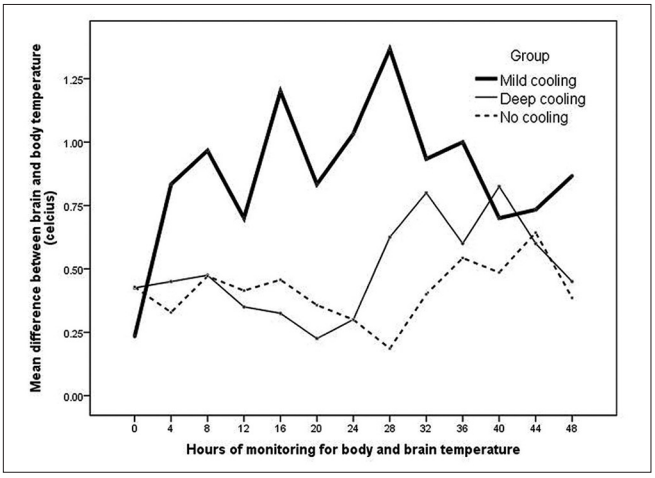

Figure 5: Trends of mean difference between brain and body temperature (brain – body temperature) for three different groups within 48 h of monitoring and therapy

studied immunological biomarkers after cooling therapy, the Wilcoxon Signed Ranked test for two related samples disclosed insignificant difference between pre- and post-cooling for all immunological parameters. This presumably related to our small sample size, which incapable to detect significant differences in those studied immunological parameters.

Correlation between studied parameters with Glasgow outcome score at 6 months post-trauma

Correlation analysis using Spearman rank correlation coefficient discloses age ($r = 0.46$) and Licox brain oxygenation ($r = 0.40$) as the only two studied parameters that reasonably correlated with outcome score at 6 months post-trauma. Table 5 illustrates the results.

Incidence of complications

Of the 32 patients, 50% ($n = 16$) had developed complications as shown in Table 6. The complications included wound infection in 21.9% ($n = 7$), CSF infection in 9.4% ($n = 3$), pneumonia in 6.25% ($n = 2$), hydrocephalus in 3.12% ($n = 1$) and brain infarct in 9.4% ($n = 3$). The number of patients who developed complications was higher in no cooling, and deep cooling groups compared with mild cooling group. Kruskal Wallis non-parametric statistical test comparing the three groups for complication disclosed insignificant difference with $P = 0.405$. In conclusion, no significant difference is found in the incidence of complication among the three groups.

Discussion

Pathophysiology of brain hypothermia, method of cooling and safety issue

Induced hypothermia for the treatment of traumatic brain injury remains a moot point. Therapeutic hypothermia was first studied in 1943 and since then, many studies reported inconsistent clinical results that dissuade its adoption as a routine evidence-based practice.[1-6,17,18] Our current, in-depth understanding on the pathophysiology of secondary brain injury is limited, but many animal studies have shown benefits

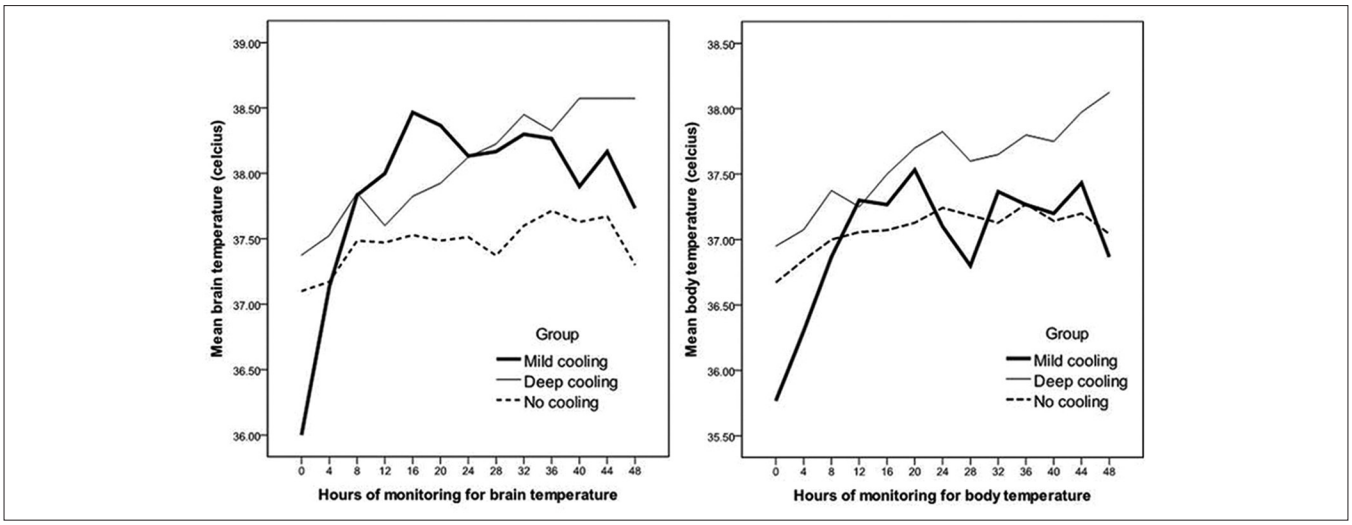

Figure 6: Brain temperature is higher (0.1-2°C higher) than body (axillary) temperature. The figures depicted in such way that the scales were aligned and therefore, the figures were comparable

Table 4: Effects of regional brain cooling (both mild and deep cooling groups combined together) on immunological parameters

	Mean±SD		Wilcoxon signed ranked test (*P* value)
	Precooling	Postcooling	
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)			
IL-1*	45.34 (130.7)	5.7 (13.0)	0.33
IL-6*	278.5 (221.1)	190.0 (208.4)	0.44
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

*Signify lower values after cooling therapy. Statistical test: Wilcoxon signed ranked test comparing pre- and post-cooling values; $P<0.05$ is regarded as significant. SD – Standard deviation; IL-1 – Interleukin; TNF – Tumor necrosis factor; WBC – White blood cell

Table 5: Correlation analysis between studied parameters with outcome score at 6 months

Studied parameter	Spearman rank correlation co-efficient	*P* value
Age	0.46	0.01
GCS	0.20	0.28
Marshall CT score	0.17	0.36
ISS	0.25	0.16
ICP	0.07	0.70
CPP	0.18	0.33
Licox brain oxygenation	0.40	0.04
Gradient brain-body temperature	0.35	0.06

Spearman rank correlation co-efficient for skewed data. GCS – Glasgow coma scale; CT – Computed tomography; ISS – Injury severity score; ICP – Intracranial pressure; CPP – Cerebral perfusion pressure

Table 6: Association between treatment groups and incidence of complication

Complication	No cooling	Mild cooling	Deep cooling	Total
Wound infection	4	1	2	7
CSF infection	0	1	2	3
Pneumonia	1	1	0	2
Hydrocephalus	0	1	0	1
Brain infarct	1	0	2	3
Total	6	4	6	16 from 32

$P=0.405$ (Kruskal-Wallis test comparing the 3 studied groups for complication). CSF – Cerebrospinal fluid

of induced hypothermia for the injured brain.[19-22] Poldermann published a review article on this issue and highlighted the benefits of induced hypothermia on the injured brain.[23] He noted pathways that promote cerebral ischemic-hypoxic events which can lead to cell death or apoptosis are mostly temperature dependent and, therefore, can be mitigated with cerebral hypothermia. The proposed neuroprotective mechanisms include: (a) Hypothermia can inhibit the activation of caspase enzymes, (b) prevents or mitigates mitochondrial dysfunction, (c) decreases the metabolism as well as decrease the overload of excitatory neurotransmitters such as glutamate and free oxygen radicals, (d) modifies the cellular disorders of intracellular ion concentrations, (e) suppresses the inflammatory and immunological responses and epileptic activity, (f) reduces the disruption in blood brain barrier, vascular permeability and edema, (g) improves the microcirculatory circuits and intra- and extra-cellular acidosis, (h) corrects the hyperthermia after brain injury and influence the local secretion of various vasoactive mediators secreted by the endothelium, and (i) enhances expression of

immediate early genes and cold shock proteins. Building on the vast benefits of cerebral hypothermia, we did a prospective study to test the null hypothesis, "cerebral hypothermia has no benefit on severely injured traumatic brain with initial GCS of 6 and 7". In the design of our study, several important issues related to induced hypothermia were put into context. First, the area of injury should be cooled. Therefore, brain cooling is the target, not body or scalp cooling. This was thought possible in patients who had decompressive craniectomy and irrigating the brain surface with cold Hartmann's solution and with second drainage tube situated outside the dura which was loosely closed. Furthermore, our experience from endoscopic intraventricular neurosurgery, by routinely irrigating the brain with a large amount of fluid seems safe, without inducing high rate of infectious complications. Second, brain temperature can be different from measured temperature of cooling method or therapy given to the patients. Statement saying "the brain was cooled to certain temperature degree needs to be stated cautiously." Measured brain temperature depends on many factors, including the location or site of the measuring tip as the inflamed area of the brain would manifest higher brain temperature than non- or less-inflamed brain area.[24] Third, by applying the concept of increase brain pulsation during compensatory phase of raise ICP, the irrigated regional fluid hopefully will be distributed to other brain regions via principles of vascular and brain pulsations.[25] Finally, induced hypothermia for the brain can be made below 32°C. An animal study by Oku *et al*. in 2009, disclosed focal brain cooling above 0°C did not induce irreversible histological change or cortical damage.[22] This study was carried out based on these four aspects of brain hypothermia and found the complication rate was indeed no difference between the cooling and control groups [Table 6].

Group comparison

It is essential to ensure the studied groups were comparable. Table 1 reveals only age has a significant difference between the studied groups. Mean age for no cooling or standard treatment group was higher than cooling groups. Nonetheless, the 95% CIs for those groups were still within non-elderly category. In terms of other parameters: Gender, GCS, ISS, Marshall score and clotting parameters, these were comparable. We purposely limited patient's inclusion to those with severely head injured patients with GCS 6 and 7 only. Since one of our main objectives is to study the true effect of cerebral hypothermia on outcomes, we thought by restricting patients to GCS 6 and 7, we can eliminate other prognostic indicators that may greatly influence the outcomes such as poor motor responses (decerebrate or decorticate posturing). By doing so, we can ascertain the "true benefit of brain cooling".

Proven benefits and reasons

Patients in cooling group had a higher percentage of good GOS and statistically had a significant difference at 6 months post-trauma when compared to non-cooling group. This finding may conclude that cooling the injured brain has indeed the potential benefits. The benefits of brain hypothermia for the severely injured brain can be explained based upon the pathophysiology of secondary brain injury as discussed above and also because of our method of cooling-our study applied direct regional brain cooling which means the cooling effect was directed toward the region of interests and perhaps via CSF pulsation, the residual cooling effect might have been distributed to the whole brain surfaces. This direct method of brain cooling is currently thought feasible for patients who had decompressive craniectomy. Further analysis on cooling-treated patients after stratifying them into two groups disclosed interesting findings: (a) Mild cooling group, treated at temperature of 30-36°C had fared better 6 months outcomes when compared to no cooling group and b) there was no significant difference for the 6 months post-trauma outcomes when the deep cooling group (temperature ranges from 20°C to 29°C) was compared to the non-cooling group. This signifies mild cooling-treated patients has the most significant benefits; and despite no apparent difference in the incidence of treatment complications, the deep cooling group surprisingly failed to be equally better as mild cooling group. The beneficial effects of mild brain cooling at temperature 30-36°C can partly be explained by our monitored parameters as discussed below.

Monitored and studied parameters; and brain cooling

Various study on hypothermia did notice reduction in ICPs, improvement in CPPs or $PtiO_2$ after cerebral hypothermia, which translated to better outcomes.[26-28] Since our study recruited only trauma patients with severe head injury and required decompressive craniectomy, reduction in ICP was not expected to be a major determinant correlated with outcomes, obviously because decompressive craniectomy itself has been shown to cause significant reduction in ICPs.[29-31] This could also be a reason why, majority of our treated patients with direct regional brain cooling had induced cerebral hypothermia for period up to 48 h only (short period). Besides ICP, cerebral blood flow (CBF) is another important parameter that must be optimized during monitoring the severely injured brain patients in neurointensive care. Interesting to note, the cooling-treated patients did have ascending or improved trends in CPP and brain oxygenation [Figures 3 and 4]. These two parameters could indirectly reflect the status of CBF. The mild cooling group did have mean CPP within accepted range of 60-75 mmHg [Figure 3] and mean $PtiO_2$ ranged from 35 to 48 mmHg [Figure 4] which is within normal range for a normal individual and proven to correlate well with outcome score [$r = 0.4$; Table 5]. As noted in other studies, reduction in ICP and optimal CBF parameters could have been contributed to the best long term outcomes for our mild-cooling-treated patients compared to deep- and no-cooling-treated patients.

Since the neuroinflammatory and metabolic responses happened inside and on the surface of the brain parenchyma, the irrigated cold fluid acts as an exogenous factor to exert mitigating effects on those responses. Therefore, the temperature of the brain should be higher and not be the same as the temperature of the irrigated fluid. This study disclosed that the intended temperature of induced cerebral hypothermia with direct regional brain cooling obviously did not correlate with brain temperature. One new observation noted from this study is brain-body temperature gradient; in mild cooling group, great gradient exists between brain-body temperature at 2-4 h after the therapy, whereas in deep cooling group, the gradient seems to become greater only after 24 h of cooling when both were compared with no cooling group [Figure 5]. The importance of this observation is not yet known and, therefore, need to be reconfirmed by other studies. Finally, findings in Figure 6 proved the previous reported study on brain temperature, which was always higher than the body temperature [0.5-1.5°C; Figure 6].[24,31]

Severe brain injury will induce significant and protracted inflammatory responses, beginning approximately 1 h after the injury and continuing for several days. Pro-inflammatory mediators such as IL-1, IL-6 and TNF are released in large quantities by astrocytes, microglia and endothelial cells. These inflammatory responses can cause significant additional brain injury via synthesis of various toxic products, activation of complements and further stimulating immune reactions in what may become a vicious circle.[12,14,32] In our study, direct regional brain hypothermia seems to suppress all these excessive inflammatory responses. The obvious benefit noted in this study was marked suppression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF [Table 4]. Therefore, our findings are in agreement with previous animal and clinical studies, which showed hypothermia decreases the levels of pro-inflammatory cytokines following brain injury.[33-35] Nonetheless, to know the true effect of regional brain cooling on immunological biomarkers, one needs also to consider levels in non-cooling group, which was not done in this study.

Limitation and recommendation

The limitation of this pilot study lies with its small sample size, and irrespective of patient randomization, recruitment of younger patients in the cooling group. Despite of the above mentioned drawbacks, this study could provide a nice foundation for future work on direct hypothermia, which can explore benefits in terms of GOS or other scoring outcomes. Future study to prove the clinical benefits of the present technique clearly need multicenter trials before inferring recommendation for the therapy as a standard of care. In addition, it is also important to consider a longer cooling period of >48 h even in the presence of normalized intracranial pressure and to do future study for patients even with GCS of <6.

Conclusions

This preliminary or pilot study found that direct regional brain hypothermia may have potential benefits in treating the severely head injured patients with initial GCS of 6 or 7. Other than a safe and practicable approach, this direct regional brain cooling therapy may serve as an added therapy for patients who require urgent decompressive craniectomy, irrespective of the underlying etiologies in the future.

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