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Original Article

Clinical outcomes and thermodynamics aspect of direct brain cooling in severe head injury

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ABSTRACT

Background: Brain cooling therapy is one of the subjects of interest, and currently, data on direct brain cooling are lacking. Hence, the objective is to investigate the clinical outcomes and discuss the thermodynamics aspect of direct brain cooling on severely injured brain patients.

Methods: This pilot study recruited the severely injured brain patients who were then randomized to either a direct brain cooling therapy group using a constant cooling temperature system or a control group. All studied patients must be subjected to an emergency neurosurgical procedure of decompressive craniectomy and were monitored with intracranial pressure, brain oxygenation, and temperature. Further, comparison was made with our historical group of patients who had direct brain cooling therapy through the old technique.

Results: The results disclosed the direct brain cooling treated patients through a newer technique obtained a better Extended Glasgow Outcome Score than a control group ($P < 001$). In addition, there is a significant outcome difference between the combined cooling treated patients (new and old technique) with the control group ($P < 0.001$). Focal brain oxygenation and temperature are likely factors that correlate with better outcomes.

Conclusion: Direct brain cooling is feasible, safe, and affects the clinical outcomes of the severely traumatized brain, and physics of thermodynamics may play a role in its pathophysiology.

Keywords: Brain cooling, Brain temperature, Brain thermodynamics, Brainwaves, Decompressive craniectomy

INTRODUCTION

The pathophysiology of traumatic brain injury can be divided into primary and secondary injuries. The secondary injuries are related to increased cell death and poor neurological outcomes.[20,23] Secondary injuries mainly involved the hypoxic-ischemic event, inflammatory cytokines, and free radicals. All of these are related to brain energy metabolism and thus are associated with heat. Energy metabolism in the brain is mainly aerobic in which most of the glucose used in the brain undergoes oxidative metabolism. Approximately 40% of the energy provided by glucose is used to produce ATP (permit electrical activity and brain function); the remainder (approximately 60%) is converted

into heat.[19] Under normal conditions, the production of heat within the brain is balanced by its dissipation. Therefore, brain temperature depends primarily on several factors: (a) local production of heat; (b) temperature of the blood inside the vessels; (c) cerebral blood flow (CBF); (d) cerebrospinal fluid (CSF), and (e) dissipation of generated heat by the heat exchangers such as cavernous sinus, pterygoid sinus, emissary veins, and air sinuses. Under abnormal conditions such as in the severely injured brain, the production of brain heat is excessive. Two studies on brain temperature in severe traumatic brain injury reported higher than the average body temperature in the post-traumatic days.[22,24] The observed elevation in brain temperature could be related to: (a) post-traumatic changes in brain metabolism (hyperglycolysis); (b) changes in CBF (hyperemia); (c) excessive inflammatory responses (increased interleukin); and (d) dysfunction of heat exchangers (venous stasis, displacement of the intracranial blood volume, and poor air sinuses ventilation due to intubation).[5,6,12,15,16] Regarding brain temperature, it is always regarded as higher than the body temperature (+0.5–1.5°C), the core of the brain is higher than the periphery (cortex), it is not stable with relatively large fluctuations (2–4°C) within the normal physiology, and minor changes in brain temperature can result in significant changes in neural cell metabolism and therefore in brain function.[1,14,18,24,25] Thus, tight control of brain temperature is critical for optimal brain function. Some studies on induced hypothermia for brain injury have found good outcomes correlated with hypothermia at temperatures of 31–35°C.[3,12,17,31] With the above introductory remarks, our study aims to investigate the effect of direct brain cooling on clinical outcomes, monitored intracranial pressure (ICP), cerebral perfusion pressure (CPP), focal brain oxygenation ($PtiO_2$), brain temperature, brainwaves, and briefly discuss the thermodynamics aspect of brain cooling.

MATERIALS AND METHODS

A newly innovated direct brain cooling therapy system was constructed by a local group of engineers and neurosurgeons using the system on chip-based and microelectronic mechanical system-based sensors. This direct brain cooling system was registered and published as D-brain cooling machine.[10] A prospective pilot study was then continued to recruit more severe head injured patients aged 12 and above. The study was designed to answer the research questions regarding the effect of synergistic approach using decompressive craniectomy (DC) and direct focal brain cooling therapy in managing the closed severe traumatic brain injuries [Figure 1a]. The study was approved by our Institutional Research and Ethics Committee with Ethics No. JEPeM/18010074. In this study, full consent was obtained for all patients who were then randomized into one of the two treatment arms: the constant cooling temperature therapy at 32°C (group A) versus the non-cooling therapy (group B). Sealed envelopes containing either paper A (for the group A) or B (for the group B), blinded to both consenting individuals (on the patients' behalf) and clinicians, were randomly chosen. A total of 30 envelopes were used, which were equally divided into groups A and B. After the assignment to the interventions, no blinding to the therapy was conducted. In summary, group A (the constant cooling temperature at 32°C) comprised patients with severe head injuries (Glasgow Coma Score [GCS] 4–7) who had therapy with direct focal brain cooling, whereas group B was the control group (also patients with severe head injuries with GCS 4–7). All recruited patients had ICP, Licox ($PtiO_2$ and temperature probes by Integra, Mielkendorf Germany), and electrocorticographic (ECoG) monitoring (NicoletOne System, Natus Neurology Incorporated, Middleton, WI) [Figure 1b]. The overall monitoring and therapy period lasted for 48 h.

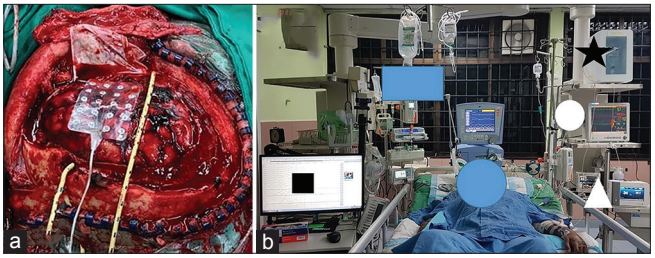

Figure 1: The direct brain cooling clinical study. (a) A severely head-injured patient was treated with decompressive craniectomy, removal of any surgical lesions, and duraplasty. The image also shows a grid electrode and a coolant catheter which were laid onto the cortical brain surface. (b) A studied patient received a direct brain hypothermia therapy (black star) and was monitored with intracranial pressure (round white circle), brain oxygenation and temperature (white triangle), and electrocorticographic brainwaves (black square).

With regard to the neurosurgical procedure, a standard decompressive craniectomy (DC) of either unilateral or bifrontal was used. The unilateral DC was used for patients with significant unilateral surgical lesion such as subdural or contusional hemorrhage with midline shift to the opposite side and effacement of basal cisterns. For the bifrontal DC, it was used whenever there was a significant surgical lesion such as contusions at the frontal lobe(s) or the presence of brain swelling with effacement of the basal cisterns without a midline shift. Our unilateral neurosurgical DC was a standard operation covering the frontal, parietal, and temporal lobes. Besides bony decompression, duraplasty with pericranium was made after the removal of any surgical lesions. At the end of the surgery, the ICP probe was inserted through a burr hole into the ventricle or parenchyma of the opposite hemisphere. For the Licox probe, it was inserted into the ipsilateral side of the DC hemisphere. The Licox catheter which measured the brain oxygenation and temperature laid superficially at the subcortical region of the brain (>5 mm in depth). The abnormally looking brain area

was selected during the surgery for its probe insertion. Finally, the ECoG grid of either 5 × 4 or 8 × 4 electrodes to monitor the brainwaves was laid onto the surface of the decompressed brain. The ECoG brainwave monitoring was completed using the NicoletOne system with adjustable sensitivity format ranging from 10 to 5000 μV/cm, low and high cuts of 1 and 50 Hz and time-based of 30 mm/s. The brainwaves' power spectrum (or energy per unit of time) (μV^2/Hz) was automatically calculated by the quantitative ECoG power band software in the NicoletOne system. For the specific alpha connectivity (coherence) and alpha power analysis, an ECOG preprocessing pipeline was used with bandpass filtering within 1–43 Hz. The excessive amplitude of filtered signal or slower frequency activity was automatically marked and excluded from analysis using the auto-reject library.

The therapies after the DC surgery were the standard ones for patients with severe head injuries – these include sedation (propofol, 10 mg/h, and fentanyl, 50 mcg/h) without muscle paralysis agent; ventilation; CSF drainage; mannitol or hypertonic saline; and finally, thiopentone coma therapy for those with persistent increase or refractory ICP of >20 mmHg. Regarding direct focal brain cooling, it was started in neurointensive care by continually irrigating the brain with cold Hartmann's solution using our newly innovated machine. The temperature of the infused fluid was made constant at 32°C throughout the treatment period. Due to the patient's head position, a second larger drained tube was inserted at the lower part of the craniectomy flap and outside the dura which was loosely closed to drain the excess fluid with a low suction pressure. For the control group, no cooling therapy was given. Nevertheless, all controlled patients were also monitored with the ICP, Licox, and ECoG grid. The assessment of the outcomes was conducted through a dichotomized Extended Glasgow Outcome Scale (GOSE) at discharge and 6 months after the trauma as (1) good neurological outcome group (GOSE 4–8) and (2) poor neurological outcome group (GOSE 1–3). The statistical analysis was completed using the Statistical Package for the Social Sciences (SPSS; IBM, Chicago, IL), version 26.0 to mainly compare the constant cooling temperature at 32°C group or group A with the non-cooling, control, or group B. In addition, we also included and compared the current data with our historical brain cooling data that consisted of a group of the first 15 recruited-patients who had direct brain cooling therapy through the old method. The whole data of this study was published in 2014.[12] The old method used cold Hartman's solution at a non-constant and wide range of temperature i.e. 20–36°C. Thus, we labeled this third group as group C with non-constant cooling temperatures. Finally, our last comparing analysis comprised mixed or all patients who had direct brain cooling (new and old method) and control or non-cooling patients. The level of statistical significance for the analyses was set at $P < 0.05$.

RESULTS

The results were divided into two parts. Part one comprised the demographic, clinical parameters, and outcomes data for the three groups whereas part two contained case examples for cooling (group A) and non-cooling (group B) patients with their related brainwave morphology, energy shift, alpha wave connectivity or coherence, and power spectrum for the alpha wave.

Clinical parameters and outcomes

There were three groups analyses: constant cooling (new/group A), control (group B), and non-constant cooling group (old/group C) [Table 1]. There were 15 patients in each group with insignificant *P*-values for mean age, gender, median GCS, and Marshall score between the compared groups. However, there was a lower score for the trauma severity in the non-constant cooling group with a significant *P*-value when compared between constant cooling and control ($P < 0.046$) and mixed cooling with control ($P < 0.012$). Overall, the demographic features of the three groups are comparable. For the monitored clinical parameters, there was a significant difference in the mean focal brain oxygenation ($P < 0.043$) and mean brain temperature ($P < 0.007$) between the constant coolant versus the non-constant coolant therapy. Regarding the ICP and CPP, despite no difference in the results for the constant versus control (ICP: $P > 0.163$; CPP: $P > 0.457$); for all cooling group versus control (ICP: $P > 0.1333$; CPP: $P > 0.753$); and for the constant versus non-constant group comparison (ICP: $P > 0.287$; CPP: $P > 0.144$), the lower mean ICP values and optimal CPP values were noted in the constant cooling group. Regarding clinical outcomes, the constant and all cooling groups have a significant difference at discharge and 6 months after the trauma ($P < 0.001$). The brain cooling treated patients at 6 months scored 5 or 6 on average for the median GOSE, while 2 for the control group. Interestingly, none of our studied patients suffered from the complications such as pneumonia, thrombosis, arrhythmia, or wound infection.

Concerning the temporal pattern of the monitored clinical parameters [Figure 2], patients who were treated with our newly innovated direct brain cooling machine at a constant temperature of 32°C showed lower ICP values with a range of 11.81–16.91 mmHg, and optimal CPP value with a range of 64.99-69.83 mmHg. Besides, our new method of cooling did give the optimal redox range for the focal brain oxygenation ($PtiO_2$): 17.94–32.44 mmHg which is within the best redox regulation between hypoxemia and hyperoxemia for the brain tissues (15–35 mmHg).[11,13,21] Similarly, the range values for the brain temperature in this group are <38°C and higher than 34°C (35.18–37.09°C with a mean of 36.23°C)

Table 1: The demographic, monitored clinical parameters, outcomes, and complications of the three comparing groups.

	New cooling (constant cooling) (Group A)	Control (Group B)	Old cooling (non-constant cooling) (Group C)	*P*-value: comparing new cooling (A) to control(B)	*P*-value: comparing all (new+old) (A+C) cooling to control(B)	*P*-value: comparing new (A) to old (C) cooling
Total no. of cases	15	15	15			
Age(mean in years) (95% CI)	31.6 (24.5–39.37)	33.2 (24.22–41.9)	29.47 (20.93–39.06)	0.795	0.629	0.739
No. of male gender	12	14	13	0.299	0.364	0.638
No. of female gender	3	1	2			
Glasgow Coma Score(median) (95% CI)	6 (5–7)	6 (5–7)	6 (6–6)	0.777	0.769	0.152
Marshall Score(median) (95% CI)	4 (4–4)	4 (3–4)	4 (3–4)	0.344	0.705	0.165
Trauma severity score(median) (95% CI)	27 (25–30)	30 (27–35)	18 (18–27)	**0.046**	**0.012**	0.658
Mean intracranial pressure(mmHg) (95% CI)	14.27 (11.81–16.91)	26.5 (19.26–33.56)	16.63 (15–18.56)	0.163	0.113	0.287
Mean cerebral perfusion pressure(mmHg) (95% CI)	67.35 (64.99–69.83)	61.73 (52.14–71.06)	72.6 (63.01–80.13)	0.457	0.753	0.144
Mean focal brain oxygenation(mmHg) (95% CI)	25.42 (17.94–32.44)	27.24 (11.66–42.60)	40.07 (31.24–52.27)	0.817	0.635	**0.043**
Mean brain temperature(°C) (95% CI)	36.23 (35.18–37.09)	34.89 (32.27–37.35)	38.23 (37.72–38.67)	0.362	0.097	**0.007**
Presence of epileptiform discharges on ECoG	All patients	All patients	-	-	-	-
Median GOSE at discharge(range)	3(2–4)	2(1–2)	4(2–5)	**0.001**	**0.001**	0.786
Median GOSE at 6 months(range)	5(3–6)	2(1–3)	6(2–7)	**0.001**	**0.001**	0.812
Complication in alive patient	None	None	None			

[1]Two groups comparison: for the normally distributed data–a parametric t-test was used, for the non-normally distributed data–a non-parametric Mann–Whitney test was used. [2]In bold are the significant *P*-values. GOSE: Extended Glasgow Outcome Scale, CI: Confidence interval, ECoG: Electrocorticography

which is within the recommended functional values for the brain temperature. The normal and well functional brain has a fluctuant temperature that falls within the range of 35.4–38.4°C (36.9±0.5–1.5°C).[24,28] For the old non-constant method of direct brain cooling of group C, the observed patterns for the ICPs are nearly similar to the new constant coolant group A, but with a higher range for CPP (63.01–80.13 mmHg), above the redox regulation range for the $PtiO_2$ (31.24–52.27 mmHg) and higher range values for the brain temperature (37.72–38.67°C with mean of 38.23°C). In control group B, the three-monitored clinical parameters were noted to be much different from the other groups. The higher ICPs and lower CPPs were noted in this group and despite having optimal brain oxygenation, the injured brains in this group failed to maintain their normal range of temperature values. The analysis did show that the control group has a much lower brain temperature range and mean when compared to the other groups (32.27–37.35°C with a mean of 34.89°C).

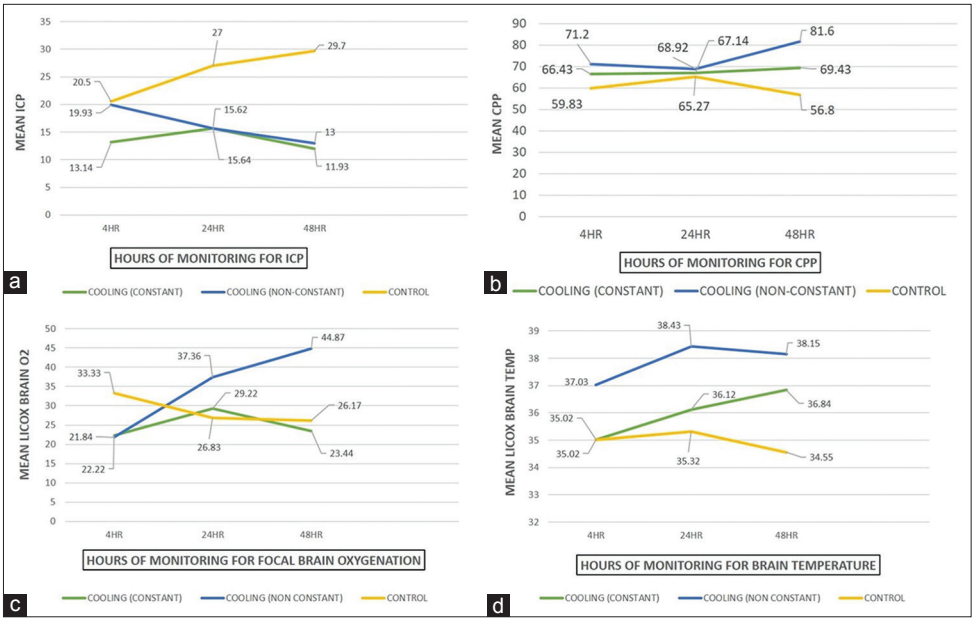

Figure 2: Temporal patterns for the average ICP (a), CPP (b), brain oxygenation (c), and brain temperature (d) for the studied patients. ICP: Intracranial pressure, CPP: Cerebral perfusion pressure.

Case examples: Brainwave morphology and energy in cooling and non-cooling patients

A case of direct brain cooling

A 30-year-old lady involved in a road traffic accident with GCS of 7 was noted to have a 1.5 cm thickness of the right frontotemporoparietal acute subdural hemorrhage (SDH), a midline shift to the opposite side of 1 cm, bifrontal contusions, traumatic subarachnoid hemorrhage (tSAH), and brain swelling with effacement of basal cisterns. Emergency DC, removal of SDH, laying of a 5 × 4 subdural grid ECoG electrode, ICP, Licox, cooling catheter insertion, and duraplasty were made. Direct brain cooling therapy at 32°C was started soon after the surgery in our neurotrauma intensive care unit (ICU). The recorded brainwave data showed the presence of persistent non-periodic abnormal epileptic activities [Figure 3a] which progressively disappeared after 24 h of direct brain cooling [Figure 3b]. The spectral analysis for the brainwave at electrodes 3–5 (contused brain) revealed a lower energy activity (more of delta to the alpha range) with a better fluctuation pattern observed during the cooling phase [Figure 3c]. She had a good neurological outcome at 6 months with GOSE of 6.

A non-cooling case

A 31-year-old man with a GCS of 6 was admitted following a road traffic accident. His urgent computed tomography brain disclosed the presence of an acute right temporal epidural hemorrhage of 2 cm in thickness, an acute right SDH of 1 cm in thickness, and an opposite acute thin SDH with contusions covering the frontal, temporal and parietal areas, tSAH, and brain swelling. He underwent emergency hemispheric DC, removal of blood clots, duraplasty, Licox, subdural grid, and ICP monitoring. His direct cortical brainwave recording revealed a persistent presence of subclinical and abnormal epileptiform discharges [Figures 3d and e] and had poorer alpha coherence (connectivity) and lower alpha power than a cooling-treated patient [Figures 4a and b]. His neurological outcome at 6 months was poor with a GOSE of 3.

DISCUSSION

Therapeutic hypothermia and clinical outcomes

Tier one through tier three are used in managing the severely injured brains with established intracranial hypertension. DC and induced mild hypothermia (32–35°C) are stated under tier three of the management. They are used after failed tier one and two which consist of sedation, analgesia, CSF drainage, mannitol, hypertonic saline, neuromuscular blockade, mild hypocapnia, and CPP management based on autoregulation assessment.[7] The use of DC after tier two is regarded as a secondary DC. The on-admission primary DC is also used in some trauma centers for those with or without intracranial surgical lesions, but presence of brain swelling and effaced basal cisterns.[2,27] In this study, the synergistic approach was made, whereby DC was combined with direct focal brain cooling at a constant temperature of 32°C (group A). The studied group A was then compared with the control (group B) and also with the historical group using the non-constant direct brain cooling method (group C). The clinical outcomes at the

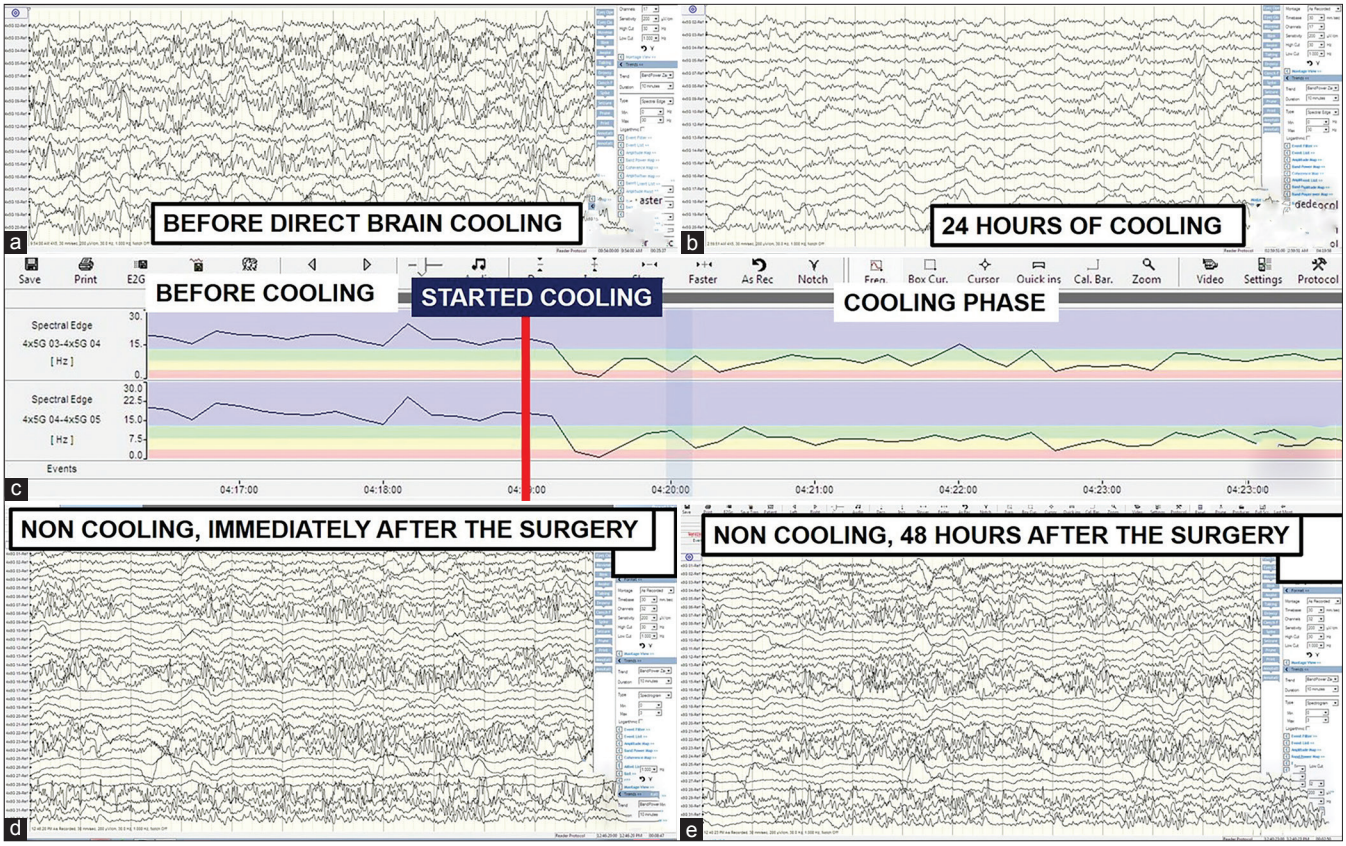

Figure 3: Brainwave morphology, epileptic activity, and energy. (a and b) A significant improvement in brainwave morphology without abnormal epileptic activities for the direct brain cooling patient. (c) Direct brain cooling of the same patient at electrodes 3–5 (contused brain) lowers the brainwave spectrum from more beta- (high energy) to delta-alpha range (low energy) with more spectral fluctuation pattern observed after the cooling. (d and e) A persistent presence of subclinical epileptic activities for the non-cooling patient.

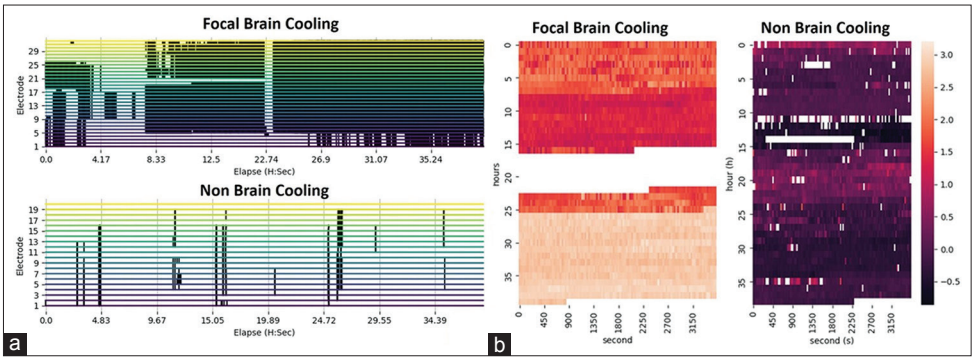

Figure 4: Brainwave connectivity (coherence) and power spectrum for the alpha waves. (a) More coherence or connectivity was observed in the cooling treated patient (green colored) for the alpha waves. (b) Alpha wave power is also higher in the cooling treated patient.

time of discharge and 6 months after the trauma disclosed a significant difference between the new constant cooling technique versus control, and all cooling patients (combination of new and old technique) with the control. Interestingly, there was no statistical difference in terms of outcomes between the constant and non-constant cooling groups. However, those in the constant cooling group did have optimal CPP and $PtiO_2$, and within a normal range of brain temperature. Our present study proves that by giving constant coolant irrigation directly onto the injured brain surface at 32°C, the clinical outcomes are far better than those receiving DC alone. The promising and positive clinical findings of our synergistic approach are in agreement with previous mice animal study that used a similar method (DC with brain cooling).[26] The reasons for

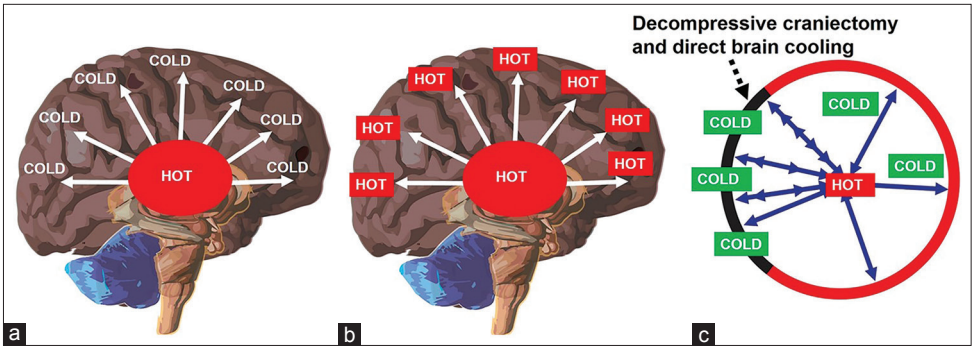

Figure 5: Decompressive craniectomy (DC) and thermodynamics aspect of brain cooling. (a) Presence of temperature gradient inside a healthy person (core is higher than periphery). (b) Loss of temperature gradient in the severely injured brain. (c) Reestablishment of temperature (heat) gradient after synergistic therapy – DC and direct brain cooling (note: cooling effect may spread to the whole brain through cerebrospinal fluid pulsation).

gaining better outcomes can be attributed to: (a) lower ICP values (11.81–16.91 mmHg); b) optimal CPP values (64.99–69.83 mmHg); (c) optimal redox range for the focal brain tissues or $PtiO_2$ (17.94–32.44 mmHg); (d) optimal range for the brain temperature (35–37°C); and (e) probably presence of optimal cerebral pulsation (due to optimal CPP) which capable in distributing the coolant to other areas of the injured brain.

Besides the commonly monitored clinical parameters, the added values of our study are related to brainwave monitoring using the gold standard subdural grid of ECoG. The direct cortical brainwave study revealed the presence of subclinical seizures in all studied patients which were mitigated or abolished by the cooling therapy. Our case examples depicted improved brainwave morphology after cooling therapy. Detailed analysis revealed lower spectral energy, improved alpha connectivity or coherence, and alpha power in the cooling treated patients. With these findings, we recommended routine ECoG monitoring for the severely injured brain who underwent either primary or secondary DC. Concerning direct brain cooling therapy, since only few reported clinical studies are available in current literature, obviously more studies are needed to ascertain its true benefits.[10,12] Perhaps, an international clinical trial on direct brain cooling therapy for severely head injured patients is a right step forward because it is a potentially important and promising intervention of severely injured brain with its attendant high mortality. To further comprehend the scientific basis behind our promising results, we briefly discuss our findings in the context of brain energy and brain thermodynamics.

Brain energy and brain thermodynamics related to DC and direct brain cooling

Brain metabolism increases in brain injury. The secondary brain injury is associated with microscopic events that increase metabolism which produces energy and heat.[3,23] In severe head injury, elevation in brain heat is also caused by: (a) hyperemia through the process of neurometabolic-neurovascular coupling; (b) impairment in airflow at the skull base air sinuses in the intubated patient; and (c) reduce the amount of intracranial CSF secondary to brain swelling (especially at the convexity and in the ventricles – slit ventricles).[4,9,29,30] Hence, heat regulation in the cranium involves the process of neurometabolism as well as conduction (blood flow and CSF), convection (air sinuses and CSF), evaporation (CSF and air sinuses), and radiation (cranial black-box). According to Hayward and Baker (1969), the brain thermal map shows a higher temperature at the core than the periphery of the brain. They found that the hypothalamus, midbrain reticular formation, and basal ganglia are the hottest part of the brain with 0.5–0.6°C higher than the periphery [Figure 5a].[8] In the presence of brain injury, excessive heat is produced, thus obliteration or distortion of the heat or temperature gradient inside the brain could happen and thus affect the function of the brain [Figure 5b]. By treating the severely injured brain with a combination of DC and direct brain cooling (synergistic approach), the brain temperature gradient can be reinstated so that optimal brain function can be achieved [Figure 5c].

Limitation and recommendation

This study has limitations in term of the sample size and deep nuclei brain temperatures were not studied. Thus, the temperature gradient was not truly established. Hence, future studies should enrol more patients and consider measuring the deep brain region temperature in the severely head-injured patients.

CONCLUSION

In a severely injured brain with compromised cerebral blood perfusion, CSF flow and airways, a rise in cerebral

metabolism to accommodate demand may end up with a further rise in ICP and brain heat. To reverse the situation, our synergistic approach using a combined DC and direct brain cooling is proven beneficial with near-normal recorded ICP, CPP, brain oxygenation, and temperature.

Declaration of patient consent

The Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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