Discrete cerebral hypothermia in the management of traumatic brain injury: a randomized controlled trial

Clinical article

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Objective. Hypothermia has been extensively evaluated in the management of traumatic brain injury (TBI), but no consensus as to its effectiveness has yet been reached. Explanatory hypotheses include a possible confounding effect of the neuroprotective benefits by adverse systemic effects. To minimize the systemic effects, the authors evaluated a selective cerebral cooling system, the CoolSystem Discrete Cerebral Hypothermia System (a “cooling cap”), in the management of TBI.

Methods. A prospective randomized controlled clinical trial was conducted at Grady Memorial Hospital, a Level I trauma center. Adults admitted with severe TBI (Glasgow Coma Scale [GCS] score ≤ 8) were eligible. Patients assigned to the treatment group received the cooling cap, while those in the control group did not. Patients in the treatment group were treated with selective cerebral hypothermia for 24 hours, then rewarmed over 24 hours. Their intracranial and bladder temperatures, cranial-bladder temperature gradient, Glasgow Outcome Scale (GOS) and Functional Independence Measure (FIM) scores, and mortality rates were evaluated. The primary outcome was to establish a cranial-bladder temperature gradient in those patients with the cooling cap. The secondary outcomes were mortality and morbidity per GOS and FIM scores.

Results. The cohort comprised 25 patients (12 in the treatment group, 13 controls). There was no significant intergroup difference in demographic data or median GCS score at enrollment (treatment group 3.0, controls 3.0; p = 0.7). After the third hour of the study, the mean intracranial temperature of the treatment group was significantly lower than that of the controls at all time points except Hours 4 (p = 0.08) and 6 (p = 0.08). However, the target intracranial temperature of 33°C was achieved in only 2 patients in the treatment group. The mean intracranial-bladder temperature gradient was not significant for the treatment group (p = 0.07) or the controls (p = 0.67). Six (50.0%) of 12 patients in the treatment group and 4 (30.8%) of 13 in the control group died (p = 0.43). The medians of the maximum change in GOS and FIM scores during the study period (28 days) for both groups were 0. There was no significant difference in complications between the groups (p value range 0.20–1.0).

Conclusions. The cooling cap was not effective in establishing a statistically significant cranial-bladder temperature gradient or in reaching the target intracranial temperature in the majority of patients. No significant difference was achieved in mortality or morbidity between the 2 groups. As the technology currently stands, the Discrete Cerebral Hypothermia System cooling cap is not beneficial for the management of TBI. Further refinement of the equipment available for the delivery of selective cranial cooling will be needed before any definite conclusions regarding the efficacy of discrete cerebral hypothermia can be reached. (DOI: 10.3171/2009.1.JNS081320)

Key Words • cooling helmet • hypothermia • trauma • traumatic brain injury

Abbreviations used in this paper: FIM = Functional Independence Measure; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; MAP = mean arterial pressure; SE = standard error; TBI = traumatic brain injury.

An estimated 2 million people sustain TBI in the US every year.1,5,12,30,34 Studies from the Centers for Disease Control and Prevention demonstrate that the rates of TBI continue to increase annually.4,6 In 2003 alone, TBI led to 1.2 million emergency department visits and 51,000 deaths in the US.3,4 Two percent of the US population currently require assistance due to disabilities resulting from TBI.3,4
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Brain injury after trauma occurs in 2 stages: 1) primary injury, the damage that occurs at the moment of impact; and 2) secondary injury, which occurs later due to processes within the brain, including intracellular release of free radicals, inflammatory processes, vasogenic edema, increased ICP, decreased cerebral blood flow, and eventually ischemia and cell death.26 Prevention is the main focus of efforts to address primary brain injury. Among the strategies studied to mitigate the effects of secondary injury is hypothermia, defined simply as a body temperature < 37°C.

Since the days of the ancient Greeks and Romans, hypothermia has been noted to have beneficial health effects. Hippocrates packed wounded patients in snow to decrease hemorrhage, and Napoleon’s surgeon general noted that wounded soldiers who were placed close to the fire died more rapidly than did those who remained cold.32 The first report describing the use of hypothermia in patients with severe head injuries was published in 1945.10 This was followed in 1959 and 1965 by studies showing benefit in dogs treated with hypothermia after ischemia or TBI.12,33 This work led to more widespread application of the procedure in neurosurgery and in cardiothoracic surgery, where deep hypothermia (15–22°C) has appeared to be an effective method of neuroprotection.2

Deep hypothermia, however, has been associated with significant secondary complications, including cardiac arrhythmia, disruption of the coagulation cascade, and systemic infection.2,7,9,21,25,31,37,38 In an attempt to address these concerns, milder degrees of hypothermia were studied. When limited to temperatures of 30–35°C, hypothermia was found to provide significant neuroprotection in animal models.2,15,17–20,35,40,42 These results led to the implementation of mild to moderate hypothermia in various clinical settings. Several clinical trials utilizing moderate hypothermia sought to establish this as a treatment modality for TBI. The benefits remained controversial, however, and the efficacy of hypothermia in the management of TBI has remained in doubt.

Meta-analyses have evaluated this topic without any definitive conclusions.13,14,24 Harris et al.13 reviewed 7 randomized clinical trials in 2002 and demonstrated that hypothermia was not beneficial in the management of severe head injury. Of note, the authors cautioned that the existing literature could neither define nor guide the clinical application of hypothermia in the management of TBI and called for more rigorously designed studies to address the various limitations. Henderson et al.14 in a meta-analysis of 8 studies on the same topic, concluded that while iatrogenic hypothermia demonstrated a trend toward benefit in neurological outcome for patients with severe TBI, there was no significant decrease in mortality. In a third meta-analysis, McIntyre et al.24 evaluated 12 randomized controlled trials of hypothermia for TBI and reached a somewhat more optimistic conclusion. Although the relative risk of death was 0.81 for hypothermia versus controls, the analysis included several poor-quality trials and trials that included duplicate data; the generalization of the conclusions is therefore limited.

Thus, the challenge of establishing hypothermia as an effective treatment modality remains. Among the key issues is the difficulty in instituting a safe, effective, and efficient means of establishing sufficient cooling while minimizing systemic confounders. To address this difficulty, a cooling device was developed to provide localized cranial cooling via a cooling cap: the Discrete Cerebral Hypothermia System by CoolSystems, Inc. (Fig. 1). This cap is intended to induce a localized cranial hypothermic state, thus gaining the potential neurological benefits of hypothermia without imposing systemic cooling and thereby avoiding many of the complications of systemic hypothermia. The CoolSys- tems cooling cap is the only noninvasive method of selective cranial cooling currently commercially available and able to be used in a practical clinical setting.

Wang et al.41 recently described a small initial study of this cooling cap in the Journal of Neurosurgery. The authors monitored 8 patients treated with the cooling cap and 6 controls. On average, 3.4 hours were needed to achieve an intracranial temperature < 34°C in the cooling cap group; in an average of 6.67 hours, systemic hypothermia < 36°C developed. A significant gradient between systemic and intracranial temperatures was achieved in the patients in the treatment group, and this was maintained throughout the 2- to 3-day hypothermic study period. The only systemic complication noted during the hypothermic period was 1 episode of asymptomatic bradycardia that resolved with a small increase in body temperature. The study was limited by small sample size, conflation of the subject group by combining trauma and stroke patients, and few outcome variables. Nonetheless, the cap appeared to be an effective device that we felt warranted further investigation.

The potential benefits of the cooling cap include providing a noninvasive selective method of cooling the brain, thereby limiting secondary injury while reducing the risks associated with systemic hypothermia, and identifying a portable system that could be used very early in treatment by healthcare personnel, including emergency medical service providers in the field. In our study we aimed to address several of the prior study’s noted limitations. Our primary goal was to further investigate the feasibility and clinical benefit of this device.

Methods

The goal of this study was to determine the effectiveness of the Discrete Cerebral Hypothermia System (“the cooling cap”) using a randomized, controlled design stratified on the extended head injury scale based on injury severity40 (with GCS scores of 3–4 representing critical injuries and scores of 5–8 representing severe injuries) to balance the injury severity between the treatment and the control groups. Our primary outcomes for this study were the effectiveness of the cooling cap in reducing the patient’s internal brain temperature and in establishing a gradient between patients’ core and brain temperatures following TBI.

The secondary objective was to perform a comparative analysis of outcome using mortality, GOS, and FIM scores following severe TBI.
Data were prospectively collected from July 2006 until August 2007 in all cases involving patients admitted to Grady Memorial Hospital (Atlanta, Georgia) after suffering TBI. Family members of all patients fitting inclusion criteria were approached for study enrollment.

Patients had to meet the following criteria to be included: 1) The patient was being treated for severe TBI, GCS score ≤ 8; 2) The patient was at least 18 years of age; 3) The patient required an ICP monitor and Foley catheter as part of routine treatment; 4) The patient was able to receive the Discrete Cerebral Hypothermia cooling cap within 48 hours of hospital admission; 5) The patient’s family member or guardian spoke English to ensure proper informed consent; and 6) The patient’s family member or guardian agreed to participate and signed an informed consent.

Patients were excluded if any of the following criteria applied: 1) The patient’s family member or guardian was unwilling or unable to sign an informed consent; 2) The physical placement of the cooling cap impeded routine treatment; 3) The patient’s core body temperature was ≤ 36°C at the time of initial assessment; and 4) Treatment could not be initiated within 48 hours of admission.

All consents were obtained by one research assistant to decrease bias. After informed consent was obtained, all study patients were blindly randomized in a 1:1 ratio to the treatment or control group; patients in the treatment group received the cooling cap and the controls did not. The randomization was determined by the Department of Biostatistics using computer-generated random numbers. These numbers were assigned to each patient based on their order in the study and GCS score on initial assessment (severe [5–8] vs critical [3–4]), to allow for block randomization and to provide an initial balance in severity between the 2 groups. All patients were treated in accordance with the Brain Trauma Foundation’s Guidelines for the Management of Severe Traumatic Brain Injury.

**Data Collection**

Demographic data including sex, age, ethnicity, mechanism of injury, date and time of injury, date and time of each temperature measurement, length of time to medical attention, length of time to study initiation, routine vital signs, GCS score on admission, associated systemic injuries, location and type of intracranial lesions, surgical interventions, adjunctive medical therapies, and duration of stay were collected for each enrolled patient.

Baseline recordings of the intracranial and bladder temperatures, ICP, and MAP were obtained for all study participants. Intracranial temperatures and intracranial pressures were recorded via ICP monitor (Camino 110–4HMT or Camino 110–4B, Integra NeuroSciences) and bladder temperatures were measured via Foley catheter.

For patients assigned to the treatment group, the cooling cap was placed on the patient’s head and secured around the neck. A compression setting of 15 mm Hg was initiated to secure the cap and provide maximum contact between the cooling layer of the cap and the patient’s scalp. The system was set to maximum cooling, with a goal of reaching a target intracranial temperature of 33°C and remaining at this temperature for 24 hours. During the first 2 hours, the medical staff monitored and recorded the patient’s intracranial and bladder temperatures, and ICP and MAP every 15 minutes (study Hours 0–2). After the first 2 hours, the patient’s temperatures and pressures were recorded hourly (study Hours 2–24). Using heating blankets, patients’ core body temperatures were kept above 36°C to avoid systemic hypothermia.

Every 12 hours, the medical staff removed the cooling cap to examine the patient’s head and neck for any adverse effects due to excessive cold on the skin. If any adverse signs were noted, they were recorded and the physician overseeing the patient determined whether to conclude the research on that patient. At the end of the initial 24 hour cooling period, patients were gradually rewarmed at a rate of 0.5°C every 3 hours for 24 hours (study Hours 25–48). The cooling cap was removed after 48 hours. Hourly throughout the rewarmin period, the medical staff monitored the temperatures and pressures. These readings continued to be monitored hourly for a 24-hour period following cap removal (study Hours 49–72). During the study, the medical staff recorded any difficulties with obtaining good skin contact or problems in obtaining adequate cooling, along with any unexpected events.

Patients allocated to the control group did not receive a cooling cap. Intracranial pressure monitors were placed per routine management. Baseline recordings of intracranial and bladder temperatures, and ICP and MAP were ob-
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tained just as in the patients in the treatment group. During the first 2 hours, the medical staff monitored and recorded these data every 15 minutes (study Hours 0–2). After the first 2 hours, the patient’s temperatures and pressures were recorded hourly for an additional 70 hours (study Hours 2–72).

Statistical Analysis

Baseline characteristics between treatment groups were compared using the Wilcoxon rank-sum test for continuous variables and the Fisher exact test for proportions.

Repeated-measures analyses for the primary end point intracranial temperature and the difference between the intracranial and bladder temperature during the helmet-on period were performed with a means model with SAS Proc Mixed software (version 9.1.3). A heterogeneous compound symmetry variance-covariance form in repeated measurements was assumed for each outcome, and robust estimates of the SEs of parameters \(^{10}\) were used to perform tests and construct 95% CIs.

The secondary end points were mortality and morbidity per GOS and modified FIM scores. Mortality rate was analyzed using the Fisher exact test as well as the log-rank test, and a Kaplan-Meier plot was provided to show the estimated cumulative mortality. The GOS scores, FIM scores, and mortality data were recorded at Days 1, 2, 3, 7, 14, 21, and 28, at 1 month and at hospital discharge, if this was prior to 1 month. The median maximum changes of GOS and FIM scores were summarized for both the intervention and control groups.

The analysis of the data was performed according to patients’ original treatment assignment (that is, an intention-to-treat analysis) and all patients were included in the analyses for as long as they contributed data. The dropout process was assumed to be missing at random. The level of significance was 0.05 for all the above analyses.

Results

Baseline Characteristics

A total of 4869 patients were admitted to Grady Memorial Hospital during the study period. Of these, 1578 were diagnosed with TBI and 274 with severe or critical TBI. Sixty-nine patients met eligibility for the study; 25 patients consented and were enrolled. These 25 patients were randomized so that 12 were placed in the treatment group and 13 were assigned to the control group. Among these 25 patients, complete data for analysis was available for 21 patients; 2 families withdrew patients from the study, the ICP monitor was dislodged in the third patient, and difficulties obtaining reliable systemic temperature data resulted in incomplete data acquisition in the fourth. Of the 21 patients with complete data for analysis, 11 were in the treatment group and 10 in the control group.

For all the study patients, the mean age (± SD) was 35.4 ± 17.3 years (range 18–90 years). Twenty-two patients were male (88%), 3 were female (12%). By race, 72% of the patients were Caucasian, 24% African-American, and 4% Hispanic. Most of the patients had suffered blunt injury (88.0%); 3 suffered penetrating injury (12.0%). There was no significant difference in demographic data between the 2 cohorts (Table 1).

The median time in the emergency department was 6.0 hours for all patients. Patients in the control group experienced a significantly longer time in the emergency department prior to transfer to the intensive care unit than did patients in the treatment group, with a median duration of 6.1 hours and 3.8 hours, respectively (p = 0.05; Table 2). The median length of hospital stay for all patients was 16 days.

Five patients in the study required craniotomy; 4 of the 5 were assigned to the treatment group, and 1 to the control group. The proportion of patients undergoing a craniotomy in the treatment group was 33.3% while that in the control group was 7.7%; this difference was not statistically significant (p = 0.2; Fisher exact test).

Only patients with GCS scores ≤ 8 were included in this study. Patients were randomized into 2 strata using the expanded head injury scale, \(^{39}\) those with critical GCS scores (3 and 4) versus those with severe GCS scores (5–8). In total, 18 patients were enrolled with a critical GCS score while 7 had a severe score. There was no significant difference in the GCS scores between the 2 groups prior to treatment (p = 1.0; Table 1).

Primary Outcome

Temperature Gradient. Intracranial and bladder temperatures were recorded for 72 hours in all study patients; every 15 minutes during the first 2 hours in each group and hourly for 70 hours thereafter. A goal of the research protocol was to achieve intracranial hypothermia in the treatment group, with minimal change in core body temp-

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* Values represent numbers of patients (%) unless otherwise indicated. There was no significant intergroup difference with respect to demographic data.
The target intracranial temperature for this group was 33°C, and the target for the systemic temperature was maintenance above 36°C.

Prior to initiating treatment, the estimated mean intracranial temperature for patients in the treatment group was 37.9°C (95% CI 37.4–38.5°C). After 12 hours of treatment with the cooling cap, the mean intracranial temperature had dropped to 36.8°C (95% CI 36.1–37.5°C). At the end of the 24-hour cap-on period, it was 36.9°C (95% CI 35.8–38.0°C). In contrast, the mean intracranial temperatures for patients in the control group at baseline, 12 hours, and 24 hours were 37.9°C (95% CI 37.6–38.2°C), 37.9°C (95% CI 37.5–38.3°C), and 38.1°C (95% CI 37.7–38.5°C), respectively. After study Hour 3, the mean intracranial temperature of the treatment group was significantly lower than that of the control group (p < 0.05) at all time points except for Hours 4 (p = 0.08) and 6 (p = 0.08). In 11 patients adequate data were available for assessing whether the target temperature was achieved; in only 2 of these 11 patients did we find that the target intracranial temperature of 33°C was achieved at any time during the cooling period (Fig. 2).

The longitudinal bladder temperature means trended lower in the treatment group than in the controls. The difference between bladder and intracranial temperatures was monitored; among the control patients, there was little difference between the 2 temperatures. Among patients with the cooling cap, the mean difference between intracranial and bladder temperature changed from −0.14°C prior to treatment to −0.36°C after 24 hours of cooling. Overall, across the cooling period, the mean difference between intracranial and bladder temperature was −0.67°C (p = 0.07) for the treatment group and 0.05°C (p = 0.67) for the controls. This showed a trend toward a greater temperature gradient in the treatment group than in the controls. However, the cooling cap neither established nor maintained a significant cranial-bladder temperature gradient (Fig. 3).

**Secondary Outcomes**

**Mortality.** Ten of the 25 patients died, establishing an overall mortality rate of 40.0%. In the treatment group, 6 (50.0%) of 12 died, while in the control group, 4 (30.8%) of 13 died (p = 0.43; Fisher exact test). Mean time to death was 15.2 days (median 8.5 days) in the treatment group versus a mean of 6.5 days (median 6.0 days) in the control group (p = 0.4). There was no significant intergroup difference in mortality rate or in time to death.

Kaplan-Meier cumulative mortality curves were generated for each patient group, and cumulative mortality

**FIG. 2.** Graph showing the mean intracranial temperatures in the 2 groups of patients. Initial mean intracranial temperature for both groups was 37.9°C. After 24 hours, the control group’s mean intracranial temperature was 38.1°C, while the mean intracranial temperature in the treatment group was 36.9°C. After study Hour 3, the mean intracranial temperature of the treatment group was significantly lower than the control group (p < 0.05) at all time points except for Hours 4 (p = 0.08) and 6 (p = 0.08). Error bars indicate 95% CIs.
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was similar for the 2 groups. The 28-day cumulative mortality among the treatment group was 41.7% (SE 14.2%) versus 30.8% (SE 12.8%) among the controls (Fig. 4). There was no significant difference in mortality rate in total study periods (p = 0.64; log-rank test).

Glasgow Outcome Scale. The GOS provides a 5-point assessment of patient condition, with scores ranging from 1 (death) to 5 (good recovery). The maximum change for all patients in 28 days and the medians of the maximum change for each group were calculated. The median length of hospital stay was 16 days.

From the first until the third study day, all 25 patients were in a minimally responsive state. The median maximum change in GOS during the 28-day study period was 0 for both study groups (p = 0.5). Therefore, there was no statistically significant intergroup difference in GOS-determined morbidity.

Functional Independence Measure. The FIM is a scale that measures patient disability after traumatic injury, while in an acute care facility. It consists of 3 components: feeding, locomotion, and motor. For each of the 3 components, a score of 1 means “dependent” (total help required), 2 represents “partially dependent,” 3 indicates “independent with device,” and 4 means “independent” (no device needed). The maximum change in FIM score for all patients in 28 days and the median of the maximum change in each group were calculated. The median change of all 3 FIM scores for both groups was 0. Again, there was no significant difference between the study and control populations.

Complications. Respiratory failure (18 patients [72.0%]), shock (7 patients [28%]), septicemia (6 patients [24%]), decubitus ulcer (2 patients [8.0%]) and cardiac arrest (2 patients [8.0%]) were the 5 most frequent complications. There was no significant difference in complications between the groups; probability values for individual complications ranged from 0.20 to 1.0 (Table 3).

Discussion

In the field of TBI, several clinical studies have sought to establish hypothermia as a treatment modality. Earlier studies suggesting benefit from hypothermia have been met with scrutiny, due to the lack of randomization and a heterogeneous subject population. The generalizability of the data were thus limited, and the efficacy of the procedure has remained in question. As a result, it has been difficult to fully assess the value of induced hypothermia and thus either endorse the procedure as beneficial or discard it as futile in the management of TBI.

Is hypothermia indeed “a good idea proved ineffective” as a 2001 editorial concluded?8 To date, the routine use of hypothermia cannot be recommended, but neither can the discontinuation of its study.

It is likely that hypothermia may be beneficial in some circumstances and among some patients, but detrimental in others. A recent clinical study reported significant improvements in neurological outcome and survival after TBI with hypothermia: In 2003, Zhi et al.43 analyzed 396 patients. In the study arm, hypothermia was induced within 24 hours and maintained for an average of 62.4
hours. The authors reported a mortality rate of 25.7% in hypothermic patients versus 36.4% in controls (p < 0.05), and rates of good neurological outcome of 38.8% in hypothermic patients versus 19.7% among controls (p < 0.05). In addition, ICP, blood lactate acid levels, and hyperglycemia were seen to decrease in the study group.

In the study of Zhi et al., hypothermia was maintained for a longer period of time than in most studies, and showed more benefit, calling into question the ideal duration of cooling and the time taken to achieve the target temperature. Some researchers have postulated that perhaps duration of hypothermic treatment should be linked to cerebral edema and thus continue for 72 hours after injury. Others have suggested that management should be tailored individually with cooling continued until ICP normalizes.

With regard to ideal time to achieve the target hypothermic temperature, the majority of the available data are limited to animal studies. Markgraf et al. demonstrated that neurological deficits in animals were decreased further if hypothermia was induced within 1 hour after trauma than if it was induced after 90 minutes or more. The difficulty remains in extrapolating this data to the clinical setting of trauma and the management of TBI.

Associated concerns limiting successful implementation of hypothermia include the rate of recovery and ideal target temperature. Animal studies have evaluated these subjects, yielding some information regarding rate of recovery, though these data have not been translated to clinical trials. One study showed that in rats who suffered TBI followed by hypoxia, the volume of contused brain was smaller if they were cooled and then rewarmed over 2 hours than if they were rewarmed over just 15 minutes.

The ideal target temperature for hypothermia remains to be determined as well. Moderate hypothermia of 32–34°C appears to be accepted by most authors. It is unknown, however, if the ideal temperature changes if discrete cerebral hypothermia is achieved in lieu of systemic hypothermia. The ideal gradient between core and intracranial temperature is also unknown.

These issues not only complicate implementation of clinical trials, but may also theoretically obscure any potential benefits of hypothermia. Key subjects of clinical concern remain hypothermia’s effect on ICP and mortality, in addition to the confounding adverse systemic effects.

Several studies have shown that hypothermia may lead to a decrease in ICP. Studies by Shiozaki et al. and Polderman et al. used hypothermia only for those patients whose intracranial hypertension was refractory to conventional treatment modalities, including barbiturate-induced coma. In the study of Shiozaki et al., mild hypothermia significantly reduced ICP and increased cerebral perfusion pressure, and significantly more hypothermic patients survived than did controls (50 vs 18%, p < 0.05). Likewise, in the study of Polderman et al., mortality rates were lower (62 vs 72%, p = 0.05) and the number of patients with good neurological outcome was higher in the group treated with moderate hypothermia than in the controls (15.7 vs 9.7%, p < 0.02). Perhaps hypothermia should be studied as a means of controlling ICP or cerebral perfusion pressure.

Our study was innovative in that it was a prospective randomized, controlled clinical trial at a Level I trauma center in which we attempted to selectively cool the brain without imposing systemic hypothermia and examined several outcome variables, including FIM and GOS scores and mortality. We attempted to strictly delineate the noted factors such as time to initiation of treatment, rate of cooling and rewarming, and ideal target temperature, in addition to minimizing systemic effects of cooling.

Our protocol was modeled after the study of this device by Wang et al. In that prior study, patients were monitored with the cooling cap in place for a range of 48–72 hours. It is not specifically stated for how long the patients were actively cooled, but in a graph in that article demonstrates a decrease in temperature after placement of the device followed by a sharp increase in temperature after Hour 24. The cooling helmets were removed in most patients after 48 hours. As in that prior study, we actively cooled all patients in the treatment group for 24 hours, then slowly rewarmed them over the next 24 hours. The cooling cap was removed at Hour 48, and the patients were monitored for a total of 72 hours.

In our study, in contrast to that of Wang et al., we did not shave patients’ heads prior to placement of the cooling helmet. Shaving the scalp may allow for superior skin-to-cap contact, better enabling the device to cool patients to the target temperature. However, one of the goals of this device, according to the paper Wang et al., which was written by 2 of the developers of the device, is to permit “ultra-early” application of cerebral hypothermia. It is not practical for paramedics to shave each patient’s entire scalp in the field after a trauma. As our study was intended to evaluate the effectiveness and applicability of this device in a clinical setting, we did not shave patients’ scalps in this study unless it was part of a specific treatment such as a craniotomy.

Another distinction between the 2 studies is that Wang et al. patients with TBI because the goal of our study was to determine the effectiveness of this cooling cap specifically for patients who had suffered trauma. Wang et al. did not delineate the number of stroke patients included in their study, but their combination of patient groups may have contributed to the divergent outcomes of the 2 studies.

Strengths of our study include the randomized prospective design and the intention-to-treat analysis. Only patients suffering TBI were included in the study to prevent conflation of data with patients who had intracranial injury due to other causes. The use of a single rater to determine GOS and FIM scores in all cases avoids the interrater variability that has been shown to decrease reliability. Attempts were also made to decrease bias in enrollment through the use of 1 research assistant to obtain all consents, and the treating team remained separate from and uninvolved in the consent process and the patient ratings, so as to further limit the potential for introduction of bias.

Unfortunately, a large percentage of the families of eligible patients (39%) were unwilling to allow us to enroll the patients in a clinical trial. A significant amount of time was dedicated to family education concerning the risks and benefits of the study and the rights of those enrolled; nonetheless, some families had negative feelings regarding clinical research. At an urban hospital with an

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indigent inner-city population, enrollment in clinical trials is historically quite low, with a percentage similar to the 40% patient return rate and compliance with medical directives seen at Grady Memorial Hospital’s neurosurgical clinics. Our study included 25 patients, a number that, while larger than the number in the previous study using this device, is still relatively small, so caution must be used in generalizing the outcome data.

The key to the uniqueness of the Discrete Cerebral Hypothermia System is its theoretical ability to effectively and selectively lower intracranial temperature. However, our primary study aim, the establishment of an intracranial-core temperature gradient was not achieved with utilization of this cooling system. The target intracranial temperature of 33°C was not maintained consistently with the cooling cap in the majority of patients. Although patients with the cap did have a lower intracranial temperature than did control patients, the average temperature was between 36 and 37°C. A mild decrease in bladder/core temperature developed within ~ 3 hours, creating a core-intracranial temperature difference of ~ 1°C. There was a trend toward a larger core-intracranial temperature gradient among the study patients than in the control population, but this did not reach statistical significance.

We found no statistically significant difference in our secondary study outcome variables of mortality and morbidity per GOS and modified FIM. There was a slightly higher rate of mortality in the patients treated with hypothermia than the controls, and a slightly longer time until death in the treated patients than the controls, but neither of these differences was statistically significant. The GOS and FIM scores were measured multiple times during the study and also showed no statistically significant variation between the 2 groups at any time point. In addition, we found no significant disparity in complications between the 2 groups.

This lack of statistically significant differences with the use of the Discrete Cerebral Hypothermia System may have been due to the failure to achieve true intracranial hypothermia in the majority of patients. In an intention-to-treat study of this modality, however, the inability to achieve the target temperature must be taken into account, as this can occur in a regular clinical setting as well.

The Discrete Cerebral Hypothermia System cooling cap demonstrated ease of use and application, as well as the benefit of portability, increasing the speed of its application; however, it was not effective at achieving true intracranial hypothermia. The limitations of the device in our study included regulation of the water temperature that circulated within and exited the device. In addition, we believe insufficient cap contact with the scalp might have been of concern. These limitations are significant and would pose a real logistical challenge if this device were to be used clinically. We believe future designs of the cap may need to include more contacts with the patient’s skin, more effective delivery of the coolant, or perhaps a coolant other than cold water.

Conclusions

When this modality is subjected to intention-to-treat analysis, no significant benefits emerge. Though a future version of this technology may be successful at realizing the potential benefits of selective cerebral hypothermia, as it currently stands, this technology is not beneficial.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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