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The EMCOOLs surface cooling system for fever control in neurocritical care patients: A pilot study

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A R T I C L E I N F O

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Brain injury

A B S T R A C T

Objectives: Fever occurs in up to 50% of critically-ill patients with acute neurological injury. Small temperature elevations have been correlated with increased morbidity and mortality in this patient population. We sought to evaluate a novel single-use surface cooling system for the treatment of fever in patients with acute brain injury.
Patients and Methods: We conducted a retrospective analysis of a prospective product evaluation using the EMCOOLS Flex.Pad™ system for acute fever (≥38.3 °C) in our 16-bed neuro-ICU. Four refrigerated pads (−18 °C) were applied to the chest, back, and anterior thighs. Core temperature (bladder) was continuously recorded over 4 h, and the highest Bedside Shivering Assessment Scale (BSAS) score was recorded hourly.
Results: Twelve subjects were included in the analysis. Mean age was 55 ± 9 years, 9 patients were men, and mean weight was 85 ± 12 kg. The most common primary diagnoses were subarachnoid (N = 5) and intracerebral (N = 4) hemorrhage. Application of the EMCOOLS system resulted in a linear 1.3 ± 0.6 °C drop (T_{0avg} = 38.9 ⁰C, T_{90avg} = 37.6 ⁰C, P = 0.0032) in mean temperature over 90 min, followed by a plateau with only one subject rebounding to > 38 °C within 4 h. Normothermia (< 38.0 ⁰C) was achieved in all but one patient (92%) in an average of 65 min. Comatose patients displayed a non-significantly higher degree of cooling at 90 min than did awake subjects (ΔT_{coma} = 1.74 °C vs ΔT_{awake} = 0.74 °C hr^{-1}, $P = 0.067$). There was no observed skin irritation upon removal of the device for any patients.
Conclusion: The EMCOOLs system is a well-tolerated, safe and effective short-term intervention for control of fever in neurological patients. Future studies are needed to compare efficacy of the EMCOOLs to other devices and interventions.

1. Introduction

Fever occurs in up to 50% of critically-ill neurological patients [1,2]. Small temperature elevations have been correlated with increased morbidity and mortality in this patient population [3–6]. Fever exacerbates ischemic and traumatic brain injury, worsens cerebral edema, and is associated with increased ICU length of stay [7–10]. Fever control is recommended in the management guidelines for ischemic stroke, intracerebral, and subarachnoid hemorrhage [11–14].

Common short-term interventions for fever include acetaminophen and other antipyretics, refrigerated saline, ice bags and water-circulating cooling blankets [15–17]. More refractory fevers are often treated with more expensive and elaborate feedback-control surface (Bard Arctic Sun®) and intravascular (Zoll Thermogard®) systems [18,19].

The EMCOOLS Flex.Pad™ cooling system (Emergency Medical Cooling Systems AG, Austria) consists of a set of pre-refrigerated, lightweight adhesive pads that can be applied to various parts of the

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torso or extremities. To date it has primarily been evaluated in patients with out-of-hospital cardiac arrest [20], and is approved for use in the United States, European Union, and Asia. This system might be a useful alternative to refrigerated fluids when rapid control of temperature is desired, prior to committing to a more expensive and elaborate feedback-controlled cooling system. In this retrospective study, we report the results of a prospective, open label, uncontrolled, single arm, cohort study evaluation of the EMCOOLS system for treatment of fever in a convenience sample of critically-ill neurological patients.

2. Patients and Methods

2.1. Study Population

Over a period of 6 months (June through December 2016) we conducted a hospital-approved safety and efficacy product evaluation of the EMCOOLS system for the treatment of refractory fever in our 16-bed neuro-ICU at Mount Sinai Hospital. A convenience sample of patients with sustained fever (≥38.3 °C) during weekday daytime hours after treatment with acetaminophen and in some cases water-circulating cooling blankets were deemed eligible. Patients with known skin conditions were not considered for this evaluation. As a nursing intervention, the reason for placement of the pads was explained to the patient or their legally-authorized representative and verbal consent was obtained. This pilot study was IRB approved as a retrospective analysis of a prospectively-conducted product evaluation. As such a clinicaltrials.gov identification number was not filed, and as a purely observational retrospective study, the requirement for written informed consent was waived. This paper conforms to STROBE checklist criteria (www.strobe-statement.org) for reports of cohort studies.

2.2. Study Intervention

The EMCOOLS Flex.Pad™ system is composed of multiple flexible pads filled with HypoCarbon™, which allows for consistent heat distribution over the treatment period. The adhesive underside results in tight skin contact, allowing for efficient energy transfer. EMCOOLS pads are lightweight, mobile, and are compatible with X-ray, CT and MRI.-, and are available for immediate use. The treatment bundle that we used included a minimum of 4 pads (Fig. 1). A single pad was placed on the anterior abdomen and on each thigh, with the fourth pad separated in thirds (along serrated "easy tear" lines) and placed under each axilla and just under the neck. Two additional pads were placed on the back on patients exceeding 90 kg. The pads are checked by direct palpation, and can be replaced up to every 1 h as needed when they are no longer cold to touch. If the temperature was not controlled after 4 h, the patient was switched to another system for cooling.

2.3. Shivering Intervention

Patients were treated for shivering using a standardized institutional protocol [21]. This anti-shivering protocol includes standing acetaminophen (for T > 38.3 °C), buspirone (30 mg every 8 h), magnesium infusion (target level 3–4 mg/dl), and skin counter-warming, with subsequent stepwise interventions of (1) dexmedetomidine, (2) fentanyl or meperidine, and (3) propofol.

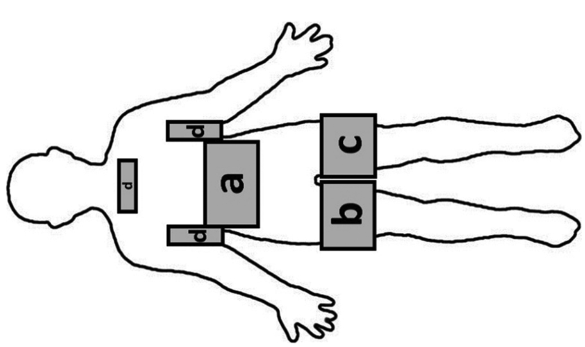

Fig. 1. Figure showing the areas where the EMCOOLs pads were placed.

2.4. Data Collection

Data was recorded for six hours after the EMCOOLS pads were applied. Core body temperature was recorded continuously in all patients with temperature-sensing Foley catheters (400 Series, Bard Medical) and stored in a clinical data acquisition system (BedmasterEx™, Excel Medical) along with standard vital signs. Shivering was assessed hourly by the bedside nurse with the Bedside Shivering Assessment Scale (BSAS), which is scaled as 0 = no shivering, 1 = shivering confined to jaw and neck, 2 = visible or palpable shivering of upper extremities, and 3 = shivering of all four extremities [22]. Baseline demographic, clinical and laboratory data for all subjects were collected through chart review.

2.5. Primary Outcome Measures

The primary outcome measure was the rate of cooling of the device in patients upon receiving this therapy. In anticipation that the rate of cooling might be multiphasic, we planned to calculate the initial rate of cooling during the initial period (in 30 min intervals) with the steepest rate of cooling. Secondary outcome measures included (1) percentage of patients attaining normothermia (T < 38.0 °C), (2) average time to attain normothermia; and (3) a comparison of the rate of cooling in patients that were awake versus in a comatose (Glasgow Coma Scale score ≤8).

2.6. Safety Outcome Measures

Skin damage upon removal of the device was evaluated. Shivering was considered an adverse event when the BSAS reached a score of 2 or 3 (gross shivering of the arms or legs).

2.7. Statistical Analysis

Temperature data was initially screened and artefactual or out-of-range values (> 45 °C or < 26 °C, or sudden fluctuations exceeding 2 °C) were removed. Continuous temperature data was then averaged over 5 min intervals and analyzed using the statistical software package R (R-project.org). The primary outcome (rate of cooling) was analyzed by calculating the average change in temperature from baseline over successive 5-minute intervals. A paired sample *t*-test was used to determine the statistical significance of the mean change in temperature during the period of highest rate (°C/hr) of cooling. All available temperature data obtained via foley thermistor during a 1 h run-in period and the 4–hour active cooling period were analyzed to minimize bias. We calculated that with a sample size of 12 patients, assuming $\alpha = 0.05$, $S(\Delta) = 0.6$, and $T = 2.201$, we would have 80% power $(1 - \beta)$ to detect a change in mean temperature of 0.533 °C or more. The Mann-Whitney U test was used to determine whether the difference in cooling between the awake vs coma group was statistically significant.

3. Results

A total of 12 patients had temperature continuously recorded by a Foley thermistor and data on EMCOOLs application during the trial evaluation period. Stroke was the prevailing diagnosis in these 12 patients, with subarachnoid hemorrhage as the most common subtype (Table 1). The mean duration of fever exceeding 38.0 °C prior to the product evaluation was 7 h. Nine patients (75%) were mechanically ventilated, all patients were given acetaminophen on the day of study

Table 1
Baseline Subject Characteristics.

Age (yrs)	55 ± 9
Female	3 (25)
Weight (kg)	85.4 ± 11.8
Primary Diagnosis	
Subarachnoid Hemorrhage	5 (42)
Intracerebral Hemorrhage	4 (33)
Subdural Hematoma	1 (8)
Altered Mental Status	1 (8)
Benign Neoplasm	1 (8)
Coma (GCS score ≤8)	7 (58)
Antipyretic Administered	12 (100)
Intravenous sedation	7 (58)
Ventilated	9 (75)

Data are n (%) or mean ± SD
GCS, Glasgow Coma Scale.

intervention, and seven (58%) were on intravenous sedation (propofol, fentanyl, midazolam or dexmeditomidine, alone or in various combinations).

Subjects showed a statistically significant (P = 0.0032) linear 1.3 ± 0.6 °C drop (T_{0avg} = 38.9 °C, T_{90avg} = 37.6 °C) in temperature over 90 min, representing a 0.9 ± 0.6 °C hr^{-1} rate of cooling, followed by a plateau (Fig. 2), with one subject rebounding within 4 h (Fig. 3). Mean temperature during the 60 min period prior to EMCOOLs placement did not vary substantially from T_{0avg} = 38.9 °C (Fig. 2). Normothermia (< 38.0 °C) was achieved in all but one patient (92%; Fig. 2, series 5) in an average of 65 min. Unconscious patients displayed a higher rate of cooling at T_{90} as compared to conscious subjects (ΔT_{coma} = 1.70 °C hr^{-1} vs ΔT_{awake} = 0.74 °C hr^{-1}, P = 0.067), but this difference did not reach statistical significance. No patients experienced a change in GCS score during the 4 -h treatment period. Seven of 12 patients required retreatment with new EMCOOLs pads during the treatment period due to warming of the original pads. One patient was switched to an alternate method of cooling due to treatment failure. Two of 12 patients (17%) developed BSAS level 2 or 3 shivering despite protocol-directed measures to counteract this. There was no observed skin injury or irritation upon removal of the device for any patients.

4. Discussion

While neurocritical care units currently have many cooling therapies to choose from, each therapy has its own set of benefits and limitations. Considerations that apply to various cooling modalities include ease of use, invasiveness, rate of cooling, ability to maintain a target temperature, tolerability, mobility, and cost. The EMCOOLS surface-cooling system appears to be easy-to-use, mobile, fast and safe, and has been used successfully in the pre-hospital phase of sudden cardiac arrest (SCA).

In this study, we evaluated the EMCOOLS system for the treatment of refractory fever in 12 critically-ill patients with various causes of brain injury. The patient population was diverse, but the majority were comatose, sedated, and mechanically-ventilated men with subarachnoid or intracerebral hemorrhage. Subjects were febrile for an average of approximately 7 h prior to treatment, and all had received antipyretic medication.

Mean temperature at the time of EMCOOLS application was 38.9 °C. Ninety minutes later mean temperature had dropped 1.3 °C, to 37.6 °C. The primary outcome was the rate of cooling, which was calculated by calculating the mean ΔT (0.9 °C hr^{-1}) during the period of active temperature reduction. Viewed another way, the fever broke in 11 of 12 subjects (92%), with a mean time to normothermia (< 38.0 °C) of 65 min. Only one subject experienced a rebound fever within 4 h of ending the therapy.

The rate of cooling that we observed is somewhat less than that reported in SCA patients in whom the goal was hypothermia. The fastest rate of cooling with the EMCOOLs system has been reported in comatose SCA patients, presumably because they are poikilothermic as a consequence of their neurological injury. In a study of 15 SCA patients, mean esophageal temperature fell 3.6 °C (from 36.6 to 33.0 °C) within 70 min (range 55–106 min), and the treatment was well-tolerated [20]. An even greater rate of temperature reduction (4.0 °C per hour) has been reported in a population largely made up of cardiac arrest patients using refrigerated (4 °C) saline (mean 2.3 L) in combination with water-circulating cooling blankets [23].

In our study subjects that were in a coma displayed higher rates of cooling than awake subjects (1.74 °C vs 0.74 °C per hour, $P = 0.067$),

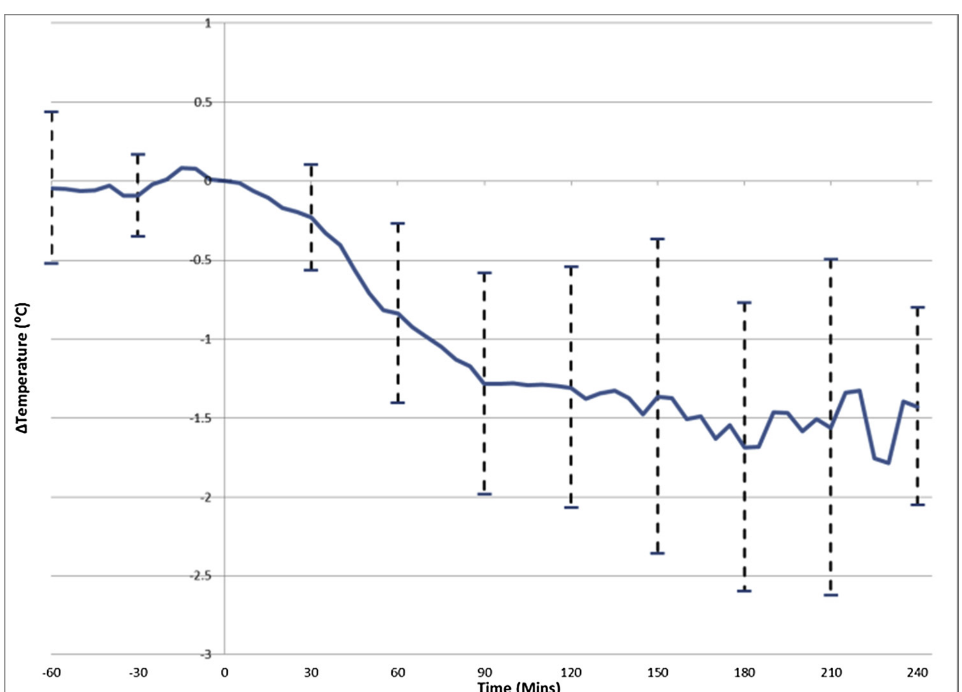

Fig. 2. Graph showing the average change in temperature over the treatment period. Error bars are standard deviation.

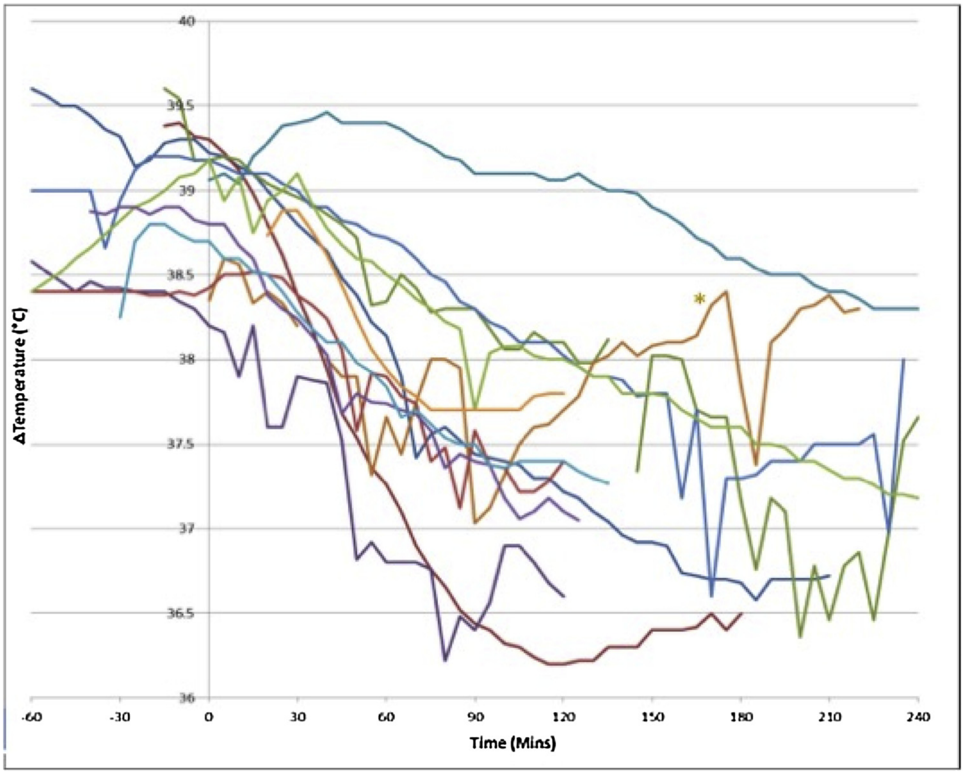

Fig. 3. Graph showing continuously-recorded temperature in individual subjects over the treatment period. The asterisk shows a single patient who experienced significant rebound fever during the 4 -h monitoring period.

which approached statistical significance. These results suggest that higher level of consciousness is associated with a more robust shivering response, and hence a smaller drop in temperature. Whole-body shivering (BSAS level 3 or 4) was reported in 2 cases, both of whom were in the awake group.

Similarly, more modest rates of cooling with the EMCOOLs system have been reported in awake patients and healthy volunteers. In a pilot feasibility study of ST segment acute coronary syndrome patients, pre-hospital cooling with EMCOOLs followed by 1 L of refrigerated saline on arrival to the catheterization lab dropped mean temperature 2.0 °C, from 36.4 to 34.4 °C, over an average period of 100 min [25]. The temperature reduction attributable to the EMCOOLs system alone was not reported. In a study of 16 healthy male volunteers treated with meperidine, buspirone and magnesium, the cooling rate was 1.1 °C per hour and the median duration of temperature drop was approximately 90 min, similar to the rate and duration of cooling observed in our study [25]. The EMCOOLs system has also reported to successfully treat a case of malignant hyperthermia in association with dantrolene and 1 L of ice water via nasogastric tube [26].

Due to the strong adhesion of the individual flex pads, there was a concern for skin damage upon removal, and patients that had any skin conditions were not considered for this therapy. It was observed that upon application, while the pads were cold, the adhesion was strongest, and once the pads warmed up they became easy to remove. No adverse skin reactions were reported in any subjects.

This study has several important limitations. The study population was relatively small. As a pilot evaluation focused on feasibility and safety there was no control group to compare our results with. Hence, the extent to which spontaneous "breaking" of fever may have contributed to the observed temperature drop is unknown. It is certainly possible with such a small study sample that a larger experience might reveal thermal skin injury with the EMCOOLs system, although the safety track record in other series has been good [20,24–26]. Similarly, a larger experience might reveal treatment failure or more rebound fever events than we observed. We did not record certain clinical details such as the timing of onset of fever or initiation of the study intervention, the presence or absence of concurrent infection, or details regarding the dosing and observed effects of specific antipyretic or analog-sedative medications. Finally, the majority of patients in this pilot study had intracranial hemorrhage, which may limit the generalizability of our findings.

In summary, we found that the EMCOOLs Flex.Pad™ system is effective and well-tolerated for control of fever in brain injured patients, particularly when comatose. This system might be a useful alternative to refrigerated fluids when rapid temperature control is needed and fluid overload is of concern, and in some cases may obviate the need to escalate to more expensive and sustained cooling systems. Future studies are needed to directly compare the efficacy of the EMCOOLs system to other treatment options for the management of fever.

Author Details

S.A. Griffiths: Data collection, Data Analysis, first draft of manuscript.

J. Ahmad: Data collection, editing of manuscript.

C.L. Francoeur: Project development, editing of manuscript.

E. Gordon: Data collection, editing of manuscript.

N.S. Dangayach: Data collection, editing of manuscript.

D. Wheelwright: Project and data management, editing of manuscript.

A. Ramineni: Data collection, editing of manuscript.

S.A. Mayer: Project conception, data analysis, final draft of manuscript.

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