COOL-ARREST: Results from a Pilot Multicenter, Prospective, Single-Arm Observational Trial to Assess Intravascular Temperature Management in the Treatment of Cardiac Arrest

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Targeted temperature management (TTM) is recommended postcardiac arrest. The cooling method with the highest safety and efficacy is unknown. The COOL-ARREST pilot trial aimed to evaluate the safety and efficacy of the most contemporary ZOLL Thermogard XP Intravascular Temperature Management (IVTM) system for providing mild TTM postcardiac arrest. This multicenter, prospective, single-arm, observational pilot trial enrolled patients at eight U.S. hospitals between July 28, 2014, and July 24, 2015. Adult (≥ 18 years old), out-of-hospital cardiac arrest subjects of presumed cardiac etiology who achieved return of spontaneous circulation (ROSC) were considered for inclusion. Patients were excluded if (1) awake or consistently following commands after ROSC, (2) significant prearrest neurological dysfunction, (3) terminal illness or advanced directives precluding aggressive care, and (4) severe hemodynamic instability or shock. Patient temperature was maintained at $33.0^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ for a total of 24 hours followed by controlled rewarming ($0.1\text{--}0.2^{\circ}\text{C/h}$). Logistic regressions were used to assess association of good functional outcome (modified Rankin Scale ≤ 3) measured at the time of hospital discharge with shockable rhythm (yes/no), age, gender, race/ethnicity, lay-rescuer cardiopulmonary resuscitation, time to basic life support (minutes), time to ROSC (minutes), lactate (mg/dL), and pH on admission. The ZOLL IVTM system was effective at inducing TTM (median time to target temperature from initiation, 89 minutes [interquartile range 42–155]). Adverse events most often included electrolyte abnormalities and dysrhythmias. Of patients surviving to hospital discharge, 16/20 patients had a good functional outcome. A total of 18 patients survived through 90-day follow-up, at which time 94% (17/18) of patients had good functional outcome. The COOL-ARREST pilot trial demonstrates high safety and efficacy of the ZOLL Thermogard XP IVTM system in the application of mild TTM postcardiac arrest. This observational trial also revealed noteworthy variability in the management of postcardiac arrest patients, particularly with the use of early withdrawal of life-sustaining therapy.

Keywords: targeted temperature management, induced hypothermia, intravascular device, safety, efficacy

Introduction

TARGETED TEMPERATURE MANAGEMENT (TTM) at a consistent temperature is recommended for comatose survivors of cardiac arrest (Callaway *et al.*, 2015). Although

controversy exists regarding the optimum target temperature (Bernard *et al.*, 2002; Hypothermia after Cardiac Arrest Study [HACA], 2002; Nielsen *et al.*, 2013), avoidance of both hyperthermia and fluctuations in temperature for at least 24 hours after return of spontaneous circulation (ROSC) is

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recommended as part of comprehensive postcardiac arrest care to improve functional outcome.

There is variation in TTM practice due to limited evidence regarding how to best induce and maintain a given target temperature, and control rewarming (Camp-Rogers *et al.*, 2013). Early clinical practices utilized ice packs, cooling blankets, and/or water blankets to induce and maintain TTM. These methods may allow unintentional overcooling and wide fluctuations in temperature (Merchant *et al.*, 2006). Ambient measures, such as room or ventilator temperature, and patient factors, such as basal metabolic rate, may interfere with tight temperature control, even if using a closed-loop system (Vanlandingham *et al.*, 2015).

There are several feedback-loop devices commercially available for temperature management, including warming or cooling from environmental exposures. The use of these devices, whether surface or intravascular, has become common for TTM postcardiac arrest. Most studies include mixed methods of TTM provision, including varied device generations. The question of which type of cooling method demonstrates the highest safety and efficacy remains unanswered. The ZOLL Thermogard XP machine provides up to 170 W of power compared with previous machines with maximum 120 W. Thus, the aim of the COOL-ARREST pilot trial was to evaluate the safety and efficacy of the ZOLL Thermogard XP Intravascular Temperature Management (IVTM) system to induce, maintain, and reverse mild TTM postcardiac arrest.

Materials and Methods

This multicenter, prospective, single-arm, observational pilot trial enrolled patients at eight U.S. hospitals between July 28, 2014, and July 24, 2015. Adult (at least 18 years old), out-of-hospital cardiac arrest (OHCA) subjects of presumed cardiac etiology who achieved ROSC were considered for inclusion if informed consent was also provided by the patient's legally authorized representative within 12 hours of ROSC. There was no randomization or stratification scheme. This investigation was approved by each of the participating hospitals' institutional review boards. The study was overseen by an independent data safety monitoring board.

Patients were excluded from this investigation if (1) awake or consistently following commands after ROSC, (2) significant prearrest neurological dysfunction, (3) terminal illness or advanced directives precluding aggressive care, and (4) severe hemodynamic instability or shock, despite aggressive resuscitative efforts. Instability or shock was defined as ongoing hypotension despite adequate fluid resuscitation and two vasopressors. All patients followed their institution-specific TTM protocol, utilizing the ZOLL Thermogard XP IVTM closed-loop cooling system (ZOLL, San Jose, CA) and strict hemodynamic monitoring in the intensive care unit.

TTM protocol

Temperature was measured preferentially by the esophagus but may have been initially by the bladder or rectum until an esophageal temperature probe was placed. Patient temperature was maintained at $33.0^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ for a total of 24 hours followed by controlled rewarming ($0.1\text{--}0.2^{\circ}\text{C/h}$). Normothermia was maintained thereafter. Metabolic, ventilatory, and hemodynamic parameters were managed according to goal-directed targets for the first 72 hours.

Data collection and outcomes

Data were collected from hospital and emergency medical service (EMS) records, including baseline demographic characteristics, EMS provision of prehospital cooling, and all relevant time intervals from time of arrest or 911 call to hospital discharge or death, according to Utstein recommendations (Cummins *et al.*, 1991). During the hospital stay, patient vital signs, laboratory results, and medications were recorded at strict intervals during TTM through hospital day 7, discharge, or death. Modified Rankin Scale (mRS) scores (Uyttenboogaart *et al.*, 2005) were recorded at hospital discharge and at 90-day follow-up as secondary outcome measures. All patients were included in an intention-to-treat analysis.

The primary outcome was the proportion of subjects in which the IVTM system could therapeutically cool subjects to a target temperature of $33^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ (as measured by the temperature probe) and maintain it for 24 hours. Secondary objectives included patient safety (observed adverse events [AEs] up to 90 days), retention (ability to enroll and complete study protocol and time to complete enrollment), and functional outcome (mRS). All AEs that occurred through completion of the final follow-up visit, whether observed by the investigator or by the subject, and if thought to be device-related, were reported in detail on the appropriate case report form and followed to resolution or the end of study participation. Potential major AEs included catheter-related injury (arteriovenous fistula, bleeding related to the catheter requiring ≥ 1 U of blood, clinically significant hematoma at catheter site requiring intervention, deep vein thrombosis unilateral to the catheter in place, known embolism [air, thrombus, and catheter fragment], nerve injury, pseudoaneurysm, vascular perforation, or dissection) and infection, either local or systemic (pneumonia, sepsis, meningitis, visceral organ).

Follow-up period and functional outcome

Subjects discharged from the hospital underwent functional outcome assessment (mRS) and evaluation for AEs. Subjects were scheduled for a 90-day postenrollment follow-up visit, preferably in-person but possibly by telephone, to include repeat functional outcome and AE assessment. An individual's legal representative or medical caregiver was interviewed in place of the subject if he or she was unable to participate.

Sample size and statistical analysis

The sample size ($n=50$) for this pilot study was determined based on primary endpoint considerations, assuming a performance rate of 85% or more. The primary analysis will be based on intention to treat.

Continuous variables, including age (years), initial temperature ($^{\circ}\text{C}$), and all time intervals (minutes or hours), are reported as means and standard deviations (SDs) or medians with interquartile ranges (IQRs); categorical variables, including functional outcome at hospital discharge and 90 days, are reported as counts and percentages. All temperature data are presented as percent of time that the patient's actual temperature, as measured by the esophageal temperature probe, was within $\pm 0.3^{\circ}\text{C}$ of the set temperature. The D'Agostino and Pearson test was to assess the normality of data.

Univariable and multivariable logistic regression was used to assess association of good functional outcome ($\text{mRS} \leq 3$)

measured at the time of hospital discharge with shockable rhythm (yes/no), age, gender, race/ethnicity (Caucasian vs. other), lay-rescuer cardiopulmonary resuscitation (yes/no), time to basic life support (BLS) (minutes), time to ROSC (minutes), lactate (mg/dL), and pH on admission. Subjects were evaluated for potential poor prognosis utilizing the Cardiac Arrest Hospital Prognosis (CAHP) score (Maupain *et al.*, 2016). Those with early withdrawal of life-sustaining therapy (WLST) were compared with those with WLST 24–72 hours and >72 hours utilizing medians and IQR of CAHP. Alpha of <0.05 was considered statistically significant. Data were analyzed with SAS (SAS Institute, NC) and Prism (Graph-Pad Software, CA).

Results

Our consort diagram is presented in Figure 1. Patient demographics, arrest characteristics, and treatment variables are summarized in Tables 1 and 2. A majority of subjects had OHCA witnessed by lay-rescuers (82%) and occurred in a home (56%) or public place (20%). Only 44% received lay-rescuer CPR before EMS arrival.

All ($n = 50$) patients were successfully cooled to the target temperature. The ZOLL IVTM system was effective at inducing TTM (median time to target temperature from initiation, 89 minutes [IQR 42–155]). Most patients were cooled for less than 24 hours (median 22.7 hours, IQR 20.0–23.6). Rewarming occurred over a median of 13.5 hours (IQR 9.2–14.8) and normothermia was maintained for a median of 7.4 hours (IQR 4.9–10.2).

A total of 47 patients completed the hypothermia phase; 3 patients were excluded due to death before this stage. Subjects remained within $\pm 0.3^{\circ}\text{C}$ of set temperature, median 98% of the time (IQR 94–100%). A total of 46 patients completed the rewarming phase, due to 1 death before completing this stage. Subjects remained within $\pm 0.3^{\circ}\text{C}$ of set temperature, median 99% of the time (IQR 86–100%). Finally, a total of 40 subjects completed the normothermia maintenance phase; 6 patients were excluded due to death before completing this stage.

Subjects remained within $\pm 0.3^{\circ}\text{C}$ of set temperature median 100% of the time. Figure 2 depicts median temperature data for the TTM treatment duration for the study cohort, demonstrating efficient achievement of target temperature and tight temperature control throughout the TTM period.

Regarding secondary outcomes, the safety profile was reasonable with no increase in AEs, while the IVTM was in place compared to any time during the study period. AEs are summarized in Supplementary Table S1. Total time from first enrollment through last patient follow-up was 364 days. Of patients surviving to hospital discharge, 16/20 patients had a good functional outcome. A total of 18 patients survived through 90-day follow-up. At the 90-day follow-up, 94% (17/18) of patients had good functional outcome (Table 3).

Association of good functional outcome with baseline and treatment characteristics

Initial shockable rhythm is highly significantly associated with good functional outcome ($p < 0.001$). Of the 50 subjects, there were 25 in the “shockable” category and 25 in the “nonshockable” category. Of the 25 nonshockable subjects, only 1/25 (4%) had a good functional outcome at hospital discharge. In comparison, 15/25 (60%) shockable subjects had a good outcome at discharge.

Regarding the other variables considered, lactate ($p = 0.049$) and pH ($p = 0.023$) were statistically significantly related to functional outcome at hospital discharge; time to BLS ($p = 0.052$) and time to ROSC ($p = 0.063$) were marginally related to functional outcome at hospital discharge; and there were no statistically significant associations observed with age, gender, race/ethnicity, lay-rescuer CPR, or automated external defibrillator. In multivariable modeling, after adjusting for the effect of initial shockable rhythm, no other covariates were significantly associated with the outcome variable. Supplementary Table S2 shows the association of good functional outcome at hospital discharge with baseline and treatment characteristics.

TABLE 1. PATIENT BASELINE CHARACTERISTICS

Characteristic	Summary
Age, mean (SD)	58.1 (15.0)
Gender	
Male, <i>n</i> (%)	27 (54)
Female, <i>n</i> (%)	23 (46)
Race	
Black, <i>n</i> (%)	14 (28)
Caucasian, <i>n</i> (%)	35 (70)
Other, <i>n</i> (%)	1 (2)
Witnessed by lay-rescuer (<i>n</i> = 50)	
Yes, <i>n</i> (%)	41 (82)
No, <i>n</i> (%)	9 (18)
Location of arrest (<i>n</i> = 50)	
Home, <i>n</i> (%)	28 (56)
Nursing care facility, <i>n</i> (%)	2 (4)
Public place, <i>n</i> (%)	20 (40)
Treated before EMS arrival (<i>n</i> = 50)	
Yes, <i>n</i> (%)	23 (46)
No, <i>n</i> (%)	27 (54)
Before EMS arrival (<i>n</i> = 50)	
Lay-rescuer ventilation, <i>n</i> (%)	20 (40)
Lay-rescuer chest compression, <i>n</i> (%)	22 (44)
Lay-rescuer defibrillation (AED), <i>n</i> (%)	8 (16)
Other (intubation, medication, BLS), <i>n</i> (%)	3 (6)
ROSC before EMS arrival (<i>n</i> = 50)	
Yes, <i>n</i> (%)	2 (4)
No, <i>n</i> (%)	48 (96)
EMS treatment before hospital (<i>n</i> = 50)	
CPR, <i>n</i> (%)	47 (94)
Defibrillation, <i>n</i> (%)	27 (55)
Medication, <i>n</i> (%)	36 (72)
Initial rhythm (<i>n</i> = 50)	
Ventricular fibrillation, <i>n</i> (%)	15 (30)
Ventricular tachycardia, <i>n</i> (%)	1 (2)
AED shock advised, <i>n</i> (%)	7 (14)
Pulseless electrical activity, <i>n</i> (%)	15 (30)
Asystole, <i>n</i> (%)	8 (16)
AED no shock advised, <i>n</i> (%)	4 (8)
ROSC after EMS arrival; before arrival to ED (<i>n</i> = 48)	
Yes, <i>n</i> (%)	30 (63)
No, <i>n</i> (%)	18 (37)
Admission pH (<i>n</i> = 49)	Mean 7.2 (range 6.80–7.46)
Admission lactate, mg/dL (<i>n</i> = 29)	Mean 7.3 (range 0.80–20.60)

AED, automated external defibrillator; BLS, basic life support; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical service; ROSC, return of spontaneous circulation; SD, standard deviation.

Withdrawal of life-sustaining treatment

Overall, 32/50 patients died, most often related to brain death (18/32). Other causes included cardiac (6/32), respiratory (6/32), and multiorgan failure (2/32). Table 4 summarizes the characteristics of patients who died early (<72 hours) versus late (>72 hours) in the hospital. Patients who died <72 hours

TABLE 2. TREATMENT INTERVALS (MEDIAN Q1–Q3 [MINUTES])

Arrest to catheter insertion (<i>n</i> = 47) (minutes)	152 (108–178)
Arrest to initiation of cooling (<i>n</i> = 49) (minutes)	213 (149–273)
Arrest to target temperature (<i>n</i> = 50) (minutes)	286 (229–390)
Hospital arrival to catheter insertion (<i>n</i> = 47) (minutes)	92 (74–134)
Hospital length of stay (discharge, <i>n</i> = 20)	215 (159–388)
Hospital length of stay (death, <i>n</i> = 29) ^a	99 (60–154)
911 call to EMS on scene time (<i>n</i> = 48) (minutes)	5 (3–8)

^aFor within-hospital deaths.

from arrest tended to be a result of WLST due to “poor prognosis” secondary to encephalopathy, repeat cardiac arrest, and multiorgan failure. Those who died early also tended to be older. In both groups, >90% had WLST due to “poor prognosis” assessment by clinical providers. Patients with WLST <48 hours from arrest had a higher risk of poor outcome with a CAHP score of 0.96, compared with patients with WLST 48–72 hours (score 0.94) and those with WLST >72 hours (score 0.93) (Supplementary Table S3). Although the sample size is small, the CAHP score, which includes age, arrest setting, initial rhythm, time till ROSC, initial pH, and epinephrine dose, does not appear to be a discriminator for WLST.

Discussion

The COOL-ARREST pilot trial demonstrates effective postcardiac arrest TTM induction, maintenance, and re-warming using the ZOLL Thermogard XP IVTM device. Patient temperatures were tightly controlled to a target temperature of 33°C ± 0.3°C using this closed-loop intravascular system in all 50 patients enrolled. Overall, 36% (18/50) survived to 90 days with few AEs observed throughout the study period. There was no increase in AEs while the IVTM system was in place. These data provide evidence to support the safety of the ZOLL IVTM device in the application of mild TTM to postcardiac arrest patients.

Our results are similar to the largest modern study evaluating TTM in postcardiac arrest patients (Nielsen *et al.*, 2013). Target temperature was achieved quickly once the IVTM device was in place and turned on, although delays to intravascular device placement and system start-up did occur (Table 2). Furthermore, tight temperature maintenance and minimal deviation from target in our study (Fig. 2) are consistent with findings from patients treated with an intravascular device during the TTM trial (Glover *et al.*, 2016). While on secondary analysis Glover *et al.* found no statistical difference between surface and intravascular device time to target temperature, they did find higher rates of temperature deviations with the surface devices. Similar to most studies evaluating the safety of TTM, AE rates were low in COOL-ARREST. Most often AEs included electrolyte abnormalities and dysrhythmias, similar to reports from other TTM studies (Bernard *et al.*, 2002; HACA, 2002; Nielsen *et al.*, 2013).

COOL-ARREST patients achieved target temperature more quickly than in the TTM trial (median 89 minutes [IQR

FIG. 2. Median patient temperature during study protocol.

42–155] vs. 210 minutes [IQR 180]) (data from Glover *et al.*, 2016) and there were fewer deviations from set temperature. Patient factors (basal metabolic rate and body mass index), ambient room temperatures, or medication effects may have contributed to these differences. In addition, all patients in COOL-ARREST were treated with the ZOLL Thermogard XP device, whereas patients in previous studies, such as the TTM trial, were treated with a mixture of both surface and IVTM devices or a mixture of Thermogard XP with earlier IVTM products with lower effective cooling power. While preclinical studies demonstrate benefits from early TTM initiation and fast rates of TTM induction (Abella *et al.*, 2004; Kim *et al.*, 2016), results from observational clinical studies are controversial (Haugk *et al.*, 2011; Sendelbach *et al.*, 2012; Perman *et al.*, 2015). Patients with more severe hypoxic brain injury may not resist being exposed to TTM and thus achieve target temperature more easily. Alternatively, quicker TTM induction can lead to a shorter overall TTM dose, which may be associated with outcome in certain postcardiac arrest phenotypes (Sawyer *et al.*, 2014; Kirkegaard *et al.*, 2017). Future studies with appropriate power are needed to assess the relationship between TTM process intervals and functional outcome.

Although our small sample size makes it problematic to draw any other conclusions, we observed a very large and statistically significant association between presenting with a shockable rhythm and outcome. Unexpectedly, we also observed a large rate of WLST before 72 hours from hospital admission (Table 4). Postcardiac arrest care guidelines have evolved to encourage withholding WLST for at least 72 hours after rewarming from TTM (Callaway *et al.*, 2015), given several observational studies demonstrating delayed awakening in patients treated with TTM (Grossestreuer *et al.*, 2013; Mulder *et al.*, 2014; Elmer *et al.*, 2016; Zanyk-McLean *et al.*, 2017). Moreover, the influence of reperfusion injury,

end-organ dysfunction, and drug metabolism/elimination on awakening remains uncertain (Anderson *et al.*, 2016). In our pilot, observational efficacy trial, there was no mandated protocol for neuro-prognostication, and thus, our observation regarding WLST reveals significant pragmatic variation in site and physician/treating team care, as well as room for hospital system improvements. Based on the CAHP scoring, classic prognosticators (i.e., age, nonshockable rhythm, time to BLS, time to ROSC, arrest location) for poor functional outcome do not appear to have influenced WLST decisions in this study.

Limitations

The primary aim for this pilot study was to evaluate the efficacy of the ZOLL Thermogard XP IVTM device for inducing and maintaining TTM in postcardiac arrest patients,

TABLE 4. PATIENTS DYING IN-HOSPITAL: EARLY (<72 HOURS) VERSUS LATE (≥72 HOURS) AFTER ADMISSION

	Death <72 hours (n = 10)	Death >72 hours (n = 19)
Mean age (SD)	66.8 (13.3)	58.9 (12.6)
Witnessed arrest, n (%)	8 (80)	16 (84)
Initial rhythm		
Shockable, n (%)	3 (30)	4 (21)
Nonshockable, n (%)	7 (70)	15 (79)
Mean time (minutes)	35.7 (24.9)	29.3 (14.0)
arrest to ROSC (SD)		
Cause of death, n (%)		
Encephalopathy	6 (60.0)	14 (73.7)
Cardiac cause	2 (20.0)	3 (15.8)
Respiratory cause	0 (0.0)	2 (10.5)
Multiorgan failure	2 (20.0)	0 (0.0)
Poor prognosis as reason for WLST, n (%)	9 (90)	18 (94.7)
Futility, instability, rearrest, n (%)	1 (10)	1 (5.3)

Three patients excluded from table for death in the emergency department (1) or after discharge from hospital (2).

WLST, withdrawal of life-sustaining therapy.

TABLE 3. FUNCTIONAL OUTCOME AT 90-DAY FOLLOW-UP BY MRS

	mRS 0–3	mRS 4–6
Shockable	16 (64%)	9 (36%)
Nonshockable	1 (4%)	24 (96%)
All	17 (34%)	33 (66%)

mRS, modified Rankin Scale.

which made blinding care providers impossible. As with any observational study, we were unable to control for all possible confounders. However, this design also gives our study strength, increasing the generalizability of our results across multiple sites and clinicians.

The lack of associations between age, lay-rescuer CPR, and time to ROSC with outcome, typically significant in OHCA studies, may also be attributed to the small sample size. It is likely that our results are also biased by local postcardiac arrest care and WLST practices. Larger studies, standardized WLST practice, and more varied experience with IVTM systems may reveal additional safety and efficacy data.

Conclusion

The COOL-ARREST pilot trial demonstrates the high safety and efficacy of the ZOLL Thermogard XP IVTM system in the application of mild TTM postcardiac arrest. This observational trial also revealed noteworthy variability in the management of postcardiac arrest patients, particularly with the use of early withdrawal of life-sustaining therapy.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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