Study Protocol and Statistical Analysis Plan

Official Title of the Study:

Anti-inflammatory Effect of Therapeutic Hypothermia in Out-hospital Cardiac Arrest Patients with cardiogenic Shock via Interleukin-6 Trans-signaling

NCT number: NCT02633358

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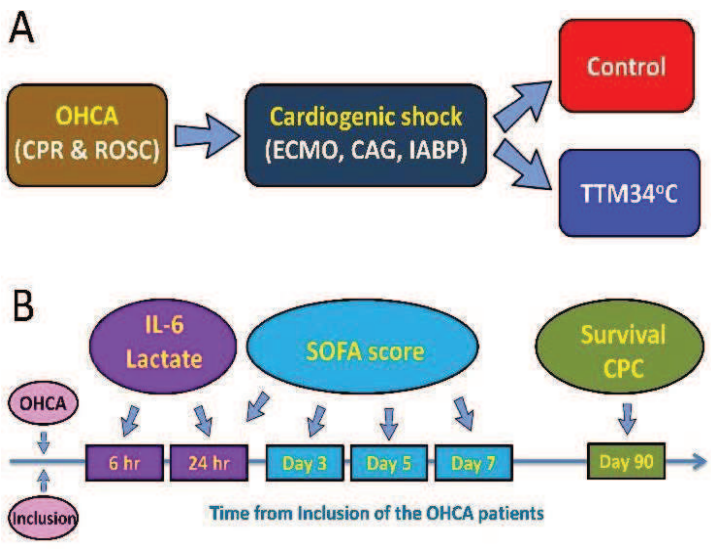
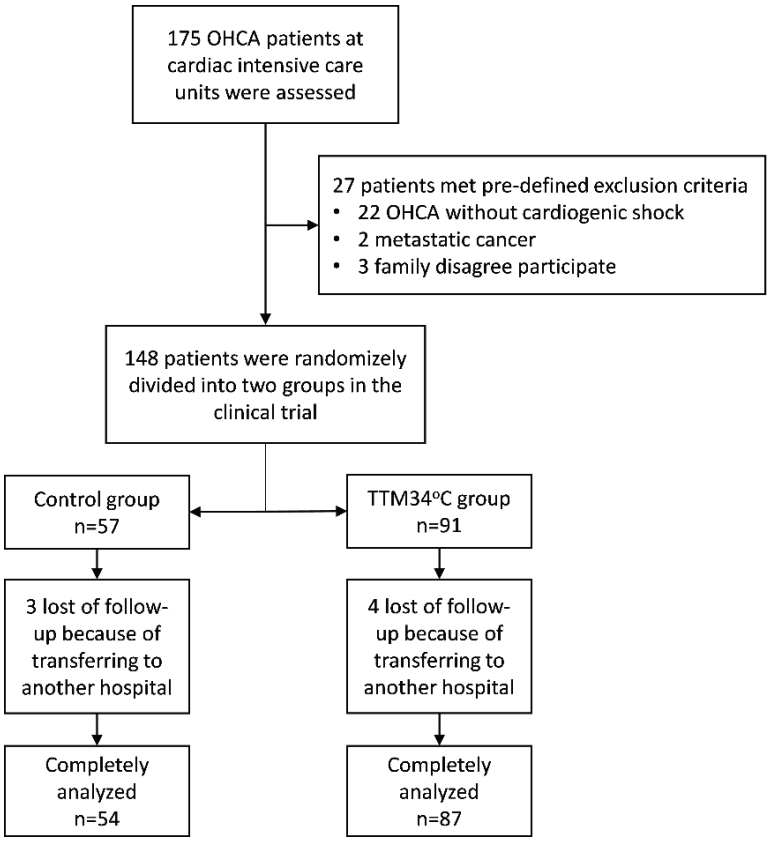
Study Design and Patients

The clinical trial was designed to evaluate the effect of therapeutic hypothermia on IL-6 trans-signaling in patients with OHCA complicated with cardiogenic shock in comparison with placebo (ClinicalTrials.gov, NCT02633358). The study was conducted at the CMU hospital, Taichung, Taiwan from January 2015 to April 2018, and was approved by the institutional review board of the CMU hospital. All participants provided written informed consent through their surrogate decision-maker.

Patients with OHCA who were aged more than 18 years old were enrolled after resuscitation. The clinical definition of cardiogenic shock used was patients with cardiac problems who require vasopressors to maintain a mean arterial pressure of more than 65 mmHg after adequate fluid hydration and an initial lactate level of more than 18 mg/dL. The study design is outlined in the right figure.



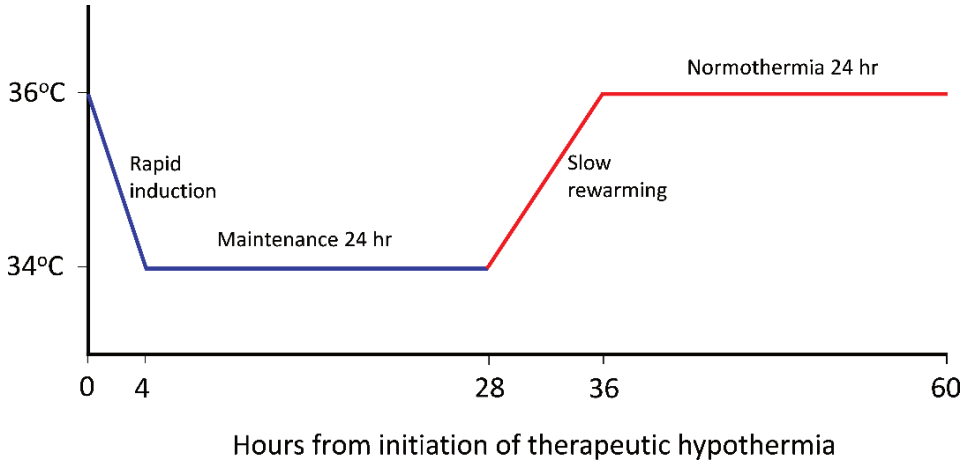
Exclusion criteria were recovery from OHCA without cardiogenic shock, pregnancy, metastatic cancer, and family disapproval of patient participation in the clinical trial. A CONSORT flow diagram is displayed in the below table.



Therapeutic Hypothermia Protocol

The therapeutic hypothermia protocol was in accordance with that proposed by Scirica et al. (2013), with minor modifications (12). The first stage was rapid immediate cooling. The second stage was maintenance of a core temperature of 33°C–35°C for at least 24 hours (TTM34°C). The third stage was slow rewarming. The fourth stage was maintenance of normothermia to prevent fever. The therapeutic hypothermia protocol

is presented in the below figure.



Several cooling devices were selected freely, including Arctic Sun (Medivance Inc., Louisville, CO, USA) and Thermogard XP (Zoll Medical, Chelmsford, MA, USA) automatic core temperature control devices in addition to classical ice blankets.

Blood Sampling Protocol

Peripheral venous blood was drawn into blood collection tubes containing ethylenediamine-tetra acetic acid to prevent coagulation at 6 and 24 hours after resuscitation. To obtain plasma, these tubes were immediately placed on melting ice and centrifuged within 30 minutes using Centrifuge 5810R (Eppendorf AG, Hamburg, Germany) set at 4°C, 450 × *g* for 25 minutes. Immediately following centrifugation, plasma was stored at −70°C in a freezer until further analyses.

IL-6 Trans-Signaling Immunoassay

The sandwich enzyme-linked immunosorbent assay was performed to measure IL-6, sIL-6R, Il-6/sIL-6R complex, and soluble glycoprotein 130 (sgp130) by using a human kit and standard protocol (R&D systems Inc., MN, USA). The absorbance of each well was determined using a Synergy™ H4 microplate reader at a 450-nm wavelength (BioTek instruments, Inc., VT, USA). Results were calculated using a 4-parameter logistic standard curve.

SOFA scores and Neurological Outcome

To evaluate the severity of organ failure, we used a SOFA score. This score reflected the severity of organ failure in cardiovascular system (mean arterial pressure), respiratory system (arterial pressure of oxygen divided by the fraction of inspired oxygen), central nervous system (Glasgow coma scale), liver (bilirubin), kidneys (creatinine), and coagulation (platelet).

Table The Sequential Organ Failure Assessment (SOFA) Score*

	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory Pao_2/Fio_2, mm Hg	>400	≤400	≤300	≤200†	≤100†
Coagulation Platelets $\times 10^3/\mu L$‡	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL‡	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d‖	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and Fio_2, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).
‖To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

Cerebral Performance Categories (CPC) scales of 1 (good recovery or slight disability) and 2 (moderate disability) were considered favorable neurological outcomes. CPC scales of 3 (severe disability) and 4 (comatose or persistent vegetative state) were considered poor neurological outcomes. A CPC scale of 5 (brain death) was considered as an indicator of mortality.

Cerebral Performance Categories Scale

CPC Scale

Note: If patient is anesthetized, paralyzed, or intubated, use "as is" clinical condition to calculate scores.
CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

Safar P. Resuscitation after Brain Ischemia, in Grenvik A and Safar P Eds: Brain Failure and Resuscitation, Churchill Livingstone, New York, 1981; 155-184.

Statistical Analysis

For assessing differences between the two groups, Student's *t*-test was used. For two time points between something before and after, paired *t*-test was used. Interaction effect, differences between the two groups and over time was analyzed by using multivariate analysis of variance (MANOVA) model. For categorical data, Chi-square test was used. Kaplan–Meier survival curves were compared between the two groups

by using the log-rank test. Risk ratios were reported as a measure of relative risk. A two-tailed *p* value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA).