JOURNAL MEETING

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102.12.02

Nielsen N, Wetterslev J, Cronberg T, et al.

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest.

N Engl J Med. 2013;:131117131833001-.

Background

- resuscitation guidelines
  → Therapeutic hypothermia
- treatment effect due to hypothermia
  or to the prevention of fever???

Methods

- Target Temperature Management (TTM)
  33°C vs. 36°C after OHCA
- randomized clinical trial
- 36 ICUs in Europe & Australia
- approved by the ethics committees
- TTM for 28 hours → gradual rewarming to 37°C (+0.5°C/hr)
- DC/taper sedation @ 36 hours
- for unconscious p'ts → maintain BT < 37.5°C until 72 hrs after the cardiac arrest

Inclusion criteria

- ≧18y/o, GCS < 8 on admission to the hospital after OHCA presumed cardiac cause
- spontaneous circulation after resuscitation
  (持續> 20mins)

exclusion criteria

- >4 hrs from ROSC to screening
- unwitnessed arrest with asystole as the initial rhythm
- suspected or known acute ICH/stroke
- BT < 30°C
- pregnancy
- bleeding diathesis except medically induced coagulopathy
- DNR、Known disease making 180 days survival unlikely
- pre-arrest CPC 3 or 4
- SBP <80 mmHg after fluid loading/vasopressor/inotropic medication/IABP (w/ 220mins)

F/u & outcome

- primary outcome
  - all-cause mortality until 180 days after the enrollment of the last patient
- secondary outcome → death or poor neurologic function
  - CPC 3~5 & modified Rankin scale 4~6 (無法獨立行走) at or around 180 days
  - CPC at discharge from ICU and from the hospital and
  - the best reported CPC during the trial period
- serious adverse events were recorded up to day 7 in the ICU

Statistical Analysis

- continuous outcome measures → Wilcoxon signed-rank test
- Kaplan–Meier survival curves → log-rank test
- Relative risks → Cochran–Mantel–Haenszel statistics
- Trends → Cochran–Armitage test
- Logistic-regression & Cox analyses, with adjustment
  - for site
  - for five baseline variables: age, sex, shockable rhythm, circulatory shock on admission, TROSC
- SAS (ver. 9.3) & SPSS (ver. 17.1)

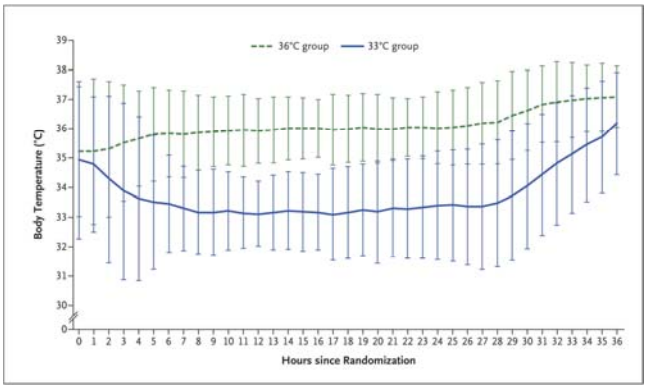
Result

P'ts

- November 2010 ~ January 2013
- 950 p'ts
  - 33°C → 473
  - 36°C → 466
- two groups had similar prerandomization characteristics

Temperature Intervention

- mean values of the initial recorded BT (tympanic)
- 35.2°C (3g) and 35.3°C (6g)
- intravascular cooling catheter (24%)
- surface cooling system (76%)



Withdrawal of Life-Sustaining Therapy

- During the first 7 days of hospitalization
  - 33°C group → 132
  - 36°C group → 115

Follow-up and Outcomes

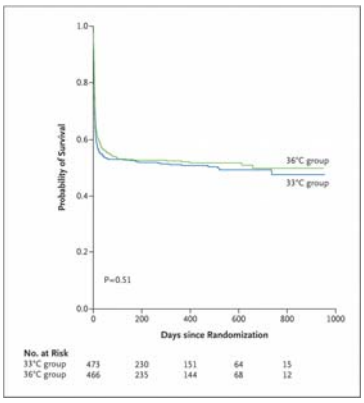
- face-to-face interview with the p't (86%)
- a structured telephone interview with the p't (6%)
- a telephone call to the p't or a relative (5%)
- a telephone call to a proxy provider of information (i.e., a staff member of a nursing home or a general practitioner) (3%)
- mean period of f/u for all p'ts → 256 days (~July 9, 2013)

Table 2. Outcomes.

Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

* The hazard ratio is shown for the primary outcome, and risk ratios are shown for the secondary outcomes. CI denotes confidence interval.

† The neurologic follow-up was specified in the protocol to be performed at 180 days ±2 weeks, but the time to follow-up was in some cases several weeks longer for logistic reasons. The Cerebral Performance Category (CPC) scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.



serious adverse events

- Hypokalemia
  - more frequent in the 33°C group (19%, vs. 13% in the 36°C group, P=0.02)

Discussion

- no significant differences between the two groups
  - in overall mortality at the end of the trial
  - in the composite of poor neurologic function or death at 180 days
- for all outcomes, none of the point estimates were in the direction of a benefit for the 33°C group

- potential benefits of temperature management on brain injury due to circulatory arrest
- whole-body hypothermia influences all organ systems
- The recommendation of BT (32~34°C) isn't from human data

difference between this trial & earlier trials

- actively controlled the BT
- prevent fever during the first 3 days after CA
- Larger sample & fewer exclusion criteria (nonshockable rhythms ~20%)

Limitations

- ICU staff members were aware of the assigned target temperature
- exclusion of a substantial proportion of eligible patients due to ethical approval requirement
- no data on the dose & type of sedation NMBs
- prehospital & critical care management have changed during the past decade
- clinically relevant benefit of controlling the body temperature at 36°C (instead of allowing fever to develop)

Conclusion

- as compared with targeting BT @ 36°C
- this trial does not provide evidence that targeting BT @ 33°C confers any benefit for unconscious patients admitted to the hospital after OHCA