Temperature management following cardiac arrest: A heated debate.

Clinical Problem

This case report details the management of a patient admitted to ICU after suffering an out-of-hospital cardiac arrest. This case was selected, as temperature management following cardiac arrest is currently an area of controversy with a recent RCT bringing our current practice into question.

Paramedics were called to a previously healthy, unresponsive 29-year-old man. That evening the patient consumed large quantities of alcohol and cocaine and was subsequently found unresponsive by a friend who alerted emergency services.
Paramedics confirmed that he was in cardiac arrest and immediately commenced CPR. No bystander CRP was undertaken during the 15 minutes between the 999 call and paramedic arrival. The exact "down-time" was uncertain but the patient was last seen alive over 90 minutes prior to being found unresponsive.

Pre-hospital attempts at IV access and intubation failed and the patient was transferred to the Emergency Department of the local district general hospital. After intubation, IV adrenaline and 2 rounds of CPR return of spontaneous circulation was achieved. He was subsequently transferred to ICU for ongoing management.
Word Count – 172

Management

Upon arrival in ICU his temperature was documented at 33°C. In light of a recent RCT we elected not to maintain this temperature but instead to allow passive re-warming to between 34-36°C for a 24-hours period. Our priority was therefore pyrexia prevention targeting a temperature of 36°C but allowing temperatures between 34-36°C for logistical reasons, minimising the likelihood of pyrexia.

Anaesthesia was maintained with proprofol and alfentanil infusions during this period and IV antibiotics were commenced to treat aspiration pneumonia. Safe ventilation was achieved with minimal pressure support. His biochemistry results were consistent with hypoxic acute liver and acute kidney injury.

Approximately 90 minutes following admission his temperature had risen to over 34°C. We then initiated active cooling measures which were successful in controlling temperature between 34-36°C.

Following the 24-hour cooling period sedation was stopped. There was no evidence of neurological recovery with a widespread flaccid paralysis, absence reflexes, extensor plantar response and bilateral dilated un-reactive pupils. Furthermore the development of profound hypertension (MAP 120 mmHg) was concerning. To control this proprofol was recommenced and a CT head was performed. This demonstrated loss of grey/white matter interface with gross cerebral oedema consistent with a severe hypoxic insult. To allow neurological prognostication proprofol was discontinued and esmolol used instead for control of hypertension. Mannitol 0.5 g/kg was administered in order to minimise intracranial hypertension.

After 3 days in ICU his pupils remained fixed and dilated. He remained mechanically ventilated. Reversible causes of coma were excluded. Although our patient developed an acute kidney and liver injury, the electrolyte abnormalities were not profound enough to exclude the patient from brain stem death testing.
Brain stem death was confirmed with family permission. The patient was not on the organ donor register. The family were counselled for organ donation however refused this. Organ support was withdrawn and the patient subsequently died.
Word Count - 306

Discussion:

The use of therapeutic hypothermia as a form of neuro-protection following cardiac arrest became standard practice and was incorporated into international guidelines[1] following two landmark papers in the New England Journal of Medicine in 2002[2],[3]. These papers concluded that improved survival and neurological outcome was associated with a period of induced hypothermia upon admission to ICU, confirming the earlier experimental studies.

The HACA trial was a multi-centred RCT, which enrolled 273 patients, who were randomised to controlled hypothermia (32-34°C) and or “normothermia” for 24 hours.

- Only VF/VT cardiac arrest rhythms were included.
- Patients were included if the time between collapse and resuscitation was between 5-15 minutes and if ROSC occurred within 60 minutes of collapse.

- Primary outcome demonstrated 55% favourable neurological outcome at 6 months in the hypothermia group versus 39% in the normothermia group.

This trial had many weaknesses including:

- the normothermia group had no temperature control and allowed to become pyrexial.
- no neurological assessment was performed prior to randomisation.
- limited utility in general population as only 8% of screened patients included in study.

The smaller study by Bernard et al was a single-centred pseudo-RCT, which enrolled 77 patients to either normothermia or hypothermia (33°C). This study found an absolute risk reduction of death or severe disability of 23% in the hypothermia group with a number needed to treat of 4.5. Again this study has major limitations:

- Small numbers,
- Statistical strength; if one more patient in the hypothermic group had a poor outcome the above risk reduction would have been lost
- No record of neurological assessment prior to randomisation.

Despite the criticism of these trials they were able to change clinical practice for over a decade. Moreover the use of therapeutic hypothermia has now been applied to non-VF/VT rhythms and in-hospital cardiac arrests, which were not supported by the original papers. Perhaps this is because as clinicians we favour the concept that an intervention is meaningful and will benefit our patients. Induced hypothermia is not the first intervention that was adopted on the basis of small, poorly designed trials, which were then later disproved by large multi-centred RCTs.

The targeted temperature management (TTM) was established to further investigate the role of induced hypothermia following cardiac arrest[5] and to answer questions generated by the inadequacies of the earlier trials. This trial aimed to compare survival following temperature control to 33°C versus 36°C in unconscious survivors of out of hospital cardiac arrest. The control temperature of 36°C was chosen as it seemed unethical to have no temperature control based upon the results of the studies above.

Compared with its predecessors this study had some notable differences in design:

- The inclusion of non-VF/VT cardiac arrest survivors
- Greater sample size which was actually double the number of the previous two trials combined
- Documentation of coma scale on arrival

- Avoidance of hyperthermia in both groups
- Guidance on prognostication

These factors make the TTM study more applicable to current clinical practice. Interesting the TTM trial did not demonstrate any difference in survival or neurological outcome based upon degree of temperature control, questioning the practice of induced hypothermia.

The criticisms of this trial include:

- More prevalent "favourable" factors in the 36°C group such as
    - "Shockable" rhythm
    - Bystander CPR
- More prevalent "unfavourable" factors in the 33°C group such as
    - Circulatory shock
    - Absent pupillary reflexes
    - Spontaneous hypothermia
    - Seizure activity
    - Greater number meeting criteria for withdrawal of care.

These factors may have biased the TTM study to have a negative result, although the survival rate in both groups compared with previous studies in encouraging and may reflect an improved standard of care in these patients.

Perhaps this study highlights the importance of temperature control and pyrexia prevention as key to improving neurological outcome. The prevention of pyrexia is widely accepted practice in preventing secondary brain injury in the context of neurosurgery and traumatic/non-traumatic brain injury. Future trials in this area are required to develop our understanding of this important subject.

Word Count – 674

Lessons learnt

Given the literature thus far, the evidence in favour of therapeutic hypothermia is weak. The TTM study was a well-designed, large-scale RCT, which demonstrated no benefit of this intervention. In this case report we did not instruct a temperature between 34-36°C to derive the benefits of hypothermia but to minimise the risk of pyrexia during the first 24 hours. It seems counter-intuitive to implement a temperature of 32-34°C as suggested by the original papers as this would lead haemodynamic instability during the hypothermic and rewarming phases in addition to confusing the prognostication process through altered sedative drug metabolism, all for uncertain benefit. If we encountered a similar patient in retrospect I would employ the same temperature management of 34-36°C as this seems the best logistical

balance between minimising the harmful effects of pyrexia without aggressively cooling patients to 32°C.

Regardless of the approach that is chosen it is clear that ICUs should adopt a defined protocol in which staff are familiar with. Survivors of cardiac arrest should have continuous temperature monitoring and aggressively pyrexia control in addition to standard neuro-protective measures.

Word Count – 181

References

1. Perberdy MA, Callaway CW, Neumar RW et al. Post cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010;122:Suppl 3:S768-S786.
2. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N N Eng J Med 2002; 346:549-556
3. Bernard SA, Gray TW, Buist MD et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. New Eng J Med 2002;346:557-63.
4. Sandroni C, Cavallaro F and Antonelli M. Therapeutic hypothermia: is it effective for non-VF/VT cardiac arrest? Critical Care 2013, 17:215.
5. Neilsen N, Wetterslev J, Cronberg T et al. Targeted temperature management at 33 ºC versus 36 ºC after cardiac arrest. N Eng J Med 2013; 369:2197-206.
6. Targeted temperature management after out-of-hospital cardiac arrest: certainties and uncertainties. Critical Care 2014; 18:459

Word Count – 141

Total word count - 1474

Domains 1.3, 3.6, 3.10, 8.1, 8.2, 8.4.