Yesterday, today and tomorrow in Targeted Temperature Management

“Tomorrow and tomorrow and tomorrow,” mused Macbeth, and indeed we are all interested in tomorrow. Despite the exponential development of many medical fields, we, as practitioners, are often faced with the dilemma: what I did for patients yesterday has been proven to be bad today. Who knows what tomorrow will bring...

Introduction

The recent publication of two trials relating to the fields of Therapeutic Hypothermia (TH) and Targeted Temperature Management (TTM) has created a great deal of confusion for Emergency Physicians attempting to practise evidence-based medicine. While hypothermia was considered to be the gold standard, it is likely that prevention of hyperthermia was more important. So what is the impact of the new studies on our practice, and what are the ramifications in resource-poor settings?

Yesterday and today

Following extensive animal modelling in the 1960s, Safar et al. pioneered the concept of induced hypothermia following cardiac arrest. However, it was not until the publication of three landmark trials early in the 21st century that TH was considered not only a viable therapeutic modality, but rather an absolute necessity. In 2001, Idrissi et al. performed a small single-centre study using TH for out-of-hospital pulseless electrical activity (PEA) or asystole and demonstrated a staggering four times improvement in survival to hospital discharge with a favourable neurological outcome. These results did not meet statistical significance due to the small size of the trial. In 2002, Holzer et al. published the now infamous HACA trial – a large multi-centre trial using TH for out-of-hospital ventricular fibrillation (VF). The authors demonstrated not only a statistically significant improvement in survival rates at hospital discharge with a favourable neurological outcome, but also that this advantage was maintained six months later. Bernard et al. published a small multi-centre trial focusing on TH following out-of-hospital VF in the same year. They, too, demonstrated the statistically significant improvement in survival rates at hospital discharge with a favourable neurological outcome in the hypothermic group.

The International Liaison Committee on Resuscitation (ILCOR) published an advisory statement in 2003 that unconscious patients with return of spontaneous circulation (ROSC) after out-of-hospital VF cardiac arrest should have TH at 32–34 °C for 12–24 h. They also advised that it may be of benefit for other cardiac arrest rhythms and for in-hospital arrests. The current American Heart Association (AHA) and ILCOR guidelines recommend TH as a Class 1 intervention in comatose patients following ROSC after out of hospital cardiac arrest secondary to VF. These recommendations suggest that induced hypothermia may be considered in comatose patients following ROSC after in-hospital cardiac arrest (any rhythm) and out-of-hospital cardiac arrest (PEA and asystole). Furthermore, healthcare providers are advised to monitor core temperature after ROSC and intervene to prevent hyperthermia – particularly in the first 48 h.

Today and tomorrow?

As 21 February 2002 marked the beginning of the TH era, so the landmark articles from 17 November 2013, 11 years later, have reinforced the core concepts of TH (control the temperature and prevent hyperthermia and fever) with the release of both the TTM trial in the NEJM and the induction of pre-hospital mild hypothermia by Kim in JAMA.

The TTM trial was designed to detect a 20% reduction in the hazard ratio for death when comparing post-cardiac arrest induced hypothermia between two different temperatures – 33 and 36 °C. They analysed the data of 939 patients who had ROSC after both shockable and non-shockable rhythms. This trial showed that there was no statistically significant outcome benefit between the two patient groups and, in fact, demonstrated possible harm for those patients who were assigned...
to the lower temperature as they had a higher risk of hypokalaemia. Although this trial had a fairly rigorous protocol, some queries remain:

- While the trial did not demonstrate a 20% reduction in hazard ratio, there may still be a benefit albeit smaller and this might only be detected if there were larger patient numbers included in the trial.
- This trial differed substantially from the original trials in that both patient groups had the intervention and hyperthermia was prevented i.e. there was still active management of the patients’ temperature. The optimum temperature target is still unknown.
- In both groups, there was a delay in instituting the intervention. From animal studies, we know this can be detrimental although from the Kim trial, there was no effect (see below).
- In the 33 °C group, re-warming took place at the faster side of the recommended rewarming rate (0.5 °C per hour). Although there are no studies which have outlined the optimum rewarming rate in cardiac arrest patients, it is plausible that slow rewarming will better preserve the neuroprotective effects of hypothermia. Therefore a faster rewarming may also have negatively impacted this group.

In the pre-hospital trial by Kim, where both VF and nonVF cardiac arrest patients received early induction of mild hypothermia compared to standard hospital induction, there was no benefit found with regard to neurological outcomes or survival. There was, however, potential harm as those patients receiving the cold intravenous fluids had a higher risk of re-arrest pre-hospital as well as an increased risk of pulmonary oedema in the first 24 h post-admission.

Application in the resource-poor environment

When considering the potential implementation of TTM in resource-poor settings, there are several factors that need to be carefully considered. Firstly, there is no evidence for or against the use of TTM following cardiac arrest in resource-limited settings. Indeed, if the evidence for TTM following cardiac arrest is unclear in the best-resourced areas of the world, then the evidence favouring TTM in low and middle income countries must be even more uncertain. Furthermore, whether the available evidence from well-resourced settings can be directly translated into such different populations is doubtful.

Secondly, TTM must be considered as only one component of a bundle of elements constituting post-cardiac arrest care. Unless the other constituents of care can be effectively administered TTM alone is likely to be of limited benefit, or may even be harmful. There are basic minimum infrastructure and staffing requirements that must be fulfilled for TTM to be feasibly implemented. While it is easy to induce hypothermia in the ED using one of several available methods (especially with a target temperature of 36 °C), the important part of TTM is the avoidance of hyperthermia for up to 72 h post-cooling. This requires intensive resources extending beyond the ED.

Clearly the level of resources at any particular facility will determine whether a post-cardiac arrest TTM programme should be instituted:

- If resources in any particular facility are routinely consumed in the management of conditions with similar (or poorer) prognosis than arrhythmogenic cardiac arrest, such as decompensated heart failure or stage 4 malignancies, then it is reasonable to motivate strongly for complete and comprehensive post-cardiac arrest care, including TTM.
- Generally a hospital below the level of a tertiary or academic centre will not be able to deliver comprehensive post-cardiac arrest care since the requirements would include the availability of technical equipment, an intensive care unit, specialised imaging facilities, highly differentiated clinical services and an infrastructure able to complete the protocol correctly.

It is an important principle that post-cardiac arrest care must be delivered in every facility where these patients are seen. Whether this is complex resuscitative care or palliative care will depend on the available resources and clinical scenario. Every facility should, however, have a written policy on the palliative care plan for the post-cardiac arrest patient.

The only studies available on TTM in resource-poor settings are those in neonates. While there is some evidence that TTM can be achieved using inexpensive methods there is no evidence of equivalence. Other studies have either recommended not to use TTM outside academic centres or have yet to produce real results.

Conclusion

In a resource-rich environment, there is no doubt that TTM is of benefit for comatose patients following ROSC after cardiac arrest. It does appear however, that some refinement in protocols is required to optimise patient care. TTM in the resource-poor environment is not as clear-cut, and needs a careful balancing act between resources consumed and benefit achieved, but comprehensive post-cardiac arrest care must be included if TTM is to be considered. The old bush-medicine lore certainly applies: do what you can – where you are – with what you have; but TTM should probably not be prioritised above other aspects of post-cardiac arrest care.

Oh, and use 36°C rather than 33°C.

References


