DEM Journal Club

Article Appraisal

Article: Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm by Lascarrou et al.

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Background and Study Objective(s):

Targeted temperature management (TTM) with mild therapeutic hypothermia (MTH), in comparison to no TTM, in post-cardiac arrest patients with initial shockable rthythms (i.e. ventricular fibrillation or pulseless ventricular tachycardia) was shown to improve neurologic outcomes in two clinical trials in 2000. However, no studies have demonstrated benefit in those with initial non-shockable rhythms. This study aimed to determine whether TTM with MTH improves neurologic outcomes in patients with nonshockable rhythms.

Study Design:

This is an RCT of 581 patients from 25 ICUs in France from 2014 to 2018. Exclusion criteria included no-flow time >10 minutes, low-flow time > 60 minutes, severe hemodynamic instability (as defined by norepinephrine > 1 mcg/kg/min), Child-Pugh class C cirrhosis, age < 18 years, pregnant/breastfeeding, or high risk of bleeding.

Patients were randomized to either TTM with MTH (T = 33° +/- 0.5° C) or TTM with targeted normothermia (T= 36.5-37.5° C). In the former group, patients were cooled and then maintained at the target temperature for 24 hours, followed by a gradual rewarming period of 24 hours, whereas the targeted normothermia group had temperature management for 48 hours. TTM was maintained (i.e. invasive or surface cooling) as per the institutions' practise. The primary outcome was neurologic outcome at 90 days using the Cerebral Performance Category score, which was measured by a blinded psychologist using a semi-structured phone interview. Secondary outcomes included mortality, mechanical ventilation duration, length of stay in ICU and hospital, infections, and hematologic adverse events. Standard practice ICU care was otherwise protocolized as best as possible to mitigate differences in treatment across various facilities and practitioners.

Results:

At hospital discharge the MTH group had neurologically favourable outcomes in 10.2% vs 5.7% in the normothermia group (4.5% difference; 95% CI 0.1-8.9, p=0.04). There were no significant differences observed with respect to any of the secondary outcomes. Survival to ICU discharge was 21.8% in the TTM with MTH group vs. 20.5% in the TTM with normothermia group, which was not statistically significant.

There was no difference in adverse outcomes between the groups, including but not limited to bleeding, arrythmia, pneumonia, bacteremia, vasopressor requirement, and need for renal replacement therapy.

Validity of Results:

This study had strong internal validity. It was a large multicentre RCT and was appropriately powered. The control and treatment groups were randomized and had similar demographics and clinical attributes. It was not possible to blind physicians and nurses to the intervention, however the independent neurologic outcome assessor was blinded to the treatment type. The trial was not stopped early. There were very few patients lost to follow-up (one in the intervention group and two in the treatment group), however given this study had a fragility index of one, meaning that a single changed outcome would have negated the statistical significance of this study. There was also a longer duration of active temperature management in the treatment group (56-64 hours versus 48 hours in the normothermia group), however it could be argued that this longer duration of temperature management was part of the intervention itself. There was some variation in how patients were cooled (e.g. external devices versus intravascular cooling devices, and dedicated closed-loop systems versus passive systems requiring human monitoring and feedback). This is a threat to internal validity and the dedicated closed-loop surface device rate was higher (47.9% vs. 34%) in the TTM with MTH group.

Generalizability of Results:

This study also had strong external validity. The patient population studied carried significant burden of disease, with mortality rates of 81 and 83% in each group. It was performed across 25 different ICUs, however all were located in a single country (France). Both groups had a high rate of bystander CPR (approx. 70%), however this is not surprising considering these were patients who achieved ROSC. Most ICUs have cooling devices and protocols already in place for treating post-arrest patients with shockable rhythms (as well as for some other clinical indications), and therefore the study intervention should be accessible to most criticial care physicians. Closed-loop cooling devices could likely provide tighter temperature control, however this was not speficially looked at in this study. A key threat to the external validity of this study was the somewhat arbitrary decision to choose 37 degrees Celsius as a normothermia target, despite previous evidence from the TTM trial in 2013 showing equivalnce between 33 and 36 degrees Celsius. This resulted in an unsurprisingly high rate of fever in the normothermia group (which has long been known to be neurologically detrimental). It is possible that had the TTM normothermia group been treated with exclusively with invasive closed-loop cooling devices, which are known to maintain tighter temperature control, that the difference in treatment could have been diminished.

The Bottom Line:

This is a landmark trial and the first to show benefit of therapeutic hypothermia in neurologic outcome in post-arrest patients with nonshockable rhythms. Interestingly, rather than provide marginal benefit to patients across all neurologic scores, therapeutic cooling seemed to shunt patients from a moderate outcome (CPC score of 3) to an improved outcome of 1 or 2, resulting in a bimodal distribution. In other words, patients who were destined for an exceptionally good or poor outcome did not benefit much from targeted cooling, however those in the middle of the distribution benefited significantly. The magnitude of effect was significant however this study had a fragility factor of one. The differences in treatment effect may have been due, in part, to the relatively high rate of fever in the normothermia group. This probably could have been corrected if the study designers chose 36 degrees as their normothermia target and/or used closed-loop temperature management devices to maintain tighter temperature control. Despite this, there was no difference in adverse effects between the groups, so targeted hypothermia is a safe intervention with substantial potential benefit. The group consensus was that txhis was a practice-changing paper and would absolutely influence the decision to cool or not in post-arrest patients with nonshockable rhythm.