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Role of Hypothermia in Cardiogenic Shock

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Abstract

While patient management in the intensive care unit has undoubtedly improved over the last 20 years, many questions remain. Neurological prognostication has become very important and aided in improving survival outcomes over time. The limited number of randomized control trials and limitations from currently completed studies leave the field with little certainty regarding targeted temperature management. In addition, implementing hypothermia can use multiple methods and protocols that impact the interpretation and comparison of results.

Keywords: hypothermia, cardiogenic shock, target temperature management

Introduction

To improve survival after sudden cardiac arrest, the American Heart Association published the concept of "the chain of survival" as early as 1991.[1] Peter Safar first used this phrase to describe the coordinated effort to gain spontaneous circulation by paramedics, emergency physicians, and intensivists.[2] As field care improved, the number of critically ill patients requiring care in the intensive care unit (ICU) grew. Currently, early mortality after resuscitation arises from the underlying cardiogenic shock state and the precipitating cause of cardiac arrest. Later mortality is largely caused by neurological injury and end-organ damage as a sequela of cardiac arrest.

Target Temperature Management

Early data from the Hypothermia After Cardiac Arrest Study Group demonstrated a benefit from target temperature management (TTM),[3] which is a strategy of deliberate temperature management with active cooling, rewarming, and extended fever control. The recommendation for all adult comatose patients with Glasgow Coma Scales less than 8 is to undergo TTM to achieve temperatures between 32.0 and 36.0°C. Cooling actively prevents pyrexia, which decreases damage to the brain and other organs by lowering tissue metabolism, reminiscent of limiting the infarct size in the heart, post-myocardial infarction by attenuating ischemia/reperfusion injury. The evidence to support this recommendation stems from data indicating that fevers greater than 37.7°C are associated with a poor outcome. The worst outcomes are associated with temperatures greater than 39.0°C. Initial clinical trials with mild hyperthermia within 12 to 24 hours of care showed improved survival and neurological outcomes after out-of-hospital cardiac arrest in patients with shockable rhythms compared to usual care.[3]

Literature Review

Written guidelines strongly recommend the use of TTM despite evidence with low certainty. In 2019, the results of an open-label trial of 584 patients from 25 ICUs were published.[4] Subjects experienced out-of-hospital cardiac arrest and were randomized to TTM or usual care regardless of shockable rhythm; the study failed to show the superiority of the use of TTM.

A more recent study from 2021 enrolled 1900 adults without a hospital cardiac arrest who were randomized to hypothermia with temperatures targeting 33°C or normothermia.[5] The results of this randomized controlled trial (RCT) showed that both the hypothermia and the normothermia groups had a 50% mortality rate, and there was no difference concerning functional outcomes at six months for survival or neurological outcomes. Interestingly, arrhythmias were more common in the hypothermia group (24 vs. 17%), but there was no difference in other prespecified adverse events.[5]

A lot has changed in the last two decades regarding ICU care; thus, it is not surprising that this study directly contradicts the study published 20 years ago where the benefit of hypothermia was reported. Further, the more recent trial has several limitations, including the lack of a true control group.[5] The intervention could not be blinded, which may have influenced the outcomes. In addition, about 20% of subjects were co-enrolled in another trial.[5] A letter to the editor commented on several concerns that mainly related to the generalizability of the study.[6] They noted that 75% of patients had a shockable rhythm, and only 80% of patients had received bystander cardiopulmonary resuscitation (CPR).[6]

With so much debate, a recent systematic review provides key takeaways.[7] Over 3400 articles from 2001 to 2020 were screened, and 32 related trials were identified. Of note, only 9 trials compared normothermia and hypothermia (32 - 34°C). Most of the trials were small feasibility or pilot studies, with only 3 trials having more than 100 patients enrolled. The overall summary of this systematic review and meta-analysis was that TTM does not clearly provide a benefit when compared to normothermia, although the certainty of the evidence was low.[7]

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has emerged as a viable therapy for cardiac arrest, particularly in the setting of extracorporeal CPR (ECPR). Studies are currently being conducted in France, the Czech Republic, and Taiwan to assess outcomes of ECPR in out-of-hospital cardiac arrest. More importantly, there have also been studies that considered V-A ECMO in an acute setting with hypothermia.[8] The 2022 Extracorporeal Life Saving Organization Registry Report confirmed the survival to hospital discharge in adults with ECPR is as low as 30%. There is no further granularity concerning TTM in these patients. In considering ECPR with hypothermia, one of the first reports was from the CHEER Trial in 2015.[8] This was a single-center, feasibility trial that compared only 26 patients. The authors concluded that hypothermia was associated with higher survival than ECPR alone.[8]

Duan and colleagues completed a meta-analysis of articles that evaluated CPR strategies for patients with cardiac arrest. They analyzed 21 full-text articles from 2000 to 2020.[9] Many of the studies enrolled patients who had out-of-hospital cardiac arrest, with most of these arrests being witnessed. There was inconsistent use of bystander CPR, and surprisingly, the time of initiation of cannulation ranged from 34 minutes to 185 minutes. More importantly, most of these studies were retrospective in nature, and only five studies were prospectively designed or included randomization and controls. Sample sizes ranged from 600 to 231 patients. There was a favorable rate of survival to hospital discharge over 28 days (odds ratio [OR] = 2.27) and better neurological outcomes in the group that received hypothermia (OR > 2.0). The benefit holds for survival outcomes at 3 months for both survival and neurological outcomes.[9]

This year, Levy and colleagues from the ECMO Net published the results of an RCT of early initiation of hypothermia versus normothermia for 24 hours in patients with cardiogenic shock supported with V-A ECMO.[10] The multi-site study in France collected data from 20 centers between 2016 and 2019. They hypothesized that early hypothermia improves survival rates of patients with cardiogenic shock supported by V-A ECMO. A total of 374 patients were randomized, and they found that the hypothermia group had a lower mortality rate when compared to the normothermia group (42% versus 51%). However, this was not statistically significant, with a P-value of only .07.[10] Likewise, a single-center experience with patients on V-A ECMO demonstrated improved neurological recovery with TTM, but there was no association with improved mortality with hypothermia.[11]

Conclusion

While patient management in the ICU has undoubtedly improved over the last 20 years, many questions remain. Neurological prognostication has become very important and aided in improving survival outcomes over time. The limited number of randomized control trials and limitations from currently completed studies leave the field with little certainty regarding temperature management. In addition, implementing hypothermia can use multiple methods and protocols that impact the interpretation and comparison of results.

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