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Complex Legacy of the TTM Trial

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In 2013, with overwhelming preclinical data supporting the principle of hypothermic neuroprotection, and a decade of clinical success implementing post-resuscitation cardiac arrest care algorithms constructed around hypothermia protocols, it seemed inconceivable that a clinical trial would show similar benefits from therapeutic hypothermia and normothermia. But in a crowded auditorium of the Dallas Convention Center in December 2013, Target Temperature Management (TTM) Trial Principle Investigator Niklas Nielsen described equivalent outcomes among patients treated after cardiac arrest at 33°C x 24 hours, then 36°C until 72 hours had elapsed, and those whose body temperature was simply held at 36°C for 72 hours. The similarity of hypothermia and normothermia was seen in multiple outcomes, including mortality, delayed functional outcome, multiple pre-specified subgroups, cognitive function, and neuron-specific enolase levels.[1–3] Additional signals in the data suggested that lower temperature had adversely affected hemodynamics, especially in patients with shock, and may have resulted in worse outcomes among that subgroup.[4] Upon publication, New England Journal editorialists – like the researchers themselves – warned readers not to confuse a lack of superiority of hypothermia with the overall ineffectiveness of temperature management.[5] Like many of us, they feared neutral trial results could lead to abandonment of TTM, and reverse hard-won gains of the prior decade.

This issue of Critical Care Medicine contains research that further clarifies the legacy of the TTM trial. Investigators from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation evaluated clinical practice, outcomes, and in-hospital mortality of 16,252 patients treated at 140 centers after resuscitation from cardiac arrest. These investigators found a difference in the coldest temperature during the initial 24 hours of ICU care when comparing the 3 years before and after the TTM trial publication, suggesting a change in temperature management practices across New Zealand and Australia after publication. The utilization of hypothermia (32–34°C) fell from 45.9% to

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24.6%. Perhaps more importantly, the incidence of post-resuscitation fever increased from 12.9 to 16.5%, and an analysis of the trend of post-resuscitation mortality showed reversal of a nine-year-long average 1.3% decrease in annual mortality to an increase in mortality of 0.6%, a net difference of +1.9%.[6] These analyses were conducted after careful adjustment for severity of illness using the ANZROD tool (perhaps an imperfect choice), and were consistent across multiple subgroups: those admitted to tertiary care centers, within each country, and above and below the age of 60. The methodology of hierarchical and segmented regression is robust and appropriate for this type of epidemiological study.

What accounts for the change in New Zealand and Australia's mortality trend? Could the publication of a scientifically sound trial that contributed a wealth of practical knowledge to the practice of post-resuscitation cardiac arrest care be the cause of worse cardiac arrest outcomes across two nations? Conversely, could the results be explained by trends in critical care practices, changes in referral patterns, or other unmeasured confounders? It is an emotional question, and the answer is: maybe.

Science drives and informs our work in medicine, yet there is unquestionably an element of mass psychology impacting our practices. New knowledge leads to better care over time, as we translate raw information into novel approaches, evidence-based therapies, and sound programs of care. New treatments create an excitement, or buzz, that drive work in quality improvement across whole systems of care. A great example of this occurred in post-resuscitation cardiac arrest care between 2002 and 2013. As clinicians implemented therapeutic hypothermia, an exciting "new" therapy, other refinements were made: patients long ignored as unsalvageable in many ICUs were transferred to tertiary centers where advanced services were available, early coronary angiography and PCI was reconsidered and applied with increasing frequency, inaccurate prognostication practices were reexamined, and efforts to standardize and improve all aspects of the critical care management of cardiac arrest survivors were intensified. In short, a single therapy that was expected to contribute a small margin of improvement to outcomes galvanized an entire community to redouble their quality improvement efforts and promote related science, resulting in a greater than expected benefit. It was a golden era for cardiac arrest care, manifest in a surge of research publications, and enormous changes in processes and systems of care. Clinical researchers described how the implementation of hypothermia protocols more than doubled survival with a favorable neurological outcome; [7,8] effects dwarfing what might be anticipated by implementation of a single therapy that can only be explained by the "ripple effect" of a new treatment – in other words, by mass psychology. This energy – a sense of limitless possibility and unity of purpose – is what may have been lost with publication of the TTM Trial.

There is irony here, since the results of the TTM trial in no way refute the benefits of temperature management. In fact, the trial embodied the most intensive and successful application of standardized temperature management ever conducted, with spectacular outcomes in both treatment groups. What changed was the introduction of doubt, where there had previously been certainty. And doubt, through its ripple effects, may affect practices and outcomes.

Science is not sentimental. Publication of the TTM trial ended a “feel-good” period for post resuscitation care, but also ushered in a more honest evaluation of which elements of post-resuscitation care truly matter, and made available abundant new data. This is how we advance – not by enthusiasm, which comes in waves and then fades, but by a constantly challenging what we think is fact, improving our knowledge base and building further on novel therapeutics based on sound biological and physiological principles. Epidemiological context for the TTM Trial, which is what this new post-implementation study provides, helps us understand which direction we may be going at this time. We take two steps forward and then one step back. As we have learned from the experience down-under, we have challenged what was considered fact; it’s now time to re-evaluate and step forward, once again.

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