The Effect of Therapeutic Hypothermia on Neurological Outcomes Following Resuscitation from Cardiac Arrest

by

Meagan Dunn

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science
in
Experimental Medicine

Department of Medicine
University of Alberta

Abstract

Therapeutic Hypothermia (TH) is a relatively new therapy used to treat those resuscitated from cardiac arrest. The purpose of the therapy is to attenuate any neurological damage resulting from the arrest, thereby increasing survival and improving subsequent quality of life. The current evidence for TH is limited in regards to neurological outcomes.

The purpose of this work was to explore neurological outcomes of patients following resuscitation from cardiac arrest, specifically those who receive TH. We conducted a systematic review of the effect of TH on neurological outcomes for patients resuscitated from cardiac arrest, including all studies which compared TH to a control group. Additionally, we prospectively created a registry of patients resuscitated from cardiac arrest, and evaluated their neurological functioning over 6 months of follow-up with the use of several tools, primarily the Montreal Cognitive Assessment (MoCA) test. We also assessed survival for these patients.

Our systematic review included 40 studies which reported on neurological outcomes following TH for cardiac arrest. We found that TH was associated with more favourable neurological outcomes compared to no TH: RR 1.75 (95% CI 1.54, 1.99; $p<0.001$). In the 37 studies that reported on survival, the benefit of TH on survival was significant: RR 1.48 (95% CI 1.33, 1.65; $p<0.001$).

Of the 110 patients enrolled in our registry, surviving patients who received TH demonstrated continuous neurological improvement over the 6 month follow-up period. Using the MoCA test, we observed a mean improvement of 3.3 (SD 2.60) and 4.3 (SD 4.72) points at 3 months and 6 months following arrest respectively, for those who received TH. Those who received TH also had a decreased hazard of death compared to the no TH group, HR 0.39 (95% CI 0.24, 0.64; $p=0.0006$).

These results confirm benefit for the use of TH for patients resuscitated from cardiac arrest. They suggest that neurological improvement continues over time, and that clinicians should consider using

appropriate tools that are sensitive to cognition when assessing neurological outcomes. Future research of neurological outcomes should focus on using multiple tools for assessment which are validated and sensitive to cognitive impairment.

Preface

This thesis is an original work by Meagan Dunn. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "The Cardiac Arrest Induced Hypothermia Registry: The 'Cool' Registry", ID. Pro00037919, JUNE 5, 2013.

Some of the research conducted for this thesis forms part of a research collaboration, led by Dr. M. Chan at the Royal Alexandra Hospital. The registry referred to in chapter 3 was conceived and designed by myself, Dr. M. Chan, Dr. Y. Al Hamarneh, and Dr. R. Tsuyuki. I performed the collection and assessment of the data, and the writing of the manuscript. I. Hassan contributed to the statistical analysis of the data. Dr. R. Tsuyuki critically reviewed and revised the manuscript.

The systematic review in chapter 2 was designed and performed by myself, Dr. Yazid Al Hamarneh, Dr. Ross Tsuyuki, T. Chatterley, and B. Vandermeer. I contributed to the conception and the design of the review, the acquisition, extraction, and assessment of the data, the writing of the manuscript, and critical review and revision the manuscript for intellectual content. Dr. Y. Al Hamarneh contributed to the conception and the design of the review, the acquisition, extraction, and assessment of the data, and critical review and revision the manuscript for intellectual content. Dr. R. Tsuyuki contributed to the conception and the design of the review, critically reviewed and revised the manuscript for intellectual content. T. Chatterley contributed to the acquisition of the data and reviewed the manuscript. B. Vandermeer reviewed the manuscript.

Both chapter 1 and chapter 4 are my original work.

No part of this thesis has been previously published.

Acknowledgements

I would like to thank the numerous people that have helped me during the completion of this thesis. My primary supervisor, Dr. Ross Tsuyuki, you have been a guide and mentor throughout this process, dedicating much precious time and advice. My co-supervisor, Dr. Michael Chan, you have given your trust and support to me from the first, and have been a great source of enthusiasm for this project. My co-supervisor, Dr. Yazid Al Hamarneh, you have been encouraging and helpful in many practical ways during the completion of this work, and have always been willing to share my burdens. Thank you sincerely each of you.

None of this project would have been possible without the commitment and dedication of the "Cool Club" nurses, who were involved from the inception of "The Cool Registry" and whose contribution of time and passion made our study a reality. Thank you immensely Elizabeth Williams, Harrison Applin, Natalie Hanson, Shelly Carson, Stephanie Brimacombe, and Valerie Dowhaniuk.

There were individuals whose helpful advice and knowledge was offered freely and openly, and who made an impact on this experience for me. Thank you to Sylvia Martin for your many insights into the research process. As well thank you to the Epicore Centre team: Deb, Glennora, Imran, Lily, and Marcie. You were all so welcoming and encouraging to me.

Helping to keep me balanced as I endured each step of this process, Kyle Dunn, you always provided the emotional support I needed to persevere. Thank you for being my husband and friend.

And to the patients of the Royal Alexandra Hospital and their families, who in their time of greatest need were willing to contribute. You are the reason for undertaking this research, and without your help it could not have happened. Thank you.

Table of Contents

List of Tables

List of Figures

Introduction

CARDIAC ARREST

Cardiac arrest is a medical emergency defined as the "cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation"[1]. Statistics from the Heart and Stroke Foundation of Canada estimate that 40,000 people fall victim to cardiac arrest annually in Canada, with most (85%) occurring out of hospital[2]. Of these, only about 5% are successfully resuscitated to be admitted to hospital. Furthermore, the mortality outcomes for those who survive to be admitted to hospital are often poor, with a low likelihood of survival to hospital discharge. In those who survive, neurological function is a concern, with many suffering from significant impairment[3]. Some are never discharged to home, and must remain in long term care due to a range of functional disability. This ranges from vegetative state through to ambulatory, but with significant cognitive dysfunction whereby patients may not be able to perform activities of daily living and remain dependent on care givers. Sadly, they can suffer significant memory loss, disorientation, and depression or other psychological disorders, which is very stressful to the patient and their families[4]. Even in those that do get discharged home, patients can still encounter subtle neurological dysfunction, possibly requiring assistance to manage their own affairs, or experiencing issues like memory deficit[5].

The neurological damage which results from cardiac arrest is caused by brain ischemia which occurs during the period of no blood flow, as well as reperfusion injury that occurs following return of spontaneous circulation (ROSC). These processes involve inflammatory responses, mitochondrial dysfunction, formation of oxygen free radicals, destabilization of the blood-brain barrier, hypotension, apoptosis, and cerebral edema[6]. The level of oxygen free radical formation and mitochondrial injury can be increased even more by the administration of high levels of oxygen immediately following reperfusion[7]. Cerebral edema also occurs, due initially to the reperfusion injury, and is worse in people

with more severe ischemia. There may also be a role played by the microvasculature of the brain, which can remain dysfunctional even after perfusion to the organ has been returned, as cerebral blood pressures are often reduced in the early days following ROSC. This contributes to lower oxygen delivery, which can be compounded further by hypoxemia of the patient due to their clinical condition. In fact the majority of the destructive processes occur after ROSC due to the reperfusion injury[8]. While specific signals which trigger the destruction of cells can happen initially following the arrest, these also continue for days following ROSC. Therefore, therapies used in the treatment of cardiac arrest patients must be targeted at not only the immediate post-arrest phase, but for subsequent days following the event if they are to have an impact on the patient's outcomes.

TREATMENT

Treatment following cardiac arrest is based on what is defined by the Heart and Stroke Foundation as the Chain of Survival[9]. The links in this chain include early access to emergency medical services, early cardiopulmonary resuscitation (CPR), early defibrillation, and effective advanced life support, including integrated post cardiac arrest care. The focus of this work relates to the post cardiac arrest care, of which the purpose is to improve quality of life. To be effective, patient care following cardiac arrest must address the underlying cause of the arrest, as well as reduce the ischemia-perfusion injury that occurs to many organ systems, like the brain[10]. According to the most recent guidelines[10], mitigation of ischemia-reperfusion injury includes hemodynamic optimization, and the controlled reduction of the patient's body temperature. This is accomplished by reducing a person's core body temperature in a controlled fashion to a pre-specified target temperature. The patient is maintained at this temperature for a pre-specified duration of time, usually about 24 hours, after which time the patient is brought back up to a normal core temperature in a slow and controlled manner. Initially, the temperature range used in the therapy was in the mild hypothermia range of 32-34 °C. This treatment is referred to as Therapeutic Hypothermia (TH). More recently, a wider therapeutic temperature range has been

espoused (32-36 °C)[11], and the term Targeted Temperature Management (TTM) has been adopted to reflect this[10].

The application of TTM requires a temperature control device, which can either involve an intravascular catheter which directly cools the blood, or surface cooling in the form of cooling blankets, vests, helmets, or even just ice packs. During the therapy the patient receives sedation and neuromuscular blocking agents, in order to prevent shivering and decrease oxygen demands. Neuroprognostication takes place following the rewarming phase, but no sooner than 72 hours following the arrest[10], as there is no clear evidence about how the induced hypothermia affects the clearance of sedating agents from the patient's system.

REVIEW OF THE LITERATURE

The use of TTM following cardiac arrest has been an evolving therapy worldwide since the landmark trials that brought the treatment into accepted use in 2002[12, 13]. Since then, many studies of various natures have been conducted, but there are few clinical trials. The differences between subsequent studies have been various: methodological, inclusion criteria, (e.g., presenting cardiac rhythm), duration of therapy, follow up periods, and definitions of good outcome.

One of the first 2 studies of TH following cardiac arrest was conducted by The Hypothermia after Cardiac Arrest study group (HACA)[12]. This was a multicentre randomized trial that assessed complications within the first week of treatment, and neurological outcomes and survival at 6 month from the arrest. Adult patients presenting with witnessed cardiac arrest and a shockable initial rhythm that was thought to be of cardiac origin were enrolled. The majority of these patients had out-of-hospital cardiac arrest. The time to Emergency Medical Services arrival had to be 5 to 15 minutes, and the total time from arrest to ROSC for the patient had to be 60 minutes or less. Following randomization, patients in the TH arm were brought to 32-34 °C using surface cooling via a cooling blanket and ice and maintained in this

temperature range for 24 hours, after which they were allowed to passively rewarm. Patients in the control arm were treated with the normal post arrest care at the time.

Neurological outcomes were assessed blindly using the Cerebral Performance Category (CPC) scale[14], which is a 5 point scoring system that categorizes the results ranging from 1 (good recovery) to 5 (death). A CPC score of 1 or 2 was considered favourable neurological recovery by the HACA group, and the patient had to be able to live independently or work at least part-time.

A total of 275 patients were enrolled over 5 years; 137 in the treatment group, and 138 in the control. The baseline characteristics of these 2 groups were similar. There was a 16% increase in favourable neurological outcome in the TH group vs. the control group within 6 months (RR 1.40; 95 percent confidence interval, 1.08 to 1.81; p=0.009). There was a 14% decrease in death in the TH group at 6 months compared to the control group (RR 0.74; 95 percent confidence interval, 0.58 to 0.95; p=0.02). There was no significant difference in the occurrence of any complication (bleeding, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores) between groups (73% in the TH group vs. 70 % in the control, P=0.70), nor in the total number of complications (P=0.09).

The HACA trial was a randomized trial that, although influential in changing practice worldwide, had relatively low numbers of enrollment. The duration for the outcome assessments was clinically important at 6 months, as this would be a realistic time frame to assess for the highest level that the patients' neurological condition would likely reach. Assessments were blinded when possible, although there was some question as to how successful this was, and double blinding was not possible. The CPC scale employed is easy to use, although it is a coarse scale, and not very sensitive to cognitive impairment[15]. The CPC scale is subjective as it uses terms like "sufficient", which is not appropriately defined within the tool[16]. Making the determination that a person has sufficient cerebral functioning for

independent activities of daily living, when only a few of these activities may have been tested and reported, may not be valid.

The second landmark study was published simultaneously by Bernard, et al[13] and included patients with out of hospital arrest, and cooled them to the same target temperature (33 °C). Unlike the HACA trial, only patients with an initial rhythm of ventricular fibrillation were included. The TH group had cooling initiated prehospital with ice, and were cooled for 12 hours instead of 24. This multicentre study was quasi-randomized using an even and odd days assignment method. Patients were dichotomized as either a good outcome or poor outcome. There was no validated scale used for quantifying neurological outcome, but rather the patients were classified as having a good outcome if they were discharged to home or rehab facility, or poor outcome if they were discharged to a long-term care facility or died.

This study enrolled 77 patients, 43 in the TH group, and 34 in the control. The TH group had 23% more "good outcomes" (OR 2.65, 95 percent confidence interval, 1.02 to 6.88; p=0.046). After adjusting for age and time from arrest to ROSC, there was an adjusted OR of 5.25, (95 percent confidence interval, 1.47 to 18.76; p=0.011). Mortality between the groups was not statistically significant (51% for TH and 68% for controls, P=0.145).

Like the HACA trial, the baseline characteristics of the groups were comparable. However, the number of subjects enrolled was also relatively small. Furthermore, although the authors claim quasi-randomization, this was not truly a randomized trial as the authors used alternate day randomization (which is actually non-random, but systematic)[17]. Blinding of clinicians was not possible during treatment, but the outcome assessors were blinded to the treatment group. Choosing to use discharge from hospital as the assessment point limits the accuracy of outcome, as a patient's condition can continue to change following discharge. The parameters used for classifying outcome may be over simplified, and may not be an appropriate indicator for how well a patient will do in the long term

neurologically, beyond the hospital stay. Classification according to discharge disposition is only possible at one time-point (hospital discharge), and may be dependent on outside influences, such as finances and the amount of personal support systems available to the patient[16]. It is therefore not an ideal measure of outcome. And, like the use of the CPC in HACA, it is a coarse outcome, likely insensitive to the range of neurological impairment present in patients who are recovering from cardiac arrest.

Since 2002, the literature includes many other studies of TH for cardiac arrest. However, there are very few randomized clinical trials. When looking into studies that use a comparable treatment, it must be noted that there are no RCTs that compare TH to control groups in patients who either present with non-shockable rhythms (e.g., asystole or pulseless electrical activity), or in populations that experience in-hospital cardiac arrest. The rest of the evidence on the topic is of lower methodologic quality, being comprised of retrospective and prospective cohort studies. These studies use heterogeneous inclusion criteria (witnessed vs. unwitnessed arrests, out-of-hospital cardiac arrest vs. in-hospital cardiac arrest, presenting cardiac rhythm, duration of time from arrest to ROSC), treatment processes (duration of therapy, method of cooling, time to initiation of therapy, rate of rewarming), follow up time (ICU discharge, hospital discharge, 30 day, 3 month, 6 month, 1 year), and outcomes assessment (Cerebral Performance Category scale[14], Modified Rankin Scale[18], discharge disposition, Glasgow Coma Scale[19], Mini-Mental State Exam[20]). With the high amount of heterogeneity between these studies, it is important to realize that there are many subgroups that lack evidence for benefit, and outcomes remain poorly, inconsistently, and often inappropriately characterized.

Another practice-changing study was published by Nielsen et al. in 2013[11]. In this multicentre trial, 950 subjects were randomized to be cooled to 33 vs. 36 degrees. They included patients with out of hospital cardiac arrest of presumed cardiac cause, with any presenting rhythm. The duration of treatment was maintained for 24 hours, and then controlled rewarming commenced. Follow up was performed at

discharge from ICU, discharge from hospital, and for at least 180 days following the arrest. The primary endpoint was all cause mortality, with secondary outcomes being a combination of mortality and poor neurological functioning. The tools used for blinded assessment of neurological outcomes were the CPC scale and the MRS scale[18]. The MRS scale is a 7-point scale ranging from MRS 0 (no symptoms at all) to MRS 6 (dead). Poor neurological functioning was considered a CPC score of 3-5 and an MRS score of 4-6. The results of this parallel-group study were that 36 °C was not superior to 33 °C for the treatment of cardiac arrest. This study was exploring the concept suggested by several authors that it is not the hypothermia that is beneficial for neurological outcome, but rather the avoidance of fever and all of its associated destructive processes, such as increased brain metabolism and increased oxygen free-radical formation[21, 22].

Enrollment numbers were high and as described in the design publication for the study, it was sufficiently powered[23]. The inclusion criteria were broader than the previous trials, and encompassed some patients not studied in previous trials (any initial rhythm). The authors used multiple follow-up times, up to 6 months, which is important because the measure of outcome in a given patient changes throughout the time following a cardiac arrest. Using the CPC and MRS scales as measures for neurological outcome presents some of the same limitations as previously described with the other trials. Although standardized, they are not validated for post cardiac arrest patients, which may be a threat to validity. Overall, the Nielsen study was a well-designed, well executed trial. However the interpretation of the results may have been erroneous. The authors concluded that there is no difference in harm or benefit between 33 °C and 36 °C. This was designed as a superiority trial, and the conclusion of “equivalence” is not appropriate from this design. The writers of the 2015 guidelines acknowledged influence from this trial[10], which may have been ill-founded, and the newest guidelines regarding treatment post cardiac arrest have broadened the targeted temperature range from 32-34 °C

in previous years, to 32-36 °C in the 2015 version. This in turn changed clinically the way TH is used worldwide. The adoption of the term TTM from TH was also a product of this study.

CURRENT GUIDELINES

Based on the available evidence, current post-resuscitation guidelines recommend the use of TTM following resuscitated cardiac arrest. For all patients who remain comatose following ROSC, TTM is strongly recommended. If they suffered shockable out-of-hospital cardiac arrest, it is a class I (strong) LOE B (randomized) recommendation. If they suffered a non-shockable or in-hospital cardiac arrest, it is a class 1 (strong) LOE C (expert opinion) recommendation. The recommendation to use a temperature range of 32-36 °C is class I (strong) LOE B (randomized)[10].

GAPS IN CURRENT EVIDENCE

The current guidelines are mainly based on 3 randomized controlled trials, and there are still many unanswered questions. The most robust data has been on patients who have experienced out-of-hospital cardiac arrest, and those presenting with shockable rhythms. There have been no trials focusing on in-hospital cardiac arrests, non-shockable initial rhythms, or other possible subgroups that might benefit. Optimum time from arrest to target temperature remains unknown. A specified best targeted temperature has not been defined, and in fact there has been raised the question about whether it is actually the avoidance of fever that may infer the neurological benefit, rather than the induction of hypothermia. And still, the impact of TTM on neurological outcomes remains under assessed. Although the majority of studies in the literature investigate neurological outcomes, they are almost wholly using assessment tools that likely only crudely represent the patient's true functional status. These coarse tools are less meaningful when describing a patient's condition, and are insensitive to the varying levels of neurological functioning seen in this population. As well, follow-up times vary, with many being inappropriately premature to truly reflect best outcomes. We know that surviving patients can continue

to improve over time following arrest, and short follow-up times (for example, on discharge from hospital) can misrepresent their status. As such, even the trajectory of neurological recovery is not well described. The latter outcomes are patient-important outcomes which are poorly understood[24].

PURPOSE OF THESIS

The purpose of this thesis is to: (1) to systematically review the literature involving therapeutic hypothermia, focusing on those studies that used a control group, and especially to assess the benefit of TH on neurological outcome and survival following cardiac arrest; and (2) report on our registry that is using more sensitive and validated tools to assess neurological outcomes as well as survival of patients who are resuscitated from cardiac arrest.

REFERENCES

(1) The ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. AHA Scientific Statement: Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports. *Circulation* 2004: 110:3385-3397.

(2) Heart and Stroke Foundation of Canada. *www.heartandstroke.com.* 2015. http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm (accessed December 28, 2015).

(3) Booth C, Boone R, Tomlinson G, Desky A. Is this patient dead, vegetative, or severely neurologically impaired? *JAMA*, 2004: 291(7):870-879.

(4) Pußwald G, Fertl E, Faltl M, Auff E. Neurological rehabilitation of severely disabled cardiac arrest survivors. Part II. Life situation of patients and families after treatment. *Resuscitation*, 2000: 47;241–248.

(5) Arawwawala D, Brett S. Clinical review: Beyond immediate survival from resuscitation – long-term outcome considerations after cardiac arrest. *Critical Care*, 2007: 11:235.

(6) Beadell N, Clark W, Lutsep H, et al. Reperfusion Injury in Stroke. *Medscape*, 2015.

(7) Neumar R, Nolan J, Adrie C, et al. "ILCOR Consensus Statement: Post cardiac arrest syndrome." *Circulation*, 2008: 118: 2452-2483.

(8) Li D, Shao Z, Vanden Hoek T, Brorson J. Reperfusion accelerates acute neuronal death induced by simulated ischemia. *Exp Neurol.*, 2007: 280-287.

(9) Heart and Stroke Foundation of Canada. *www.heartandstroke.com.* 2015. https://resuscitation.heartandstroke.ca/guidelines/chain_of_survival (accessed January 18, 2016).

(10) Callaway C, Donnino M, Fink E, et al. 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care, part 8: post–cardiac arrest care. *Circulation*, 2015: S465-S482.

(11) Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*, 2013: 369:2197-2206.

(12) The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*, 2002: 346:549-556.

(13) Bernard S, Gray T, Buist M, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*, 2002: 346:557-563.

(14) Stiell IG, Nesbitt LP, Nichol G, et al. Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann Emergency Med*, 2009: 53(2):241-248.

(15) Raina K, Callaway C, Rittenberger J, Holm M. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation*, 2008: 79(2): 249–256.

(16) Rittenberger J, Raina K, Holm M, Kim Y, Callaway C. Association between Cerebral Performance Category, Modified Rankin Scale, and Discharge Disposition after Cardiac Arrest. *Resuscitation*, 2011: 82(8): 1036–1040.

(17) Schulz K, Grimes D. Generation of allocation sequences in randomized trials: chance, not choice. *The Lancet*, 2002: 359: 515–19.

(18) Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, 1988: 19(5):604-607.

(19) Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-84.

(20) Folstein M, Folstein SE, McHugh PR. "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12(3);189-198.

(21) Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med.*, 2001: 161(16):2007-2012.

(22) Gebhardt K, Guyette F, Doshi A, Callaway C, The Post Cardiac Arrest Service. Prevalence and effect of fever on outcome following resuscitation. *Resuscitation*, 2013: 1062-1067.

(23) Nielsen N, Wetterslev J, al-Subaie N, et al. Target temperature management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. *American Heart Journal*, 2012: 163(4):541–548.

(24) Guyatt G, Cairns J, Churchill D, et al. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA*, 1992: 268(17):2420-242.

Therapeutic Hypothermia for Cardiac Arrest: A Systematic Review

Meagan E Dunn, RN, BScN[a], Yazid N Al Hamarneh, BSc(Pharm), PhD[a], Trish Chatterley, MLIS[b], Ben Vandermeer, MSc[c], Ross T Tsuyuki, BSc(Pharm), PharmD, MSc[a].

[a] Department of Medicine, University of Alberta, Edmonton, Canada

[b] John W. Scott Health Sciences Library, University of Alberta, Edmonton, Canada

[c] Alberta Research Centre for Health Evidence (ARCHE), University of Alberta, Edmonton, Canada

ABSTRACT

Background Therapeutic Hypothermia (TH) is a commonly applied therapy following resuscitation from cardiac arrest. The intent of the therapy is to mitigate neurological damage that results from ischemia that occurs during the cardiac arrest, as well as to improve survival. The effect of TH on neurological outcomes is not well documented.

Objective To conduct a systematic review of TH effect on neurological outcomes in patients resuscitated from cardiac arrest.

Methods We systematically searched for all studies until March 16, 2015, which assessed adult patients resuscitated from cardiac arrest who subsequently received TH for $\geq$ 12 hours, as compared with a control group that did not receive TH. The outcome of interest was neurological outcome and survival.

Results We initially retrieved 1749 titles, and included 40 studies (17,627 patients) in our review. We found that TH was associated with more favourable neurological outcomes: RR 1.75 (95% CI 1.54, 1.99; $p<0.001$). In the 36 studies that reported on survival, the benefit of TH on survival was significant: RR 1.48 (95% CI 1.33, 1.65; $p<0.001$).

Conclusions In conclusion, this systematic review supports the use of TH in the treatment of patients resuscitated from cardiac arrest. We identified a need for more studies that are prospective in design, with longer follow-up periods and systematic evaluation of neurological outcomes.

INTRODUCTION

Improving survival is considered the main objective in the treatment of cardiac arrest. Yet, one must also consider that quality of life of cardiac arrest survivors is often severely affected following an arrest, as the patients' neurological function is impaired as a result of ischemic brain injury[1].

Therapeutic hypothermia is a treatment applied following resuscitation from cardiac arrest. The treatment reduces a patient's core temperature in a controlled manner for a defined period of time (usually 24 hours) to a target temperature in a range that is considered to be mild hypothermia (usually 32-34 °C). The intent of this treatment is to reduce the degree of cell apoptosis, stabilize the blood-brain barrier, and reduce oxygen demand and consumption[2]. This will lead to decreased damage to the brain, as well as improved survival.

In 2002, two landmark randomized controlled trials[3, 4] assessed the effect of therapeutic hypothermia on neurological outcomes in individuals who had been resuscitated from cardiac arrest. The results of these studies indicated improved neurological outcomes and survival in patients who had suffered cardiac arrest, been successfully resuscitated, and subsequently underwent therapeutic hypothermia. The results of these studies formed the basis for the inclusion of therapeutic hypothermia in the international guidelines for resuscitation, and as part of the recommended post arrest treatment approach.[5]

Therapeutic hypothermia is considered the primary treatment for neurological protection post resuscitation[6]. Since publication of the landmark trials many more studies have been reported, mostly non-randomized cohort studies. A systematic review and meta-analysis[7] included only a few trials, as there are a limited number of published randomized controlled trials in this area. None of the trials included in the aforementioned systematic review used an outcome measure which was sensitive to cognitive impairment, but rather measured dysfunction using coarse scales. As such, we sought to

determine the impact of therapeutic hypothermia on neurological outcomes using the latest and best available evidence.

OBJECTIVE

To assess the effectiveness of mild therapeutic hypothermia on neurological outcome in resuscitated cardiac arrest patients. The primary outcome was to be measured using an objective, validated tool assessing cognitive function. We also evaluated survival as a secondary outcome.

METHODS

Criteria for Studies

Types of Studies: We included all study designs that used a control group: randomized controlled trials, quasi-randomized controlled trials, retrospective cohort, and prospective cohort designs.

Participants: We included studies conducted in adult patients (≥18years) who were resuscitated from in-hospital or out-of-hospital cardiac arrest with any initial cardiac rhythm. The arrest could be either witnessed or unwitnessed, and could be of cardiac or non-cardiac origin.

Types of Interventions: Mild to moderate therapeutic hypothermia (cooling to 30-35 °C) was the intervention of interest. Induction of therapeutic hypothermia could be by any method (intravascular or surface devices), and therapy duration had to be at least 12 hours. Control groups were defined as those that did not receive therapeutic hypothermia (>35 °C).

Types of Outcome Measures: The primary outcome was attainment of a favourable neurological outcome. We assessed favourable neurological outcome as defined by the study authors, despite the fact that there were several definitions of this outcome described throughout the studies. The secondary outcome was survival.

In addition to pooling the results of all studies, we analysed results categorized as measured at ≥ 3 months after arrest, and <3 months after arrest separately. We assume that neurological outcome and survival at ≥ 3 months is important, as it is indicative of longer-term outcomes, and is meaningful to the patients and their families as it directly relates to quality of life. This follow-up period was therefore identified as adequate for purposes of quality and bias assessment.

Search Methods: With the assistance of a systematic review librarian, we identified studies by performing systematic searches of the following databases: the Cochrane Library (inception to March 2015), MEDLINE (1946-2015), EMBASE (1974-2015), CINAHL (1937-2015), and SCOPUS (inception to present).

No language restrictions were applied, and conference abstracts were excluded from the results. The initial search was performed on October 10, 2014, and was updated on March 16, 2015. See Appendix 1.

Data Collection and Analysis

Selection of Studies: All search results were imported into RefWorks. After eliminating duplicates, two reviewers independently assessed the search results to identify relevance of titles, abstracts, and full articles. Following each phase, cases of discrepancy were resolved using discussion or a third reviewer as arbiter.

Data Extraction: Two reviewers independently extracted all relevant data using a predefined form. Discrepancies were resolved using discussion or a third reviewer as arbiter. The extracted data was entered into RevMan 5.3[8].

Risk of Bias Assessment: Bias assessment was performed using the Newcastle-Ottawa Scale (NOS)[9] for Quality Assessment of cohort studies. The scale uses a star system which assesses the study in three categories: selection, comparability, and outcome ascertainment. A maximum of nine stars can be

awarded. We categorized overall study quality as low (0-3 stars), unclear (4-6 stars), and high (7-9 stars). Two reviewers independently assessed the included studies for quality, and resolved any discrepancy using discussion.

Measures of Effect: If able, we planned to combine data. If unable to combine data, we planned to dichotomise neurological outcomes as favourable vs. not favourable. We recorded data as reported by the authors within the text, tables, and figures of the studies.

We planned to calculate the Risk Ratio (RR) and 95% confidence intervals of having a favourable neurological outcome, as well as of survival, after receiving therapeutic hypothermia.

Dealing with Missing Data: We did not obtain access to individual patient data. Analysis was performed using data as presented by the authors in the articles. Pair-wise comparison was performed and outcomes were dichotomised.

Assessment of Heterogeneity: Studies were assessed for clinical and statistical heterogeneity. We inspected data for clinical heterogeneity by looking at intervention characteristics (cooling temperature and duration), participant characteristics (initial rhythm, witnessed vs. unwitnessed arrest, arrest location, cause of arrest), and the type (scale used) and timing (hospital discharge, 3 months, 6 months) of outcome measures. We assessed statistical heterogeneity using the I^2 test, categorized as low, moderate, or high (25%, 50%, or 75%).

Assessment of Reporting Bias: A funnel plot was used both visually and statistically (using Egger's test) to assess for possible publication bias.

Data Synthesis: We calculated Risk Ratio (RR) and the 95% Confidence Intervals (CI) of extracted data using RevMan 5.3. Data were pooled using a DerSimonian-Laird random-effects model.

Subgroup Analysis: We performed subgroup analyses on the following variables: study design and outcome measurement time. We could not do subgroup analysis of other variables that might be of interest (e.g., initial cardiac rhythm, witnessed vs. unwitnessed arrest), as many of the studies either did not specify or combined other relevant subgroups, and we did not have access to individual patient data.

Sensitivity Analysis: We performed sensitivity analysis by examining the studies according to their assessed quality (highest quality studies).

RESULTS

Search Results: Our initial and updated search produced 1,749 titles. After removal of duplicates and screening of the titles, abstracts, and then full text articles, 53 papers were identified for data extraction and complete review, including quality assessment. After excluding 13 of these (8 were incomplete or did not provide full breakdown of outcomes, 3 were not original data, and 2 further duplicates were found), 40 studies were included in our review. See figure 1.1 for the flow diagram of the process.

Characteristics of Included Studies: 40 studies encompassing 17,627 patients were included in the analysis. Of these, 3 were randomized controlled trials or quasi-randomized trials, 13 were prospectively designed, and 23 were retrospective analyses. Most (75%) of the studies reported neurological outcome using a Cerebral Performance Category scale (CPC) [10]. One study used the Glasgow Coma Scale (GCS) [11.] Four studies used the Glasgow Outcome Category Scale (GOC) [12]. Three studies defined favourable neurological outcome as being discharged to home or to a rehab facility. One study used the Mini Mental State Exam (MMSE) [13], and one study used the Modified Rankin Scale (MRS) [14]. See table 1.1 for detailed characteristics of included studies.

Risk of Bias Assessment: The Newcastle-Ottawa Scale (NOS) for Quality Assessment of cohort studies was used to assess the way studies addressed selection, adjusted for confounders, and assessed

outcome, including follow-up. Eighteen of 40 studies were deemed to have a high level of quality (7 or more stars). Twenty two studies had an unclear level of quality (4-6 stars), and none of the studies were of low quality (0-3 stars). Selection bias and ascertainment of exposure were not a concern with the included studies because exposed and non-exposed cohorts were easy to allocate and representative of the typical cardiac arrest. Only 4 of the included studies commented on the participants' neurological status prior to their arrest. Nearly half (47.5%) of the included studies did not comment on adjusting for possible confounders, such as gender, age, initial rhythm, duration of pulselessness, location of arrest, and other baseline characteristics. The majority of the studies had adequate outcome assessment (82.5%) and follow-up (95%) as defined by the quality assessment tool. However, only 11 of the 40 studies had an adequate follow-up period, which was predefined by the reviewers as ≥ 3 months after the arrest. See table 1.2 for details of the bias and quality assessment.

Outcomes: Outcomes were assessed and reported at varying follow-up times across the included studies. We used outcomes reported at the furthest time point from cardiac arrest, and aimed to report both primary and secondary outcomes for the same time within each study.

Primary Outcome-Favourable Neurological Outcome: Favourable neurological outcomes were reported in 2357 (37%) of those who received therapeutic hypothermia and 2,246 (20%) of those who did not receive therapeutic hypothermia. The pooled results were in favour of therapeutic hypothermia: RR 1.74 (95% CI 1.53, 1.98; $p<0.001$) (figure 1.2).

Survival: Thirty six of the 40 eligible studies reported survival. These included a total of 16,215 patients; of those, 5,505 patients received therapeutic hypothermia while 10,710 patients did not. Approximately half (48.8%) of those who received therapeutic hypothermia survived, compared to a 34.6% survival rate in those who did not receive therapeutic hypothermia: RR 1.48 (95% CI 1.33, 1.65; $p<0.001$) (figure 1.3).

Subgroup Analysis-Study Design: We conducted a subgroup analysis for randomized and quasi-randomized trials. Three studies with 1,258 patients were included in this analysis. Neurological benefit was demonstrated in 48.7% (308/632) of the patients who received therapeutic hypothermia, and 44.9% (281/626) in those who served as controls: RR 1.31 (95% CI 0.86, 1.98; p=0.21).

There were 37 non-randomized trials which included 16,348 patients. Thirty six percent (2,039/5,717) of the patients who received therapeutic hypothermia experienced neurological benefits as compared 18.4% (1,959/10,631) of the patients in the control groups: RR 1.81 (95% CI 1.59, 2.07; p<0.001).

After assessing survival data for the 3 randomized and quasi-randomized trials, we found that 328 out of 653 (50.2%) patients who received therapeutic hypothermia and 293 of 638 (45.9%) in the control group survived: RR 1.18 (95% CI 0.93, 1.48; p=0.17). While in the non-randomized studies (33 studies with 14,924 patients) survival was demonstrated in 48.6% (2,357/4,852) of the patients who received therapeutic hypothermia versus 33.9% (3,410/10,072) of controls: RR 1.52 (95% CI 1.35, 1.69; p<0.001).

Subgroup Analysis-Follow-up duration: When categorized by outcome assessment duration, 11 studies had adequate follow-up at ≥3 months. This included a total of 2,666 patients, of which 1,341 patients received therapeutic hypothermia while 1,325 did not. Around half (46.5%) of those who received therapeutic hypothermia had favourable neurological outcomes compared to just over a third (34.1%) of those who did not receive therapeutic hypothermia: RR 1.56 (95% CI 1.19, 2.04; p=0.001).

Only 10 out of the 36 studies that reported on survival had adequate follow-up duration. This included 2,580 patients. Of which, 1,288 received therapeutic hypothermia while 1,292 did not. More than half of those (51.5%) who received therapeutic hypothermia survived compared to 38.6% of those who did not receive therapeutic hypothermia: RR 1.39 (95% CI 1.11, 1.73; p=0.004).

Reporting Bias: We used a funnel plot to assess the possibility of publication bias for the primary and secondary outcomes. For favourable neurological outcome, there was strong evidence of publication bias toward studies that supported therapeutic hypothermia (Egger's test: $p < 0.0005$). When assessing the outcome of survival, there appeared to be no evidence of publication bias (Egger's test: $p= 0.15$) (figures 1.4 and 1.5).

Heterogeneity: The intervention characteristics were clinically similar across the studies. Methods were either surface or intravascular devices, and most sites used a protocol for induction of hypothermia. Although we had allowed for a target temperature range of 30-35 C, the included studies aimed for 32-34 C. All studies maintained the target temperature for at least 12 hours, with the vast majority targeting 24 hours. The reviewed studies included a wide range of baseline characteristics. Twenty four of the 40 included only out-of-hospital arrest, 1 specified in-hospital arrest only, and the rest accepted either. The majority of studies did not differentiate between witnessed and unwitnessed arrests, with only 6 specifying witnessed. Initial cardiac rhythm also generally could be shockable or non-shockable, with 6 studies identifying only shockable rhythms in their inclusion criteria. The majority of the reviewed studies (75%) used the Cerebral Performance Category scale as an outcome assessment tool. Only one study used a validated tool that was sensitive to cognitive dysfunction (Mini Mental State Examination). Sixty three percent of the studies assessed outcomes at discharge from ICU or hospital. Only 11 studies had adequate follow-up periods as defined by the reviewers.

There was a high amount of overall statistical heterogeneity among the studies for both outcomes (I-squared ≥ 75%). This persisted when subgroup analysis was conducted. However, despite the heterogeneity of the included studies, when looking at the Forest plots, there is an obvious trend towards improved neurological outcomes and survival rates in patients who receive therapeutic hypothermia after resuscitation from cardiac arrest (figures 1.2 and 1.3).

DISCUSSION

Our systematic review of 40 studies including almost 18,000 patients demonstrates a statistically significant increase in favourable neurological outcomes for patients who received therapeutic hypothermia after resuscitation from cardiac arrest, when compared to patients who did not receive the therapy. There was also a statistically significant reduction in mortality for this group of patients. Using a broad approach to evaluate all available data, we included data from 40 studies that included cohorts of patients receiving therapeutic hypothermia and controls. Therapeutic hypothermia was associated with favourable neurological outcomes in 36 of those studies, whilst it was associated with higher survival rate in 32 out of 36 studies which reported survival rates. Taken together, our results confirm the beneficial effect of therapeutic hypothermia in survivors of cardiac arrest.

These findings are consistent and add to an older systematic review and meta-analysis of 5 randomized and quasi-randomized controlled trials by Arrich et al., who reported improved neurological outcome and survival in patients who received therapeutic hypothermia following successful resuscitation from cardiac arrest.

The decision to include any study which used a control group creates some limitations when interpreting the results of this review. Statistical heterogeneity was present in all outcome assessments of the pooled data. As such, the methodological quality of the included studies was variable. Over half were retrospective analyses, and only 3 randomized controlled trials were included. When looking at the study design subgroup analysis, the effect of therapeutic hypothermia seems to be less significant when looking at the randomized and quasi-randomized controlled trials group. This was the case for both the primary and secondary outcomes and is not unexpected. Only 18 of the included studies were assessed as being of high quality, leaving over half of the studies as either low or unclear quality. Although the baseline characteristics of the populations were comparable and the intervention methods were similar

across all of the studies, the outcome measures varied in their definition of favourable neurological outcome and follow up time. Our review included data as reported in the published papers, as we did not have access to individual patient data. By conducting a systematic review of all studies that include a control group, we were able to look at a much larger pool of data. This represents a variety of approaches to the therapy, which is clinically relevant as it reflects real world experiences (perhaps with higher external validity) with therapeutic hypothermia. As well, the large number of included studies in our review yielded a large number of total patients (17,627), which increases generalizability.

This literature review identified areas where improvement in the available evidence may be indicated, and so we recommend that future studies in therapeutic hypothermia should use prospective design, a longer follow up period, and a more sensitive tool for assessment of neurological outcomes (such as the Mini Mental State Examination), as those would likely provide more meaningful results and better indication of the quality of life of cardiac arrest survivors.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests None

Contributors MD, YA, and RT contributed to the conception and the design of the review. MD, YA, and TC contributed to the acquisition of the data. MD and YA contributed to the extraction and assessment of the data. BV provided statistical advice. MD, YA, and RT critically reviewed and revised the manuscript for intellectual content. TC and BV reviewed the manuscript.

Figure 1.1: Search Process

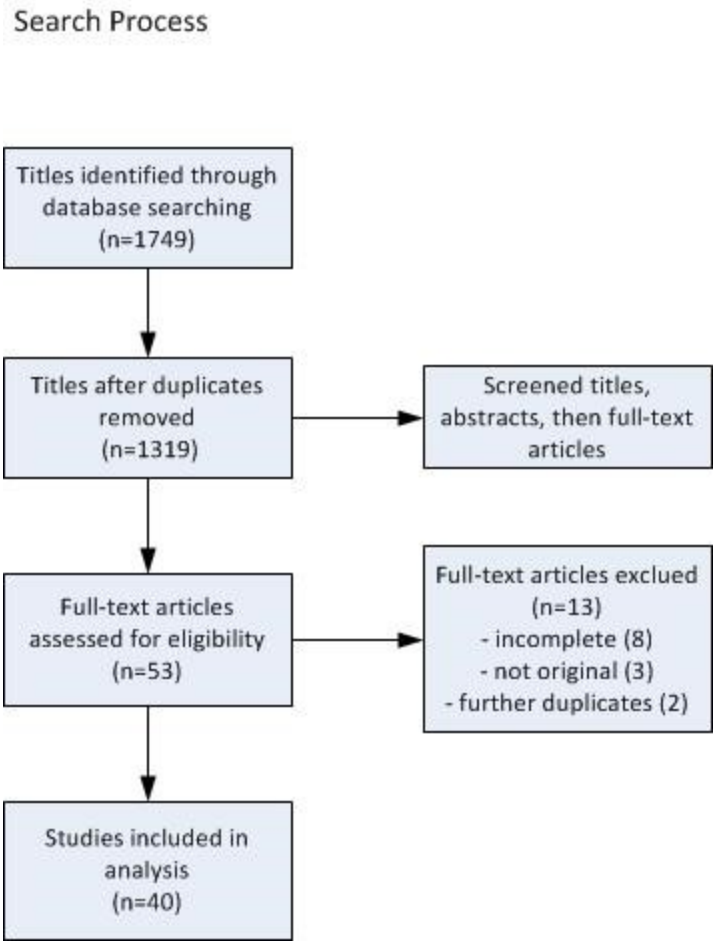


Figure 1.2: All Studies, Therapeutic Hypothermia (TH) versus No Therapeutic Hypothermia (No TH). Outcome: Favourable Neurological Outcome.

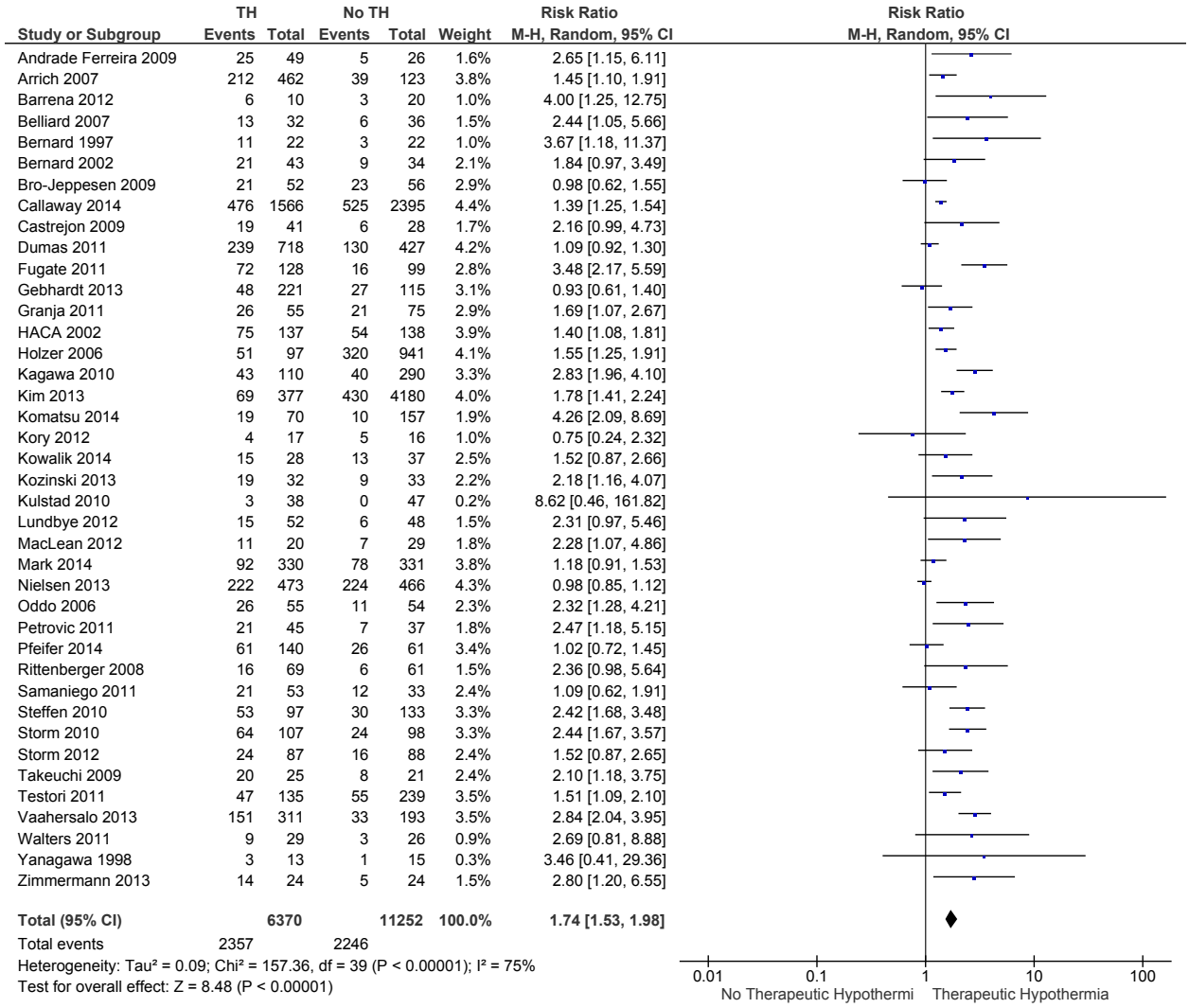


Figure 1.3: All Studies, Therapeutic Hypothermia (TH) versus No Therapeutic Hypothermia (No TH).

Outcome: Survival.

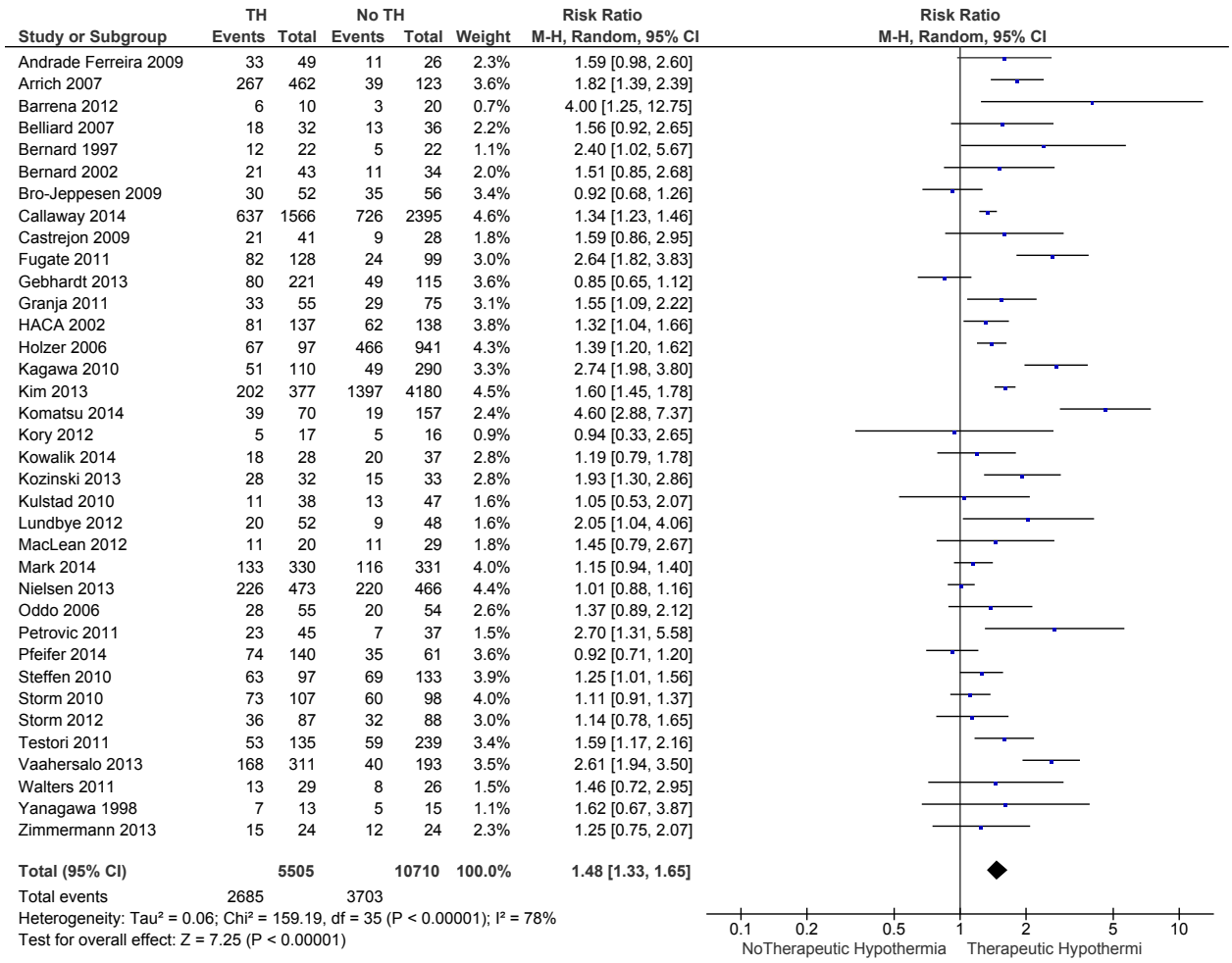


Figure 1.4: Funnel Plot for Favourable Neurological Outcome.

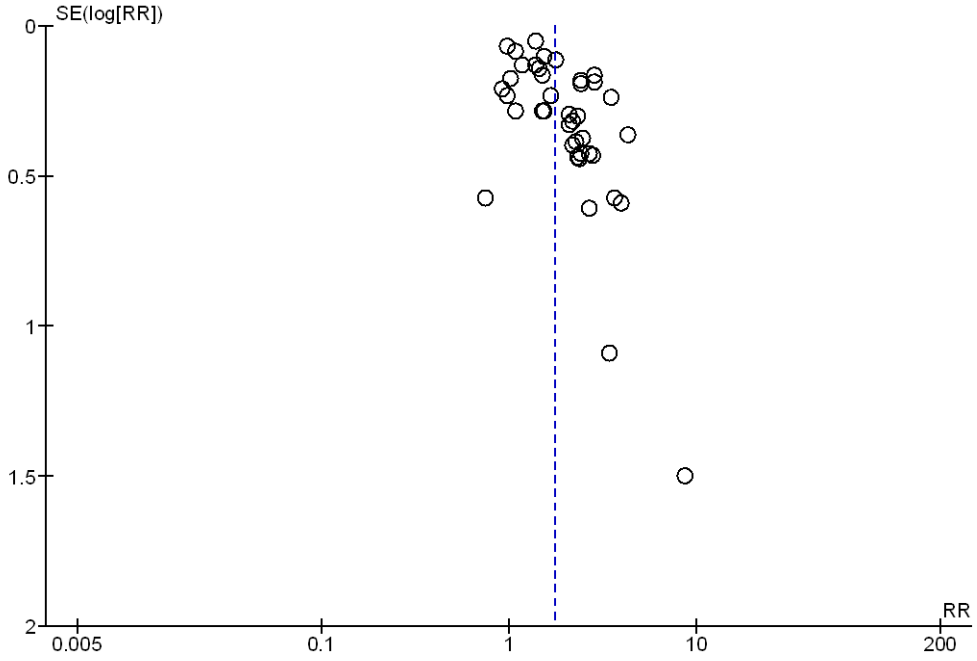


Figure 1.5: Funnel Plot for Survival.

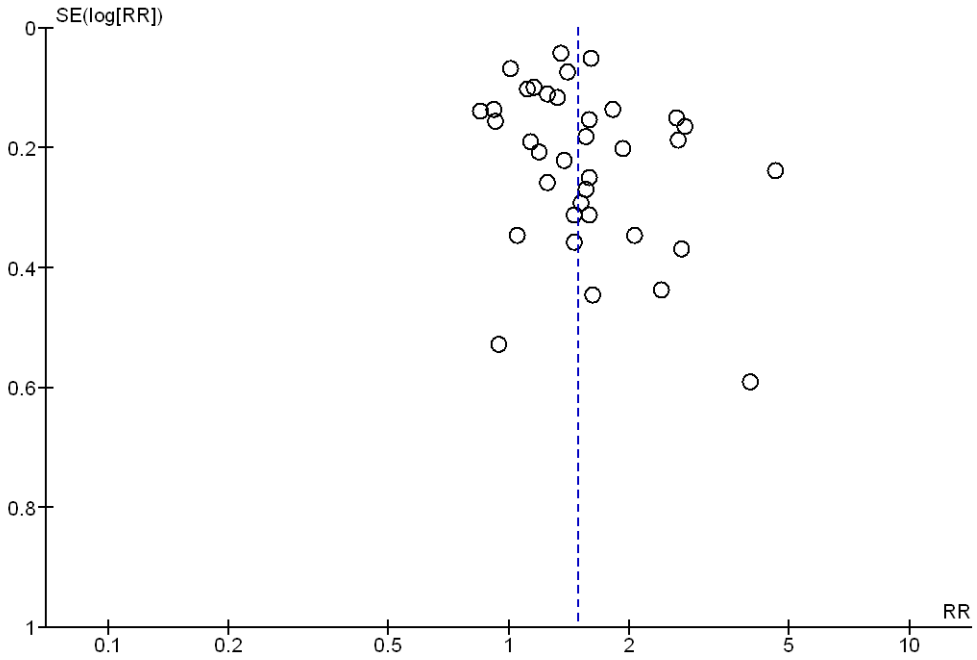


Table 1.1: Characteristics of Included Studies.

Primary Author & Publication Year	Study Design	Cause of Arrest	Location	Witnessed/ Unwitnessed Arrest	Initial Rhythm	Favourable Neurological Outcome Measure & Time	Total Participants (n)	Cooled (n)	Not cooled (n)	Survival Reported	Study Quality
Andrade Ferreira 2009[15]	Retrospective analysis	Cardiac	OHCA	NS	Any	CPC 1-2 Discharge	75	49	26	Yes	6
Arrich 2007[16]	Registry	Any	Any	Any	Any	CPC 1-2 Discharge	587	462	123	Yes	5
Barrrena Oceja 2012[17]	Retrospective analysis	Any	Any	Any	Any	CPC 1-2 NS	30	10	20	Yes	4
Belliard 2007[18]	Retrospective analysis	Any	OHCA	Witnessed	VF	GOC >6 month	68	32	36	Yes	7
Bernard 2002[3]	Quasi-randomized control trial	Cardiac	OHCA	Any	VF	Discharge to home or rehab	77	43	34	Yes	7
Bernard 1997[19]	Prospective with historical control	NS	OHCA	Any	Any	GOC 1-2 Discharge	44	22	22	Yes	5
Bro-Jeppesen 2008[20]	Prospective with historical control	NS	OHCA	Any	Any-only assessed VF/VT for neuro	MMSE >24 6 month	108	52	56	Yes	7
Callaway 2014[21]	Randomized control trial	NS	OHCA	Any	Any	MRS <3 discharge	3981	1566	2395	Yes	7
Castrejon 2009[22]	Retrospective analysis	NS	Any	NS	VF/VT	CPC 1-2 6 month	69	41	28	Yes	8
Dumas 2011[23]	Prospective with historical control	Any	OHCA	Any	Any	CPC 1-2 Discharge	1145	718	427	No	7
Fugate 2011[24]	Retrospective analysis	Any	Any	NS	Any	CPC1-2 Discharge	227	128	99	Yes	4
Gebhardt 2013[25]	Prospective	NS	Any	NS	Any	Discharge home or to rehab	336	221	115	Yes	7
Granja 2011[26]	Retrospective analysis	Any	Any	Any	Any	CPC 1-2 6 months	130	55	75	Yes- at discharge	4
Holzer 2006[27]	Retrospective analysis	Any	Any	Witnessed	Any	CPC 1-2 30 days	1038	97	941	Yes	7
HACA 2002[4]	Randomized control trial	Any	OHCA	Witnessed	VF/VT	CPC 1-2 6 months	275	137	138	Yes	8
Kagawa 2010[28]	Retrospective analysis	Cardiac	OHCA	Witnessed	Any	CPC 1-2 Discharge	400	110	290	Yes	8
Kim 2013[29]	Retrospective analysis	Cardiac	OHCA	Any	Any	CPC 1-2 Discharge	4557	377	4180	Yes	7
Komatsu 2013[30]	Retrospective analysis	Cardiac	OHCA	Any	Any	CPC 1-2 Discharge	227	70	157	Yes	7

Primary Author & Publication Year	Study Design	Cause of Arrest	Location	Witnessed/ Unwitnessed Arrest	Initial Rhythm	Favourable Neurological Outcome Measure & Time	Total Participants (n)	Cooled (n)	Not cooled (n)	Survival Reported	Study Quality
Kory 2012[31]	Retrospective analysis	NS	IHCA	Any	Any	CPC 1-2 Discharge	33	17	16	Yes	6
Kowalik 2014[32]	Retrospective analysis	NS	OHCA	NS	Any	GCS ≥ 13 6 months	65	28	37	Yes	6
Kozinski 2013[33]	Retrospective analysis	NS	OHCA	NS	Any	CPC 1-2 Discharge	65	32	33	Yes	8
Kulstad 2010[34]	Retrospective analysis	NS	OHCA	Any	Any	CPC 1-2 Discharge	85	38	47	Yes	5
Lundbye 2012[35]	Retrospective analysis	NS	Any	Any	PEA/ Asystole	CPC 1-2 Discharge	100	52	48	Yes	7
MacLean 2012[36]	Retrospective analysis	Cardiac	OHCA	NS	Any	CPC 1-2 Discharge	49	20	29	Yes	5
Mark 2014[37]	Retrospective analysis	Any	OHCA	Any	Any	CPC 1-2 discharge	660	330	331	Yes	5
Nielsen 2013[38]	Randomized control trial	Cardiac	OHCA	Any	Any	CPC 1-2 6 months	939	473	466	Yes	8
Oddo 2006[39]	Retrospective analysis	NS	OHCA	NS	Any	CPC 1-2 Discharge	109	55	54	Yes	5
Petrovic 2011[40]	Prospective	NS	OHCA	NS	VF	CPC 1 30 days	82	45	37	Yes	4
Pfeifer 2014[41]	Retrospective analysis	NS	Any	Witnessed	Any	CPC 1-3 1 month	201	140	61	Yes	4
Rittenberger 2008[42]	Retrospective analysis	NS	Any	NS	Any	Discharge home or to rehab	130	69	61	No	5
Samaniego 2010[43]	Prospective	Any	Any	NS	Any	GOC 3-5 3 months	86	53	33	No	5
Steffen 2010[44]	Prospective with historical control	Any	Any	NS	Any	CPC 1-2 Discharge	230	97	133	Yes	5
Storm 2010[45]	Prospective with historical control	Any	Any	NS	VF	CPC 1-2 Discharge from ICU	205	107	98	Yes	5
Storm 2012[46]	Prospective with historical control	Any	Any	NS	PEA/ asystole	CPC 1-2 Discharge from ICU	175	87	88	Yes	5
Takeuchi 2009[47]	Prospective with historical control	NS	OHCA	Any	VF	CPC 1-2 Discharge from ICU	46	25	21	No	5
Testori 2011[48]	Retrospective analysis	Any	OHCA	Witnessed	PEA/ asystole	CPC 1-2 6 months	374	135	239	Yes	9
Vaahersalo 2013[49]	Prospective	Any	OHCA	Any	Any	CPC 1-2 1 year	504	311	193	Yes	8
Walters 2011[50]	Prospective with historical control	NS	OHCA	NS	Any	CPC 1-2 Discharge	55	29	26	Yes	5

Primary Author & Publication Year	Study Design	Cause of Arrest	Location	Witnessed/ Unwitnessed Arrest	Initial Rhythm	Favourable Neurological Outcome Measure & Time	Total Participants (n)	Cooled (n)	Not cooled (n)	Survival Reported	Study Quality
Yanagawa 1998[51]	Prospective with historical control	Any	OHCA	Any	Any	GOC 1 Discharge	28	13	15	Yes	5
Zimmermann 2013[52]	Retrospective analysis	Cardiac	OHCA	Witnessed	Any	CPC 1-2 1 year	48	24	24	Yes	7

Legend: **NS** – Not Specified; **OHCA** – Out-of-hospital cardiac arrest; **IHCA** – In-hospital cardiac arrest; **VF** – Ventricular fibrillation; **VT** – Ventricular tachycardia; **PEA** – Pulseless electrical activity; **CPC** – Cerebral performance category; **GOC** – Glasgow outcome category; **MMSE** – Mini Mental State Examination; **MRS** – Modified Rankin Scale. Study Quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies (NOS). The reviewers have assessed risk of bias as low (score of 7-9), unclear (score of 4-6), or high (score of 0-3).

Table 1.2: Bias and Quality Assessment Details

Study	Selection (4)	Comparability (2)	Outcome (3)	Total (9)
Andrade Ferreira 2009	3	1	3	6
Arrich 2007	3	0	2	5
Barrrena Oceja 2012	2	0	2	4
Belliard 2007	3	2	2	7
Bernard 2002	3	2	2	7
Bernard 1997	3	0	2	5
Bro-Jeppesen 2008	3	2	2	7
Callaway 2014	3	2	2	7
Castrejon 2009	3	2	3	8
Dumas 2011	3	2	2	7
Fugate 2011	3	0	1	4
Gebhardt 2013	3	2	2	7
Granja 2011	3	0	1	4
Holzer 2006	3	2	2	7
HACA 2002	3	2	3	8
Kagawa 2010	4	2	2	8
Kim 2013	3	2	2	7
Komatsu 2013	3	2	2	7
Kory 2012	4	0	2	6
Kowalik 2014	3	0	3	6
Kozinski 2013	4	2	2	8
Kulstad 2010	3	0	2	5
Lundbye 2012	3	2	2	7
MacLean 2012	3	0	2	5
Mark 2014	3	0	2	5
Nielsen 2013	3	2	3	8
Oddo 2006	3	0	2	5
Petrovic 2011	3	0	1	4
Pfeifer 2014	3	0	1	4
Rittenberger 2008	3	0	2	5
Samaniego 2010	3	0	2	5
Steffen 2010	3	0	2	5
Storm 2010	3	0	2	5
Storm 2012	3	0	2	5
Takeuchi 2009	3	0	2	5
Testori 2011	4	2	3	9
Vaahersalo 2013	3	2	3	8
Walters 2011	3	0	2	5
Yanagawa 1998	3	0	2	5
Zimmermann 2013	3	2	2	7

REFERENCES

(1) Geocadin RG, Koenig MA, Jia X, Stevens RD, Peberdy MA. Management of brain injury after resuscitation from cardiac arrest. *Neurol Clin* 2008;26(2):487-506.

(2) Liu L, Yenari M. Therapeutic hypothermia: neuroprotective mechanisms. *Frontiers in Bioscience* 2007;12:816-825.

(3) Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;21;346(8):557-563.

(4) The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New Engl J Med* 2002;346(8):549-556.

(5) Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation* 2010;81:1219-1276.

(6) Mongardon N, Dumas F, Ricome S, et al. Postcardiac arrest syndrome from immediate resuscitation to long-term outcome. *Ann Intensive Care* 2011;1:45

(7) Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2012; Issue 9.

(8) Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

(9) Wells G, Shea B, O'Connell D, et al. The Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2012. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on November 14, 2014.

(10) Stiell IG, Nesbitt LP, Nichol G, et al. Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann Emergency Med* 2009;53(2):241-248.

(11)Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-84.

(12)Jennet B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet* 1975;1(7905):480-4.

(13)Folstein M, Folstein SE, McHugh PR. "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3);189-198.

(14)Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19(5):604-607.

(15)Andrade Ferreira I, Schutte M, Oosterloo E, et al. Therapeutic mild hypothermia improves outcome after out-of-hospital cardiac arrest. *Netherlands Heart Journal* 2009;17(10):378-384.

(16)Arrich J, European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007;35(4):1041-1047.

(17)Barreña Oceja I, Gil Martín FJ, García de Vicuña Meléndez A, Rodríguez Delgadillo MA, Gutiérrez Herrador G, Vázquez Naveira MP. Results of using a therapeutic hypothermia protocol after cardiac arrest: Design and application by an emergency medical service and a hospital emergency department. *Emerg* 2012;24(1):39-43.

(18)Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation* 2007;75(2):252-259.

(19)Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med* 1997;30(2):146-153.

(20)Bro-Jeppesen J, Kjaergaard J, Horsted TI, et al. The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. *Resuscitation* 2009;80(2):171-176.

(21)Callaway CW, Schmicker RH, Brown SP, et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. *Resuscitation* 2014;85:657-663.

(22)Castrejon S, Cortes M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. *Rev Esp Cardiol* 2009;62(7):733-741.

(23)Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. *Circulation* 2011;123(8):877-886.

(24)Fugate JE, Wijdicks EF, White RD, Rabinstein AA. Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors? *Neurology* 2011;77(14):1346-1350.

(25)Gebhardt K, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC. Post Cardiac Arrest Service. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation* 2013;84(8):1062-1067.

(26)Granja C, Ferreira P, Ribeiro O, Pina J. Improved survival with therapeutic hypothermia after cardiac arrest with cold saline and surfacing cooling: Keep it simple. *Emerg Med Int* 2011.

(27)Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke* 2006;37(7):1792-1797.

(28)Kagawa E, Inoue I, Kawagoe T, et al. Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. *Crit Care* 2010;14

(29)Kim JY, Shin SD, Ro YS, et al. Post-resuscitation care and outcomes of out-of-hospital cardiac arrest: a nationwide propensity score-matching analysis. *Resuscitation* 2013;84(8):1068-1077.

(30)Komatsu T, Kinoshita K, Sakurai A, et al. Shorter time until return of spontaneous circulation is the only independent factor for a good neurological outcome in patients with postcardiac arrest syndrome. *Emerg Med J* 2014;31(7):549-555.

(31)Kory P, Fukunaga M, Mathew JP, et al. Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. *Neurocrit Care* 2012;16(3):406-412.

(32)Kowalik R, Szczerba E, Koltowski L, et al. Cardiac arrest survivors treated with or without mild therapeutic hypothermia: performance status and quality of life assessment. *Scand J Trauma Resusc Emerg Med* 2014;22:76.

(33)Kozinski M, Pstragowski K, Kubica JM, et al. ACS network-based implementation of therapeutic hypothermia for the treatment of comatose out-of-hospital cardiac arrest survivors improves clinical outcomes: The first European experience. *Scand J Trauma Resusc Emerg Med* 2013;21(1).

(34)Kulstad CE, Holt SC, Abrahamsen AA, Lovell EO. Therapeutic hypothermia protocol in a community emergency department. *West J Emerg Med* 2010;11(4):367-372.

(35)Lundbye JB, Rai M, Ramu B, et al. Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. *Resuscitation* 2012;83(2):202-207.

(36)Maclean DA, Stevenson RS, Bata I, Green RS. Therapeutic hypothermia for out-of-hospital cardiac arrest: An analysis comparing cooled and not cooled groups at a Canadian center. *J Emerg Trauma Shock* 2012;5(4):328-332.

(37)Mark DG, Vinson DR, Hung Y, et al. Lack of improved outcomes with increased use of targeted temperature management following out-of-hospital cardiac arrest: A multicenter retrospective cohort study. *Resuscitation* 2014;85:1549-1556.

(38)Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *New Engl J Med* 2013;369:2197-2206.

(39)Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* 2006;34(7):1865-1873.

(40)Petrovic M, Panic G, Jovelic A, et al. Therapeutic hypothermia and neurological outcome after cardiac arrest. *Vojnosanii Pregl* 2011;68(6):495-499.

(41)Pfeifer R, Franz M, Figulla HR. Hypothermia after cardiac arrest does not affect serum levels of neuron-specific enolase and protein S-100b. *Acta Anaesthesiol Scand* 2014;58(9):1093-1100.

(42)Rittenberger JC, Guyette FX, Tisherman SA, DeVita MA, Alvarez RJ, Callaway CW. Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. *Resuscitation* 2008;79(2):198-204.

(43)Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit Care* 2011;15(1):113-119.

(44)Steffen I G, Hasper D, Ploner CJ, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care* 2010;14.

(45)Storm C, Nee J, Krueger A, Schefold JC, Hasper D. 2-year survival of patients undergoing mild hypothermia treatment after ventricular fibrillation cardiac arrest is significantly improved compared to historical controls. *Scand J Trauma Resusc Emerg Med* 2010;18(1).

(46)Storm C, Nee J, Roser M, Jorres A, Hasper D. Mild hypothermia treatment in patients resuscitated from non-shockable cardiac arrest. *Emerg Med J* 2012;29(2):100-103.

(47)Takeuchi I, Takehana H, Satoh D, et al. Effect of hypothermia therapy after outpatient cardiac arrest due to ventricular fibrillation. *Circ J* 2009;73(10):1877-1880.

(48)Testori C, Sterz F, Behringer W, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation* 2011;82(9):1162-1167.

(49)Vaahersalo J, Hiltunen P, Tiainen M, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med* 2013;39(5):826-837.

(50)Walters EL, Morawski K, Dorotta I, et al. Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after out-of-hospital cardiac arrest: A feasibility study. *Shock* 2011;35(4):360-366.

(51)Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation* 1998;39(1-2):61-66.

(52)Zimmermann S, Flachskampf FA, Schneider R, et al. Mild therapeutic hypothermia after out-of-hospital cardiac arrest complicating ST-elevation myocardial infarction: long-term results in clinical practice. *Clin Cardiol* 2013;36(7):414-421.

APPENDIX 1

We searched using the following terms:

"induced hypothermia" or "therapeutic hypothermia" or "resuscitative hypothermia" or "mild hypothermia" or "moderate hypothermia" or "therapeutic temperature management" or "brain cooling" or "cooling helmet" or "cooling blanket" or "surface cooling" or "intravascular cooling" or "cooling method".

"cardiac arrest", "heart arrest", "sudden cardiac death", "cardiopulmonary arrest",

"randomized", "placebo", "randomly", "trial", "groups", "quasi-random", "match", "cohort".

NOT "animal" or "porcine" or "rats" or "rabbits" or "dogs" or "swine" or "mice" or "monkeys"

The Therapeutic Hypothermia for Cardiac Arrest Registry: The "Cool" Registry

Meagan E Dunn, RN, BScN[a], Yazid N Al Hamarneh, BSc(Pharm), PhD[a], Michael Chan, MD, MBBS, FRCPC[a], Ross T Tsuyuki, BSc(Pharm), PharmD, MSc[a].

[a] Department of Medicine, University of Alberta, Edmonton, Canada

ABSTRACT

Background Therapeutic Hypothermia (TH) is a commonly applied therapy following resuscitation from cardiac arrest. The goal of TH is to reduce neurological damage that results from anoxic and reperfusion injury due to the cardiac arrest, as well as to improve survival. Measurements of neurological outcomes tend to use coarse tools and short durations of follow-up.

Objective To create a prospective registry of cardiac arrest survivors, and to determine the effect of TH on neurological outcomes in patients who received TH and those who did not.

Methods We enrolled all patients resuscitated from cardiac arrest that remained unresponsive and were admitted to the Cardiac Care Unit and the Intensive Care Unit at the Royal Alexandra Hospital in Edmonton, Canada between March 2014 and August 2015. The outcomes of interest were neurological outcome and survival. We assessed neurological outcomes up to 6 months following the arrest, using multiple tools, primarily the Montreal Cognitive Assessment (MoCA) test.

Results We enrolled 110 patients over 1.5 years. We found that TH was associated with continuing improvements in neurological functioning over the follow-up period. The MoCA test measured a mean improvement of 3.3 (SD 2.60) and 4.3 (SD 4.72) points (out of 30) at 3 months and 6 months following arrest respectively, for those who received TH. Those who received TH also had a decreased hazard of death compared to the no TH group, HR 0.39 (95% CI 0.24, 0.64; p=0.0006).

Conclusions In conclusion, this registry supports the use of TH in the treatment of patients resuscitated from cardiac arrest. Clinicians should consider the use of multiple validated tools for evaluation of neurological outcomes which are sensitive to cognitive dysfunction. We encourage more studies that are prospective in design, using long follow-up periods, and comparing different targeted temperatures.

INTRODUCTION

It is estimated that 40,000 people fall victim to cardiac arrest annually in Canada[1]. Very few of these patients survive to hospital discharge, and many will suffer from some degree of neurological damage from the arrest. The neurological damage experienced following a cardiac arrest is due to the initial anoxic event as well as reperfusion injury. This includes many mechanisms such as oxygen free radical production, blood brain barrier destabilization, cerebral edema, and high cerebral oxygen demand[2].

Therapeutic Hypothermia (TH) is recommended for patients following resuscitation from cardiac arrest[3]. The purpose of TH is to decrease the burden of neurological damage resulting from the ischemic event. TH is a controlled lowering of a person's core body temperature to induce a mild hypothermia, historically in the 32-34 °C range. The patient is maintained in this range for approximately 24 hours, and then slowly and in a controlled manner, is rewarmed to normal body temperature.

The evidence for TH has largely been driven by 2 landmark trials published in 2002. The Hypothermia after Cardiac Arrest Study Group (HACA) [4] was a randomized trial that looked at 275 subjects who suffered arrest with shockable initial rhythms, mainly out-of-hospital cardiac arrests. Patients were randomized to receive TH or standardized care. Neurological improvement was measured using the 5-point Cerebral Performance Category (CPC) scale[5], which ranges from good cerebral performance to brain death. The authors defined a CPC score of 1 or 2 as a good outcome. After 6 months, they found better neurological outcomes (CPC score of 1 or 2) for patients who received TH for 24 hours, compared to the control group that did not (RR 1.40; 95 percent confidence interval, 1.08 to 1.81; p=0.009), as well as improved mortality for the TH group (RR 0.74; 95 percent confidence interval, 0.58 to 0.95; p=0.02). In a simultaneous publication, Bernard, et al[6] reported on a quasi-randomized trial that followed 77 out-of-hospital cardiac arrest patients with initial shockable rhythm. The intervention group received TH for

12 hours, and the control group received the standard care. At discharge from hospital, the TH group had more "good" outcomes (defined as discharge to either home or to a rehab facility) than the control group (adjusted OR=5.25; 95 percent confidence interval, 1.47 to 18.76), although mortality was not significantly different. Both studies were relatively small and used crude measures of assessment for neurological outcomes.

A Cochrane review published in 2012[7] aimed to review the current literature and pool the evidence for TH after cardiac arrest. This review included 4 studies and 1 abstract. The authors' analysis of 3 of the included studies which used conventional methods and were of good quality used individual patient data, and demonstrated that patients who received TH achieved better neurological outcomes (defined as good or bad, using measures as described by the authors of the included studies) (RR 1.55; 95% CI 1.22 to 1.96; p<0.001), and better survival to hospital discharge (RR 1.35; 95% CI 1.10 to 1.65; p<0.01). Dunn, et al also performed an updated systematic review, looking at neurological outcomes and mortality for patients who receive TH following cardiac arrest, compared to a control group who did not. This review included 40 studies, 3 of which were randomized controlled trials, which applied TH for at least 12 hours to patients with any initial rhythm and location of arrest. The pooled results were more favourable neurological outcomes (defined by the criteria used in each included study) (RR 1.74; 95% CI 1.53, 1.98; p<0.001) and improved survival (RR 1.48; 95% CI 1.33, 1.65; p<0.001) for the TH cohort.

The eventual neurologic status of a patient who survives cardiac arrest has a direct impact on quality of life following the event. Although survival is undeniably an important outcome, neurological outcomes are exceedingly relevant to the patient and their family as direct determinants of quality of life. To survive the event only to be left vegetative or severely dependent is an outcome that many would likely not choose given the option. Most studies that have looked into neurological functioning following

cardiac arrest have used coarse scales to measure this. Commonly used is the 5-point Cerebral Performance Category (CPC) scale[5]. Because these assessment tools are insensitive to cognition[8], the true burden of neurological dysfunction following cardiac arrest is likely not fully appreciated. The experience of quality of life as it relates to neurological function is not so easily classified into 5 categories. Moreover, the CPC scale as used in previous studies has not been validated for the cardiac arrest population, and so may not be optimal when assessing outcomes in these patients. In addition, follow up times are often short, with many studies only following until hospital discharge. This likely does not provide a very accurate representation of how the patient will be at their fullest recovery point (which may be well after hospital discharge). Finally, the trajectory of neurologic recovery after resuscitated cardiac arrest has not been well described.

Given the limitations of previous studies looking at neurological recovery, we developed a prospective registry of cardiac arrest survivors, including patients who received TH and as well as those who did not, in order to determine the impact of TH on neurological outcomes and survival. Herein we report the results of the registry after 1.5 years of enrolment.

METHODS

Objectives

The purpose of this study is to evaluate the effect of therapeutic hypothermia on the neurological outcomes in cardiac arrest patients. The primary objective was to evaluate neurological outcomes using the Montreal Cognitive Assessment (MoCA) tool[9]. Secondary objectives were to assess neurological outcomes using the CPC scale and the Modified Rankin Scale (MRS)[10]. We also aimed to evaluate the effect of therapeutic hypothermia on the survival rates of cardiac arrest patients (Tables 2.1, 2.2, and 2.3).

Study Design and Setting

This was a prospective registry conducted at the Royal Alexandra Hospital in Edmonton, Alberta, Canada from March 2014 to August 2015. The Royal Alexandra Hospital is a tertiary care hospital that provides services to a large population and geographical area, as it is the largest northernmost centre to provide cardiac angiography and intervention in Northern Alberta, as well as serving the Northwest Territories, Yukon, and Northern British Columbia.

Inclusion and Exclusion

Patients included in this registry were those adults 18 years or over who had been resuscitated from cardiac arrest and were admitted to either the Cardiac Care Unit (CCU) or the Intensive Care Unit (ICU) at the Royal Alexandra Hospital, including both in-hospital and out-of-hospital cardiac arrest. We included patients with any initial rhythm whether shockable or not. We included patients with an initial Glasgow Coma Scale[11] (GCS) of less than or equal to 13 and not rapidly improving. The time from cardiac arrest to return of spontaneous circulation (ROSC) had to be less than or equal to 90 minutes. Induced hypothermia may or may not have been prescribed. Exclusion criteria to enrolment in the registry were: a body temperature below 30 °C; patient comatose before the arrest; patient responsive to verbal commands; patient terminally ill before the arrest; or pre-existing cognitive or psychiatric disorders which would preclude the administration of the Montreal Cognitive Assessment (MoCA) tool, which was the primary assessment of interest.

Induced Hypothermia Process

The patients' body temperature was lowered to a temperature prescribed by the attending physician. The hypothermia process followed the cooling patient care order set used at the Royal Alexandra Hospital. This includes: administration of analgesia and sedation, as well as neuromuscular blocking

agents; application of the Arctic Sun®2000 or 5000 (Medivance Corp, Louisville, Co.) temperature control device, which uses surface cooling to lower the patient's core temperature; administration of cooled (4 °C) intravenous fluids; continuous end tidal CO2 monitoring with hourly pupil checks; a minimum of every four hours monitoring of basic neurological assessments, arterial blood gases, and electrolytes. Once goal temperature was reached, the temperature was maintained as per the physician discretion. This was almost exclusively for 24 hours. Following the active cooling phase, the re-warming phase began by setting the Arctic Sun to increase the patient's temperature by 0.5 °C per hour. Once normothermia was reached (36 °C) neuromuscular blocking agents were stopped, and sedation and analgesic titrated down to allow for assessment of neurological status. Formal assessment by neurology service was requested at 72 hours following arrest in those patients who did not self-declare full neurological recovery within this time.

Generally at the RAH the goal temperature is 32-34 °C. Occasionally a physician may decide on a different target temperature below 37 °C, usually in the 36 to 37 °C range. Although not the typical standard of care at the RAH for TH, we included these patients in a separate cohort which utilized Targeted Temperature Management (TTM), a term adopted following the publication of a study by Nielsen, et al[12], which investigated temperature ranges for TH that were broader than 32-34 °C. The use of temperatures outside of the standard 32-34 °C began at the RAH in April 2014.

Follow-up and Outcomes

Primary Outcome: We used the Montreal Cognitive Assessment (MoCA) score[9], a well-validated neurological screening tool that is sensitive to mild cognitive impairment. The MoCA tests major cognitive domains, is precise and specific, and scores people out of 30 possible points based on their written and verbal responses to questions. A resulting score of ≥26 points is considered normal cognitive

function. Mild cognitive impairment is associated with a score between 18 and 25, moderate cognitive impairment is 10-17, and less than 10 points is considered severe cognitive impairment. Our primary outcome of interest was the difference in the change of the MoCA score between the first MoCA score obtained (baseline) and 3 months following arrest, comparing patients who were treated with TH and those who were not.

Assessment of outcomes was conducted at 4 time points for enrolled patients. A different version of the MoCA test was used at each time point to reduce the possibility of learning effect and recall bias due to repeating the test frequently. These times were: at decision to discharge from the critical care area (version 7.1); decision to discharge from hospital (version 7.2); 3 months following the arrest (version 7.3); and 6 months following the arrest (repeat version 7.1).

Secondary Outcomes: The difference in the change of the MoCA score between the first MoCA score obtained and 6 months following arrest was assessed as a secondary outcome, comparing those who received TH and those who did not.

Secondary outcomes included the Cerebral Performance Category (CPC) score and the Modified Rankin Scale (MRS) score[10]. The CPC and MRS are commonly used scales for neurological status, although they are not very sensitive to cognitive dysfunction. The CPC is a 5-point scale that ranges from CPC 1 (good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit) to CPC 5 (brain death: apnea, areflexia, EEG silence, etc.) and was used in the pivotal HACA trial[4]. The MRS focuses more on functional ability than the CPC, and is a 7-point scale that ranges from MRS 0 (no symptoms at all) to MRS 6 (dead). The difference in the change of the CPC and MRS scores between the first score obtained and 3 months following arrest were compared, for patients who received TH and those who did not. This was compared again at 6 months following arrest.

We evaluated mortality using survival analysis at 3 and 6 months in patients who were treated with TH and those who were not.

Data Collection

Data was collected using a data collection form in the "Utstein style"[13], and obtained from hospital records. Data was collected and managed using REDCap electronic data capture tools hosted at the University of Alberta[14]. Data collection, consent obtainment, and outcomes assessment was performed by trained study registered nurses under the supervision of the Principal Investigator and the study coordinator.

Third party consent by the next of kin was obtained prior to any assessment that was outside of the standard of care, since the patients were initially comatose. Waiver of consent was used in cases where assessment results were available as part of the usual standard of care. Subject consent was sought from all patients who survived and were able, at whatever assessment point this became evident.

This study had administrative and operational approval from Alberta Health Services, as well as ethics approval from the Health Research Ethics Board at the University of Alberta.

Statistical Analysis

Statistical analysis was performed using Small Stata® version 14.0 for Windows (StataCorp, College Station, Texas). Data are presented as mean and SD for reporting of neurological outcomes. We planned to use the t-test to analyze the difference in the change of the MoCA, CPC, and MRS scores. Survival was assessed using the Kaplan-Meier estimate. This was calculated using the date of the cardiac arrest, to either death or the final follow up assessment. The Log–rank test was used to compare survival functions to assess overall survivor experience between groups. Multivariable analysis was performed by Cox regression. We did not blindly follow any automatic variable selection procedures to select

covariates. Rather we used clinical judgement along with Collet's model selection approach[15], which involves univariate analysis, forward, backward and stepwise selection respectively.

RESULTS

As of August 18, 2015, we screened 159 patients admitted to the ICU and CCU during the 18 months of the study. After excluding for various factors such as pre-existing terminal illness and rapidly improving neurological status, 110 subjects were enrolled in the registry. This included 56 patients in the TH cohort, 44 patients in the no TH cohort, and 10 patients in the TTM cohort (Figure 2.1). The demographics of the patients in the 3 groups were comparable (Table 2.4), with the majority being males with witnessed OHCA, presenting with shockable initial rhythms, who received bystander CPR. The mean duration of the arrests is also similar across the groups, with the TH group being 26.5 minutes, the no TH group being 26.1 minutes, and the TTM group being 26.4 minutes. Age was slightly higher in the TH population (61.2 years, SD=12.8), with the mean age in the no TH group being 58.0 years (SD=15.7), and in the TTM group 48.1 years (SD=18.8). Of notable difference is the proportion of patients with shockable initial rhythms and myocardial infarction as the presumed cause of the arrest. In the TH group 85.7% presented with shockable rhythms, vs 11.4% in the no TH group, and 10.0% in the TTM group. These differences are in alignment with current post arrest guidelines[3], which are supported by stronger evidence for TH in patients presenting with shockable rhythms. As for myocardial infarction leading to the arrests, this was thought to be the case in 64.3% of the TH patients, and only 11.4% of the no TH patients and 30.0% of the TTM patients.

Primary Outcome

Change in MoCA at 3 months after arrest: The MoCA could only be assessed in 21/110 subjects, as many of the subjects were deceased at this point, and others could not be followed up due to distance from

our centre. Because of the low number of assessments obtained, no statistical testing was possible between or within groups. We compared the mean change from the first MoCA score to the 3 month MoCA score (Figure 2.2). The TH group included 8 observations with a mean change in score of 3.3 points (SD 2.60). There were no observations of MoCA score obtained in the no TH group because most patients had died. The TTM group only yielded 1 observation, with a change in score of 8 points between first MoCA and 3 month MoCA.

Secondary Outcomes

Change in MoCA at 6 months after arrest: For the mean change in MoCA score from initial assessment to 6 month follow up, the TH group had a change of 4.3 points (SD 4.72) based upon 7 observations (Figure 2.2). The no TH group had no observations for the time period, and the TTM group had 1 observation, with a change in score of 7 points.

Change in CPC at 3 and 6 months after arrest: For the TH group, the mean change in CPC score from first assessment to 3 month follow up was 0.7 points (SD .72) with 15 observations. There was again low numbers of observations for this outcome, and the no TH group had only 1 observation, with a change of 1 point on the scale. The TTM group also had only 1 observation, and no change was noted for their score. Between first assessment and 6 month follow up of CPC scores, the TH group had 15 observations with a mean change in score of 0.7 points (SD 0.8). The no TH group had no observations at this time point, and the TTM group had 1 observation, with no change assessed in score.

Change in MRS at 3 and 6 months after arrest: For the TH group at 3 months, there was a mean change in score of 1.5 points (SD 1.13) with 15 observations. The no TH group had 1 observation with a change in score of 2 points. The TTM group also had only one observation, with a change of score of 1 point.

When examining the mean change in MRS score at 6 months, we observed a change of 1.9 points (SD 1.36) for 15 observations in the TH group. There were no observations at this time point for the no TH group, and the TTM group had 1 observation with a change in score of 1 point over the time period.

Survival

Survival analysis was undertaken using Kaplan–Meier survival (Figure 2.3). There was a survival advantage in the subjects who received TH. The proportion of subjects surviving at 3 and 6 months following cardiac arrest is identical within each cohort, as there were no deaths after approximately 1 month following arrest. The TH group demonstrated a survival proportion of 46.1% (95% CI 32.1-59%).The no TH group proportion was 13.7% (95% CI 5.1-26.5%) and the TTM group was 10% (95% CI 0.6-35.8%). At 6 month follow up the proportion surviving was the same in the TH and TTM groups as at 3 months, but there was no data at this time point for the no TH group.

After adjusting for multiple comparisons using a Bonferroni correction, there was a significant difference in overall survival experience between the no TH and TH groups and the TH and TTM groups. Median survival times for the TH, no TH, and TTM groups were 16, 3, and 2 days respectively. The TH group had a decreased hazard of death compared to the no TH group, HR 0.39 (95% CI 0.24 0.64; p=0.0006). The TTM group had an increased hazard of death compared to the TH group, HR=3.64 (95% CI 1.69 7.85; p=0.003). There was no significant difference between the no TH and TTM groups regarding mortality, HR=1.42 (95% CI 0.68 2.96; p>0.99).

Multivariable Analysis

Based on clinical judgement, we performed univariable analysis of likely clinical variables that would influence outcomes. These included treatment allocation, gender, age, initial rhythm, arrest location, arrest witnessed or unwitnessed, bystander CPR, total downtime, and whether or not MI was thought to

be the mechanism of the arrest. Following individual analysis of the variables, those with a p ≤0.20 were included in the regression analysis. Then a final model was selected using Collet's approach[15]. Those variables that showed statistical significance (p ≤0.05) following multivariate analysis were age, gender, and whether initial rhythm was shockable or non-shockable (Table 2.5).

DISCUSSION

Our "real world" registry adds to the evidence for the benefit of TH in survivors of cardiac arrest. While we could not make a comparison of patients who received TH vs those who did not (chiefly because the survival of patients who did not receive TH was so poor), we demonstrated that patients who received TH showed a marked improvement in neurological outcomes over 6 months with the MoCA tool, CPC scale, and MRS scale. We also observed a significant improvement in survival in patients who received TH vs. those who did not.

This is an interim analysis of an ongoing registry. We learned that the implementation of a cardiac arrest registry was feasible and that standardized neurological assessment tools can be used to assess the level and trajectory of neurological outcomes in this population. We were limited by poor survival in the patients not receiving TH and therefore could not compare neurological outcomes between these groups.

Our results are consistent with the existing body of evidence on the subject. In the majority of studies comparing a TH group to a no TH control group, the TH groups' neurological outcomes and survival are improved. Our study results are similar to the outcomes reported by HACA[4] which demonstrated a 14% decrease in death in the TH group compared to the control. Bernard, et al[6] also reported 23% more good outcomes in the TH cohort compared to the control, although mortality in that trial was not significantly different between groups. Our study was better able to quantify the improvements in

neurological status using the more sensitive MoCA, compared to the almost dichotomous tools used by previous investigators.

A trial by Nielson, et al[12] compared TH with TTM and demonstrated no significant difference in harm or in benefit between the groups, whereas our registry identified a difference between these groups. Our results showed that there was harm for the TTM group compared to the TH group, with increased hazard of death. While the Nielsen study was a randomized trial, ours was a registry, and affected by allocation bias (i.e., patients who were most likely to do well after a cardiac arrest recieve TH, whereas those with poor prognosis do not typically receive TH). As well, our registry had a low sample size overall, and especially in the TTM group with only 10 patients. The result is that the registry was greatly underpowered to detect a real difference in survival between the groups. Almost certainly these factors impacted our assessment of outcomes, which in turn resulted in this contrast in outcomes.

Strengths

The prospective nature of this study enabled the systematic use of a sensitive tool (MoCA) for neurological assessments of the subject. The length of follow-up as well was much longer than usual practice and indeed, in many clinical trials. This is important, as patients may have not reached their highest level of recovery by hospital discharge. Although this did not show impact for the survival data, there was a demonstrated continuing of neurological improvement once the patients were discharged from hospital in this registry that many prior studies could not capture due to shorter follow-up times.

The MoCA tool is validated and systematic. The use of this tool, combined with the fact that there was a small group of trained nurses who performed the follow-up visits, helped control for any deviation when assessing neurological outcomes.

Limitations

One must take into consideration the multiple limitations of this study when interpreting these results. Although prospective in nature, this remains a registry, with all the confounding that these types of studies entail. Indeed, our survival analysis demonstrated severe confounding by indication, to the point where treatment allocation was rendered a non-significant variable when initial rhythm was included in to the regression analysis. Presenting with a shockable initial rhythm is one of the primary indicators for receiving TH in the guidelines. Treatment allocation was made by clinicians, almost certainly selecting for patients who would do well with TH, and, conversely opting not to treat those with a poor prognosis. Indeed, we observed a very high mortality rate in those patients who did not receive TH, which precludes any comparison of TH efficacy. This does not allow for a fair comparison of the therapy outcomes, and creates a self-fulfilling prophecy when patients put into one group are expected to have life-sustaining therapy withdrawn relatively early on in their care. On the other hand, meta-analysis has already demonstrated the effect of TH on mortality.

Cardiac arrest is associated with a high mortality rate. As such, longitudinal follow-up for neurological recovery is difficult. This made it difficult to fully evaluate the outcomes of interest. The MoCA test in particular was difficult to obtain results for, as only patients who had improved significantly were able to attempt the assessment tool. This tool is sensitive to minor cognitive dysfunction, but patients do require a certain level of neurological functioning to attempt the assessment. Thus the yield of observations in this area was low. The other neurological tests (CPC and MRS) are coarser tools and easier to obtain a score for, even if the patient had poor neurological outcome. As well, CPC and MRS scores, and survival information, could be obtained via phone call follow up. MoCA scores could not, which is relevant as many patients who survived live upwards of 1,500 km from the study site. Along with typical losses to follow up, the result was even lower observations for the MoCA scores in

particular. Blinding to a patient's treatment cohort was not possible in this study, but this was balanced by the strict method required when administering the MoCA tool.

Another factor that was intrinsically impossible to account for was the subjects' baseline neurological status. Although patient history reports and questioning of the next of kin were ways to establish general cognitive status prior to the cardiac arrest, most people have never had MoCA screening in the past. Thus we were not able to quantify precisely how much damage an individual suffered from the arrest, but rather how much improvement they made following the arrest on awakening. Patients who had a history of cognitive dysfunction that would preclude the administration of the MoCA prior to their arrest were excluded from the registry during initial screening. This was hoped to reduce the impact of poor baseline functioning on this outcome during follow up.

Clinical Implications

Using the MoCA tool for neurological assessment following cardiac arrest demonstrated continued improvement over time when assessing cognitive function, which suggests that patients may have not reached their best neurological state by 3 months. Improvement continues up until 6 months, and possibly longer. Using the MoCA test, clinicians could expect a change in score to the extent of 3 points by 3 months, and 4 points at 6 months. When compared to the commonly used CPC scale, which demonstrated the same neurological condition at 3 months and 6 months following arrest, it is clear that in order to thoroughly assess a person's neurological status clinicians should consider using a tool like the MoCA test. This provides for a more specific assessment of their current status and neurological condition. For patients who cannot be assessed in person (e.g. live long distances away), the use of more than one tool is recommended to capture outcomes in these patients. This would still give some indication of any improvement beyond hospital discharge.

Clinicians should consider TH for victims of cardiac arrest, as it demonstrated a significant improvement in survival rates when compared to those who did not receive TH. It is clear that in this study that there was too much bias in how the subjects were allocated to effectively compare the TH and TTM groups. More clinical trials comparing these two treatment groups are necessary to establish if any set temperature offers superior protection for cardiac arrest patients.

Conclusion

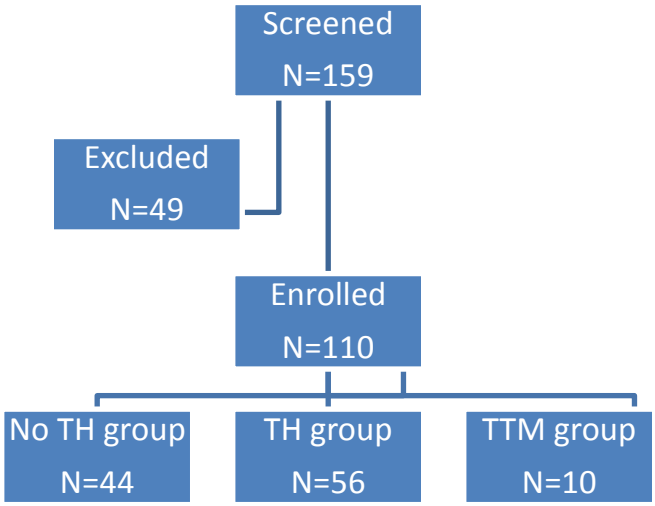
In a single centre registry of cardiac arrest survivors we observed continuing improvements in neurological functioning over time in patients who received TH following cardiac arrest, and high mortality in those who did not. Future plans include the continuation of this registry, to further evaluate outcomes of cardiac arrest survivors.

Funding This research received a restricted grant from the Royal Alexandra Hospital Foundation.

Competing Interests None

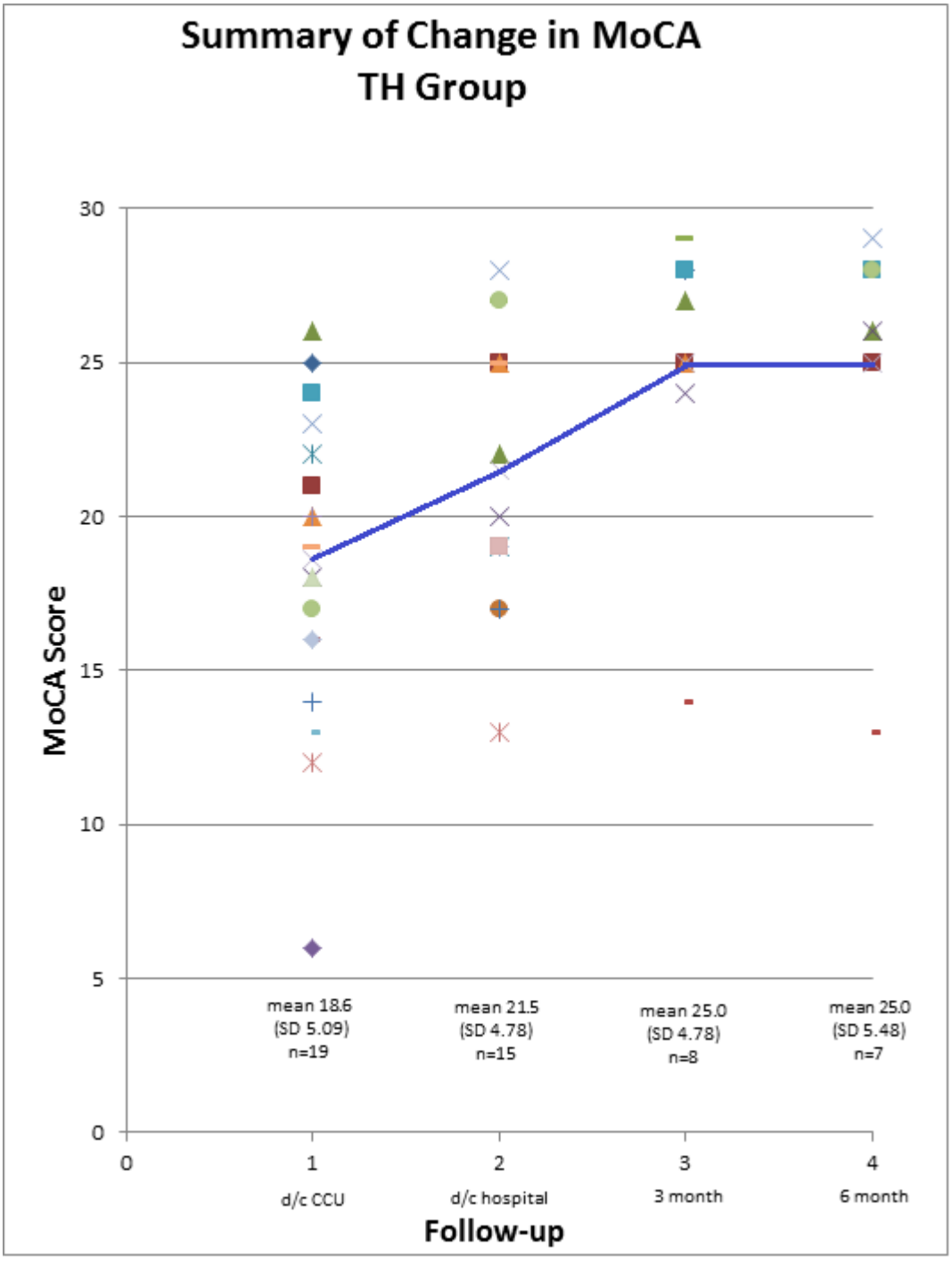
Contributors MD, YA, MC, and RT contributed to the conception and the design of the registry. MD contributed to the collection of the data. MD and RT contributed to assessment of the data. MD and RT critically reviewed and revised the manuscript for intellectual content.

Figure 2.1: Enrolment Process



Reasons for exclusion: GCS>13/rapid improvement n=27; low baseline cognition n=7; not true cardiac arrest n=6; terminal disease n=4; ROSC >90 minutes n=2; hypothermia < 30 °C on presentation n=1; refused consent n=2.

Figure 2.2: Summary of Change in MoCA



Mean change in MoCA: 3 months= 3.3 points (SD 2.60; n=8); 6 months= 4.3 points (SD 4.72; n=7).

Figure 2.3: Kaplan-Meier Survival Curve

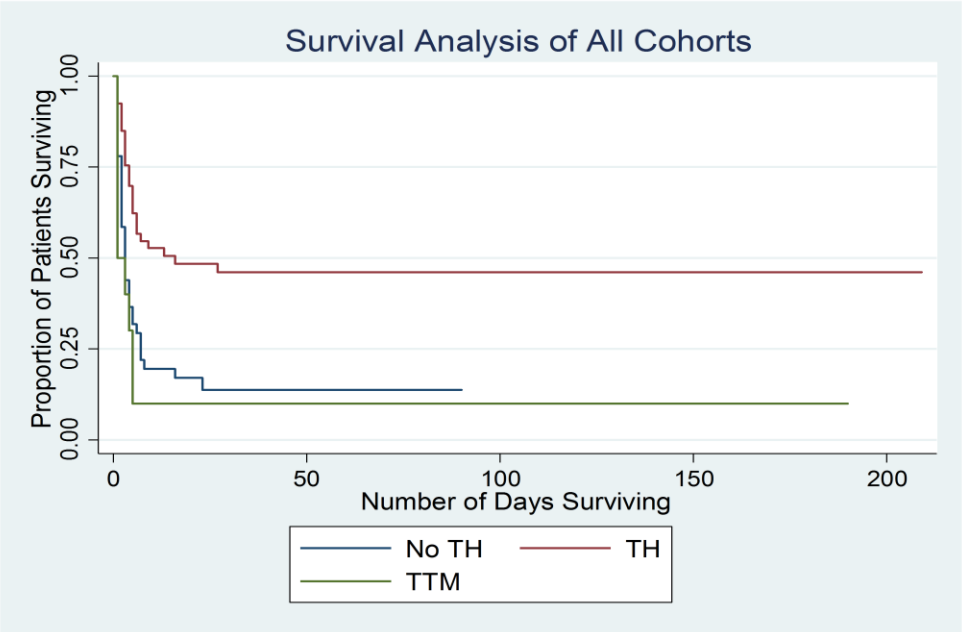


Table 2.1: Cerebral Performance Categories Scale

Cerebral Performance Categories Scale	
CPC 1	Good Cerebral Performance (Normal Life): Conscious, alert, able to work and lead a normal life. May have minor psychological or neurologic deficits (mild dysphasia, nonincapacitating hemiparesis, or minor cranial nerve abnormalities).
CPC 2	Moderate Cerebral Disability (Disabled but Independent): Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.
CPC 3	Severe Cerebral Disability (Conscious but Disabled and Dependent): Conscious; dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence to those who are paralyzed and can communicate only with their eyes, as in the locked-in syndrome.
CPC 4	Coma/Vegetative State (Unconscious): Unconscious, unaware of surroundings, no cognition. No verbal or psychologic interaction with environment.
CPC 5	Brain Death (Certified brain dead or dead by traditional criteria): Certified brain dead or dead by traditional criteria.

Scale taken from Stiell et al. Reference (5).

Table 2.2: Modified Rankin Scale

Modified Rankin Scale	
MRS 0	No symptoms at all.
MRS 1	No significant disability despite symptoms; able to carry out all usual duties and activities.
MRS 2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
MRS 3	Moderate disability; requiring some help, but able to walk without assistance.
MRS 4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
MRS 5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
MRS 6	Dead.

Scale taken from Van Swieten et al. Reference (10).

Table 2.3: Montreal Cognitive Assessment Test

Montreal Cognitive Assessment Test	
MoCA score ≥ 26	Normal.
MoCA score 18-25	Mild cognitive impairment.
MoCA score 10-17	Moderate cognitive impairment.
MoCA score <10	Severe cognitive impairment.

Scale taken from Nasreddin Z. Reference (9).

Table 2.4: Patient Characteristics

	TH (n=56) **n (%)**	**No TH (n=44)** **n (%)**	**TTM (n=10)** **n (%)**
Gender			
Male	40 (71.43)	30 (68.18)	7 (70.00)
Female	16 (28.57)	14 (31.82)	3 (30.00)
Age Mean(SD)	61.23214 (SD=12.84734)	57.97727 (SD=15.7384)	48.1 (SD=18.788)
Location of arrest			
IHCA	4 (7.14)	12 (27.27)	2 (20.00)
OHCA	52 (92.86)	32 (72.73)	8 (80.00)
Initial Rhythm			
Shockable	48 (85.71)	5 (11.36)	1 (10.00)
Vfib	35 (72.92)	4 (80.00)	1 (100.00)
Pulseless Vtach	3 (6.25)	1 (20.00)	0
Unknown	10 (20.83)	0	0
Non-shockable	8 (14.29)	39 (88.64)	9 (90.00)
PEA	6 (75.00)	16 (41.03)	2 (22.22)
Asystole	2 (25.00)	22 (56.41)	7 (77.78)
Unknown	0	1 (2.56)	0
Witnessed	43 (76.79)	31 (70.45)	8 (80.00)
Unwitnessed	13 (23.21)	13 (29.55)	2 (20.00)
Bystander CPR			
Yes	40 (71.43)	25 (56.82)	6 (60.00)
No	14 (25.00)	16 (36.36)	2 (20.00)
Unknown	2 (3.57)	3 (6.82)	2 (20.00)
Total downtime Mean(SD)	Observations: 52 26.53846 (SD=14.05237)	Observations: 37 26.05405 (SD=14.1597)	Observations: 10 26.4 (SD=22.50037)
MI Cause of Arrest			
Yes	36 (64.29)	5 (11.36)	3 (30.00)
No	20 (35.71)	39 (88.64)	7 (70.00)
Deceased	31 (55.36)	38 (86.36)	9 (90.00)

Legend: TH-Therapeutic Hypothermia; No TH-No Therapeutic Hypothermia; TTM-Targeted Temperature Management; IHCA-In Hospital Cardiac Arrest; OHCA-Out-of-Hospital Cardiac Arrest; Vfib-Ventricular Fibrillation; Vtach-Ventricular Tachycardia; PEA-Pulseless Electrical Activity.

Table 2.5: Multivariate Analysis

Covariate	Hazard Ratio	95% Confidence Interval	p-value
TH	0.96	(0.46 to 2.02)	0.92
TTM	1.81	(0.76 to 4.36)	0.18
Age	1.02	(1.00 to 1.04)	0.02
Gender	2.10	(1.21 to 3.65)	0.008
Initial Rhythm	4.11	(1.92 to 8.80)	0.0002
Bystander CPR	1.63	(0.91 to 2.91)	0.10
Total Downtime	0.99	(0.96 to 1.01)	0.21

Arrest Location, Arrest Witnessed or Unwitnessed, and MI as Likely Cause of Arrest were variables not included in the final model.

REFERENCES

(1) Heart and Stroke Foundation of Canada. www.heartandstroke.com. 2015. http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm (accessed December 28, 2015).

(2) Beadell N, Clark W, Lutsep H, et al. Reperfusion Injury in Stroke. *Medscape* 2015.

(3) Callaway C, Donnino M, Fink E, et al. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Post–Cardiac Arrest Care. *Circulation* 2015: S465-S482.

(4) The Hypothermia after Cardiac Arrest Study Group. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. *N Engl J Med* 2002: 346:549-556.

(5) Stiell IG, Nesbitt LP, Nichol G, et al. Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann Emergency Med* 2009: 53(2):241-248.

(6) Bernard S, Gray T, Buist M, et al. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. *N Engl J Med* 2002: 346:557-563.

(7) Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2012: Issue 9.

(8) Raina K, Callaway C, Rittenberger J, Holm M. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation* 2008: 79(2): 249–256.

(9) Nasreddin, Z. MoCA-Montreal Cognitive Assessment. 2016. http://www.mocatest.org (accessed January 14, 2016).

(10) Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988: 19(5):604-607.

(11)Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-84.

(12)Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013: 369:2197-2206.

(13)Jacobs I, Nadkarni V, the ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Update and Simplification of the Utstein Templates for Resuscitation Registries: A Statement for Healthcare Professionals from a Task Force of the International Liaison Committee on Resuscitation. *Circulation* 2004: 110: 3385-3397.

(14)Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Infom* 2009: 42(2):377-81.

(15) Collet, D. Modelling survival data in medical research. CRC press, 2014.

Conclusion

RECAP

Neurological condition is of paramount concern when treating patients resuscitated from cardiac arrest. Although improving survival is the first step when treating these patients, one could argue that the outcome of greatest patient and family importance is the functional status of the patient. This directly impacts the patient's day to day experience, and overall quality of life. Therapeutic hypothermia (TH) has been a mainstay of treatment for people successfully resuscitated from cardiac arrest for over a decade, with the intent to improve survival and neurological outcomes. Although adopted into the international guidelines for post resuscitation care, these guidelines are based upon limited high quality evidence. Indeed, the current literature includes a heterogeneous mix that has investigated survival and neurological outcomes in this population. However, due to the very heterogeneous methodology, it is difficult to draw definitive conclusions from this evidence. As well, neurological outcomes have only been very crudely described. As such, we embarked on 2 studies of TH after cardiac arrest. This included performing a systematic review to assess the current status of the literature on the topic of TH, specifically in regards to neurological outcomes. We also developed a prospective registry for cardiac arrest patients, for which the intent was to assess neurological outcomes over time using a tool sensitive to cognitive dysfunction, as well as to assess survival. Our aim was to be very inclusive, which would give us the opportunity to look at a wide range of subgroups that might benefit from TH.

In our systematic review, we found that receiving TH after cardiac arrest was associated with more good neurological outcomes when compared to those who did not receive TH: RR 1.74 (95% CI 1.53, 1.98; $p<0.001$). We noted that the measures of neurological outcomes were mainly crude scales. As for mortality, TH was associated with improved survival compared to those who did not receive TH: RR 1.48

(95% CI 1.33, 1.65; p<0.001). This was based on the pooled results of 40 studies included for review (36 for the survival analysis), which were of varying methodologies and quality.

Our registry included 110 patients who had been admitted to hospital with any etiology of cardiac arrest. We found that for the 8 patients who received TH and were able to perform the MoCA tool, the mean change in their MoCA score from baseline to 3 months following their arrest was 3.3 points out of 30 (SD=2.60). There were no observations in the no TH group for this outcome time (due to high mortality in this group), and for the TTM group there was 1 observation, with a change in MoCA score of 8 points. Owing to the low number of observations, statistical analysis was not possible for this outcome. As for survival, adjusted hazard ratios demonstrated a better survival experience for TH overall. The TH group had a decreased hazard of death compared to the no TH group, HR 0.39 (95% CI 0.24 0.64; p=0.0006). The TTM group had an increased hazard of death compared to the TH group, HR=3.64 (95% CI 1.69 7.85; p=0.003). When comparing survival between the no TH group and the TTM group, there was no significant difference, HR=1.42 (95% CI 0.68 2.96; p>0.99). Median survival times for the TH, no TH, and TTM groups were 16, 3, and 2 days respectively.

CHALLENGES

Previous studies evaluating neurological outcomes of TH after cardiac arrest vary in regards to follow-up times and assessment criteria. What we did that was different from previous studies, and meaningful, was use a sensitive tool to look at change in neurological functioning over time following cardiac arrest. Indeed, in our systematic review, we found that neurological outcomes were mostly assessed at a single time point, and the scales used to assess the outcomes are mostly coarse and insensitive. In our registry, we chose to assess outcomes at 4 time points, which was felt to provide a more accurate representation of patients' long term outlook. We used the MoCA test, which has been well validated for cognitive

functioning. The range in scores that is measured by this scale is much larger (out of a possible 30 points) than with the rough 5-point CPC scale which is commonly used, which uses categorical descriptions such as “good”, “vegetative”, and “brain death”. This is important when attempting to describe something as complex as neurological functioning as it relates to quality of life.

The population investigated in our registry are innately at high risk of death due to various factors, such as the presenting etiology of the arrest and serious comorbidities. Thus, it is not surprising that a high proportion of the subjects enrolled in our registry died. In the attempt to use the most appropriate measures, our results became even more limited in regards to the number of observations we achieved. We chose the MoCA score as our primary outcome measure. Although it is a sensitive measure for cognitive dysfunction, the use of this test for our primary outcome presented challenges we had not anticipated. Notwithstanding the high mortality rate, the patients who survived were not all able to perform the MoCA test at multiple time points (often due to initially poor neurological function), and so it was difficult to obtain a measure of the change in score. As well, the MoCA is not a score that can be obtained from information contained in the patient record, and the test must be executed face to face. And so, with many of our patients living at distances too far for in-person follow-up, we could not always measure the MoCA score even if the patient was cognitively able. This created a situation where there was a low number of surviving patients for which neurological outcome assessment was possible.

IMPLICATIONS

In conducting our systematic review, we were able to confirm that there was improved neurological recovery and survival for patients who received TH following cardiac arrest, compared to those who did not. We did discover that the majority of studies use over simplified tools to describe neurological outcomes, which is a very important outcome in regards to the patient’s experience of quality of life.

Our registry also confirmed a survival benefit for TH, and furthermore demonstrated that there appears to be neurological benefit, on the magnitude of 3 and 4 points on the MoCA scale at 3 and 6 months respectively.

NEXT STEPS AND FUTURE RESEARCH

The registry that we developed continues with enrollment and follow-up. It is hoped that we will increase the number of outcome measurements for the MoCA scores, and all other outcomes. Future research in this area should focus on using follow-up times that are longer than hospital discharge, and therefore allow for a more accurate representation of the improvement made by the patient. And the use of multiple tools for outcome assessment would also be helpful, specifically including one that is sensitive to cognitive dysfunction, like the MoCA. Our study has demonstrated that this is feasible and meaningful. Although changes in practice are in progress on the CCU and ICU, we have experienced a heightened awareness of the importance of neurological outcomes, and the need for the systematic assessment of these outcomes.

Due to small numbers in our registry, we could not evaluate the effect of TTM. However, based upon the study by Nielsen, et al[1], TTM has been included in recent guidelines for resuscitation[2]. This inclusion is surprising, considering that the trial was not designed to detect equivalence between TH and TTM. And yet TTM has appeared in current guidelines, is represented as being equivalent to TH, and admittedly by the writers of the recommendations is based upon this poor evidence. Therefore, the true efficacy of TTM requires more study, and future research should focus specifically on ascertainment of optimal target temperatures.

CONCLUSIONS

In our systematic review, we confirmed the benefits of TH, but showed that only crude measures of neurological recovery have been reported. In our registry, we noted for the TH group an improvement in survival, and neurological improvement of about 3-4 points on the MoCA scale over 3-6 months. Thus, it is important to realize that improvement in neurological condition continues over time, and that we cannot accurately assess outcomes at short follow-up times, like hospital discharge. We recommend the use of TH for patients resuscitated from cardiac arrest, and encourage further study of neurological outcomes using a variety of tools, which should include those sensitive to cognitive impairment and validated for cardiac arrest survivors.

REFERENCES

(1) Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*, 2013: 369:2197-2206.

(2) Callaway C, Donnino M, Fink E, et al. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Post–Cardiac Arrest Care. *Circulation*, 2015: S465-S482.

Bibliography

Andrade Ferreira I, S. M. (2009). Therapeuric mild hypothermia improves outcome after out-of-hospital cardiac arrest. *Netherlands Heart Journal*, 17(10):378-384.

Arawwawala D, B. S. (2007). Clinical review: Beyond immediate survival from resuscitation – long-term outcome considerations after cardiac arrest. *Critical Care*, 11:235.

Arrich J, European resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. (2007). Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med*, 35(4):1041-1047.

Arrich J, H. M. (2012). Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev*, Issue 9.

Barreña Oceja I, G. M. (2012). Results of using a therapeutic hypothermia protocol after cardiac arrest: Design and application by an emergency medical service and a hospital emergency department. *Emerg*, 24(1):39-43.

Beadell N, C. W. (2015). Reperfusion Injury in Stroke. *Medscape*.

Belliard G, C. E. (2007). Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscittion*, 75(2):252-259.

Bernard S, G. T. (2002). Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. *N Engl J Med*, 346:557-563.

Bernard SA, J. B. (1997). Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med*, 30(2):146-153.

Booth C, B. R. (2004). Is this patient dead, vegetative, or severely neurologically impaired? *JAMA*, 291(7):870-879.

Bro-Jeppesen J, K. J. (2009). The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. *Resuscitation*, 80(2):171-176.

Callaway C, D. M. (2015). 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Post–Cardiac Arrest Care. *Circulation*, S465-S482.

Callaway CW, S. R. (2014). Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. *Resuscitation*, 85:657-663.

Castrejon S, C. M. (2009). Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. *Rev Esp Cardiol*, 62(7):733-741.

Collet, D. (2014). *Modelling survival data in medical research.* CRC press.

Dumas F, G. D. (2011). Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. *Circulation*, 123(8):877-886.

ECC Committee, ECC Subcommittees, and ECC Task Forces. (2005). 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care; Part 7.5: Postresuscitation Support. *Circulation*, 112: IV-84-IV-88.

Folstein M, F. S. (1975). "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, 12(3):189-198.

Fugate JE, W. E. (2011). Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors? *Neurology*, 77(14):1346-1350.

Gebhardt K, G. F. (2013). Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation*, 84(8):1062-1067.

Geocadin RG, K. M. (2008). Management of brain injury after resuscitation from cardiac arrest. *Neurol Clin*, 26(2):487-506.

Granja C, F. P. (2011). Improved survival with therapeutic hypothermia after cardiac arrest with cold saline and surface cooling: Keep it simple. *Emerg Med Int*.

Guyatt G, C. J. (1992). Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA*, 268(17):2420-242.

Harris P, T. R. (2009). Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support,. *J Biomed Infom*, 42(2):377-81.

Heart and Stroke Foundation of Canada. (2015). *www.heartandstroke.com*. Retrieved January 18, 2016, from www.heartandstroke.com: https://resuscitation.heartandstroke.ca/guidelines/chain_of_survival

Heart and Stroke Foundation of Canada. (2015). *www.heartandstroke.com*. Retrieved December 28, 2015, from http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm

Holzer M, M. M. (2006). Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke*, 37(7):1792-1797.

Jacobs I, N. V. (2004). Update and Simplification of the Utstein Templates for Resuscitation Registries: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation. *Circulation*, 110: 3385-3397.

Jennet B, B. M. (1975). Assessment of outcome after severe brain damage: A practical scale. *Lancet*, 1(7905):480-484.

Kagawa E, I. I. (2010). Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. *Crit Care*, 14.

Kim JY, S. S. (2013). Post-resuscitation care and outcomes of out-of-hospital cardiac arrest: a nationwide propensity score-matching analysis. *Resuscitation*, 84(8):1068-1077.

Komatsu T, K. K. (2014). Shorter time until return of spontaneous circulation is the only independent factor for a good neurological outcome in patients with postcardiac arrest syndrome. *Emerg Med J*, 31(7):549-555.

Kory P, F. M. (2012). Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. *Neurocrit Care*, 16(3):406-412.

Kowalik R, S. E. (2014). Cardiac arrest survivors treated with or without mild therapeutic hypothermia: performance status and quality of life assessment. *Scand J Trauma Resusc Emerg Med*, 22:76.

Kozinski M, P. K. (2013). ACS network-based implementation of therapeutic hypothermia for the treatment of comatose out-of-hospital cardiac arrest survivors improves clinical outcomes: The first European experience. *Scand J Trauma Resusc Emerg Med*, 21(1).

Kulstad CE, H. S. (2010). Therapeutic hypothermia protocol in a community emergency department. *West J Emerg Med*, 11(4):367-372.

Li D, S. Z. (2007). Reperfusion accelerates acute neuronal death induced by simulated ischemia. *Exp Neurol.*, 280-287.

Liu L, Y. M. (2007). Therapeutic hypothermia: neuroprotective mechanisms. *Frontiers in Bioscience*, 12:816-825.

Lundbye JB, R. M. (2012). Therapeutic hypothermia is associated with improved neurological outcome and survival in cardiac arrest survivors of non-shockable rhythms. *Resuscitation*, 83(2):202-207.

Maclean DA, S. R. (2012). Therapeutic hypothermia for out-of-hospital cardiac arrest: An analysis comparing cooled and not cooled groups at a Canadian center. *J Emerg Trauma Shock*, 5(4):328-332.

Mark DG, V. D. (2014). Lack of improved outcomes with increased use of targeted temperature management following out-of-hospital cardiac arrest: A multicenter retrospective cohort study. *Resuscitation*, 85:1549-1556.

Mongardon N, D. F. (2011). Postcardiac arrest syndrome from immediate resuscitation to long-term outcome. *Ann Intensive Care*, 1:45.

Nasreddin, Z. (2016). *MoCA-Montreal Cognitive Assessment*. Retrieved January 14, 2016, from www.mocatest.org: http://www.mocatest.org

Neumar R, N. J. (2008). ILCOR Consensus Statement: Post cardiac arrest syndrome. *Circulation*, 118: 2452-2483.

Nielsen N, W. J. (2013). Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*, 369:2197-2206.

Nielsen N, W. J.-S. (2012). Target temperature management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. *American Heart Journal*, 163(4):541–548.

Nolan JP, S. J. (2010). European resuscitation council guidelines for resuscitation 2010: Executive summary. *Resuscitation*, 81:1219-1276.

Oddo M, S. M. (2006). From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med*, 34(7):1865-1873.

Peberdy M A, C. C. (2010). 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science; Part 9: Post–Cardiac Arrest Care. *Circulation*, 122: S768-S786.

Petrovic M, P. G. (2011). Therapeutic hypothermia and neurological outcome after cardiac arrest. *Vojnosanii Pregl*, 68(6):495-499.

Pfeifer R, F. M. (2014). Hypothermia after cardiac arrest does not affect serum levels of neuron-specific enolase and protein S-100b. *Acta Anaesthsiol Scand*, 58(9):1093-1100.

Pußwald G, F. E. (2000). Neurological rehabilitation of severely disabled cardiac arrest survivors. Part II. Life situation of patients and families after treatment. *Resuscitation*, 47;241–248.

Raina K, C. C. (2008). Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation*, 79(2): 249–256.

Rittenberger J, R. K. (2011). Association between Cerebral Performance Category, Modified Rankin Scale, and Discharge Disposition after Cardiac Arrest. *Resuscitation*, 82(8): 1036–1040.

Rittenberger JC, G. F. (2008). Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. *Resuscitation*, 79(2):198-204.

Samaniego EA, M. M. (2011). Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit Care*, 15(1):113-119.

Schulz K, G. D. (2002). Generation of allocation sequences in randomised trials: chance, not choice. *The Lancet*, 359: 515–19.

Steffen I G, H. D. (2010). Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care*, 14.

Stiell IG, N. L. (2009). Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann Emergency Med*, 53(2):241-248.

Storm C, N. J. (2010). 2-year survival of patients undergoing mild hypothermia treatment after ventricular fibrillation cardiac arrest is significantly improved compared to historical controls. *Scand J Trauma Resusc Emerg Med*, 18(1).

Storm C, N. J. (2012). Mild ypothermia treatment in patients resuscitated from non-shockable cardiac arrest. *Emerg Med J*, 29(2):100-103.

Takeuchi I, T. H. (2009). Effect of hypothermia therapy after outpatient cardiac arrest due to ventricular fibrillation. *Circ J*, 73(10):1877-1880.

Teasdale G, J. B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*, 2:81-84.

Testori C, S. F. (2011). Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation*, 82(9):1162-1167.

The Cochrane Collaboration. (2014.). Review Manager (RevMan) [Computer program]. Version 5.3. . Copenhagen: The Nordic Cochrane Centre.

The Cochrane Collabortion. (2014). Review manager (RevMan) [Computer Program] Version 5.3. Copenhagen.

The Hypothermia after Cardiac Arrest Study Group . (2002). Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. *N Engl J Med*, 346:549-556.

The ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. (2004). AHA Scientific Statement: Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports. *Circulation*, 110:3385-3397.

Vaahersalo J, H. P. (2013). Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med*, 39(5):826-837.

Van Swieten JC, K. P. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, 19(5):604-607.

Walters EL, M. K. (2011). Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after out-f-hospital cardiac arrest: A feasibility study. *Shock*, 35(4):360-366.

Wells G, S. B. (2012). *The Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* Retrieved November 14, 2014, from The Ottawa Hospital Research Institute: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Yanagawa Y, I. S. (1998). Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation*, 39(1-2):61-66.

Zeiner A, H. M. (2001). Hyperthermia After Cardiac Arrest Is Associated With an Unfavorable Neurologic Outcome. *Arch Intern Med.*, 161(16):2007-2012.

Zimmermann S, F. F. (2013). Mild therapeutic hypothermia after out-of-hospital cardiac arrest complicating ST-elevation myocardial infarction: long-term results in clinical practice. *Clin Cardiol*, 36(7):414-421.