LITERATURE REVIEW

Therapeutic hypothermia for neuroprotection after out-of-hospital cardiac arrest: Too cool for school?

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CLINICAL POINTS

- Inducing mild therapeutic hypothermia in unconscious out-of hospital
- Cardiac arrest survivors after return of spontaneous circulation is found to improve survival and neurological outcome.
- Inducing mild therapeutic hypothermia appears to be a safe practice. Methods include application of ice packs and infusion of ice cold intravenous fluids.
- Mild therapeutic hypothermia for out-of hospital cardiac arrest continues to be underutilised despite much data indicating its efficacy.
- More research is required to elucidate the long term outcome of patients who initially benefit from mild therapeutic hypothermia.

ABSTRACT

Approximately 5000 people in Ireland suffer an out-of-hospital cardiac arrest annually, and surprisingly, only 5.4% are expected to survive such an event. A significant number of those who do survive to hospital discharge encounter varying degrees of neurological deficit. Many studies indicate that survival and neurological outcome after suffering an out-of-hospital cardiac arrest can be improved by inducing mild hypothermia for up to 24 hours following the return of spontaneous circulation. Although the exact physiological processes underlying this intervention are not clearly understood, hypothermia is thought to interfere with the mechanisms associated with ischaemic and reperfusion injury. Several methods to induce therapeutic hypothermia have been developed and include external cooling, intravascular cooling and combinations of both. Clinical trials examining the safety of therapeutic hypothermia suggest it presents little risk to patients. However, these studies have inherent limitations in their research methodology. A number of international surveys of physicians suggest that this treatment is underutilised due to a lack of both published data on its safety profile and the absence of local protocols. The use of therapeutic hypothermia in Ireland is yet to be analysed and there is little published data available on Irish out-of-hospital cardiac arrest survival.

INTRODUCTION

Cardiac arrest is described as a condition where absent or inadequate contraction of the heart, commonly due to ventricular fibrillation, causes circulatory failure, loss of consciousness and brain death within approximately 10 minutes if normal heart rhythm is not restored[1]. The Task Force on Sudden Cardiac Death advise that 5000 people experience an out-of-hospital cardiac arrest (OHCA) in Ireland each year, an event with a poor prognosis in terms of morbidity and mortality[1]. Patients in cardiac arrest who receive prompt interventions may be successfully resuscitated and experience return of spontaneous circulation (ROSC). ROSC is defined as the restoration of a palpable arterial pulse when cardiopulmonary resuscitation is paused[2]. While these patients demonstrate adequate cardiac function after ROSC, they often encounter some degree of neurological deficit.

Since the 1950s, a growing body of evidence has revealed that inducing mild hypothermia at a temperature of 32-34°C for 12-24 hours in comatose ROSC patients, improves both their survival and neurological outcome[3]. Traditionally, therapeutic hypothermia has been associated with the treatment of traumatic brain injury and raised intracranial pressure. Historical accounts of the initial use of hypothermia in the early 1800s describe one method of 'resuscitation' in Russia, which involved burial of the victim in snow while hoping for ROSC. It has since evolved into a novel neuroprotective therapy. Methods to induce hypothermia include the external application of cold packs or cooling blankets and administration of ice cold (4°C) intravenous fluids. Neuromuscular blocking agents are administered adjunctively to prevent shivering. This paper intends to review the current literature on efficacy, safety and implementation of mild therapeutic hypothermia for neuroprotection in adults who have experienced an OHCA.

PATHOPHYSIOLOGY

Patients who suffer a cardiac arrest and subsequent ROSC commonly encounter a number of detrimental neurological effects. These are a result of anoxic brain injury, an insult associated with the period in which

no oxygen is delivered to the brain. During an ischaemic episode, the cell resorts to anaerobic glycolysis for the production of energy, yielding only modest quantities of adenosine triphosphate (ATP). Accumulation of lactate, a product of anaerobic glycolysis, quickly ensues. This results in localised acidosis while the inactivity of ATP-dependant membrane pumps leads to electrolyte disturbance[4]. In addition, the excitatory neurotransmitter glutamate is released from neurones during cerebral ischaemia, causing further neuronal damage. A significant amount of damage also appears to be caused by the re-establishment of oxygen supply to the brain after an anoxic episode. This phenomenon is known as reperfusion injury. When oxygenated blood is reintroduced to an ischaemic area, a cascade of reactions occurs involving the release of inflammatory mediators and the production of deleterious oxygen free radicals[4,5]. The combination of these processes results in cell apoptosis.

Clinical trials involving animals in the 1950s indicated that the pathophysiological effects of ischaemia and reperfusion injury could be inhibited by hypothermia[3]. While the mechanisms of the neuroprotective properties of mild hypothermia are not yet clearly understood, animal trials indicate that mild hypothermia in the normal brain reduces the cerebral oxygen consumption by 6% for every 1°C reduction in temperature, thereby reducing ischaemic injury[6]. A decrease in electrical activity due to hypothermia also appears to suppress the chemical reactions associated with reperfusion injury. Aside from its use in neuroprotection, hypothermia has been utilised for its vasoconstrictive properties. This effect underlies its traditional therapeutic use in the treatment of traumatic brain injury and raised intracranial pressure. Therapeutic hypothermia has since fallen out of favour as a treatment for head trauma due to adverse events associated with its use in these patient groups[3].

While initial trials have focused on cardiac arrest in animal models, more recent studies have been conducted demonstrating the efficacy and benefits of mild therapeutic hypothermia (MTH) in OHCA survivors[7-12].

Efficacy

Two landmark papers, both published in the New England Journal of Medicine (impact factor = 50.017) in 2002, provide conclusive evidence that MTH has beneficial effects on the morbidity and mortality of OHCA patients. Bernard et al[7], in their Australian randomised controlled trail, assigned treatment of ROSC patients to one of two groups. Participants were randomly allocated to either group. The study group received MTH whereas the control group were subjected to normothermic treatment. The mean age of the study subjects was 65 years and 65% of those studied were male. Patient outcome was measured in terms of survival to discharge with good neurological outcome. The paper reported that 49% of the therapeutic hypothermia group (n = 21/43) survived to discharge with favourable neurological outcome, while only 26% of the normothermic group (n = 9/34) experienced an analogous recovery. It was impossible to blind the treating clinicians involved in this study however blind assessment of the participant's outcomes did take place. The second large study examining the use of MTH in human subjects provides comparable results. The Hypothermia After Cardiac Arrest Study Group (2002) conducted a multicentre, randomised control trial across Europe involving nine emergency departments[8]. Boasting a large sample size (n = 275, 76% males), the researchers compared the 6 month mortality and neurological outcome of consecutive OHCA patients who were treated with MTH compared to a control group treated at normothermic temperature. The assignment of patients to either group was randomised. A history of coronary heart disease was present in 37% of the sample whose mean age was 59 years. Blind assessment of patients was conducted to elicit the outcomes of those involves. Whereas 55% of the hypothermia group displayed a good neurological outcome 6 months after successful resuscitation, only 39% of the control group had a comparable outcome. The 6 month mortality rate among the hypothermia group was found to be 14% lower than that of the control group. Both of these initial studies utilised external cooling methods to induce hypothermia. The publications appeared to generate heightened interest in MTH and in 2003 the International Liaison Committee on Resuscitation (ILCOR) published an advisory statement suggesting that therapeutic hypothermia be considered for all comatose patients with ROSC after experiencing OHCA.

More recent studies also confirm the beneficial effects of MTH on both recovery rate and length of stay in hospital. A prospective observational study in Germany by Storm et al[9] examined the results of 52 consecutive ROSC patients treated with MTH against a historical cohort of 74 normothermic patients. Hypothermia was induced using a combination of external and intravascular methods. It was demonstrated that survivors in the MTH group spent an average of 14 days in the Intensive Care Unit (ICU). In contrast, members of the normothermia group spent an average of 21 days in ICU. These results are further supported by a recent Japanese study by Takeuchi et al[10]. While comparing the recovery rate of patients after the introduction of an MTH policy in their facility, it was found

that patients treated with MTH (n = 25) displayed an 80% recovery rate. Conversely patients in the normothermic group (n = 21) had a 38% recovery rate. This amounted to a very significant doubling in recovery rate for ROSC patients. This trial, along with other recent studies[13,14] examining the efficacy of MTH, has failed to employ a randomised study design, a shortcoming that should be addressed by future research. Despite this limitation, the literature provides clear evidence that MTH is a valuable therapy which offers ROSC patients a better chance of survival and a desirable neurological outcome. However, studies examining the long term (>1 year) advantages of MTH could not be identified and thus present an area that should be explored through further research. Although the literature presents much data concerning the efficacy of MTH, several papers also address its safety.

Safety and adverse events

The introduction of new interventions such as MTH must be deemed clinically safe prior to implementation to ensure the ethical principle of *Primum non Nocere,* or 'first, do no harm', is maintained. Older studies[3] have identified a higher risk of arrhythmia, pneumonia and coagulopathy with the use of therapeutic hypothermia. However, many modern trials examining its use for OHCA patients have suggested that it is clinically safe[12-14]. In fact, the incidence of adverse events encountered among patients treated with MTH is statistically similar to that of ROSC patients treated at normothermia[7,8]. Intravascular cooling was examined in an American study by Kim et al[13] who identified no adverse effects during or after the rapid intravenous administration of ice cold fluids. While monitoring core temperature and haemodynamic status of 17 ROSC patients during induction and maintenance of hypothermia, no cardiovascular detriment or side effects were encountered. The researchers used echocardiography and invasive manometry to monitor patients throughout treatment. Hypocoagulation and electrolyte disturbances were also out ruled with regular sampling and analysis.

While the above study provides strong evidence for the safety of inducing MTH, another trial by Nielsen et al[12] describes the prevalence of adverse events in ROSC patients who underwent MTH across 34 centres. The impressive sample size (n=975) had a mean age of 63 years and 74% of patients were male. Half of the sample survived, with over 90% displaying a good neurological outcome. Adverse events included 41% of patients developing pneumonia and 33% experiencing arrhythmia. Bleeding requiring a transfusion occurred in only 4%. Mechanically ventilated patients commonly experience adverse events such as pneumonia and it is difficult to interpret these findings without a control group. None of the recent studies which assess the safety of MTH were randomised controlled trials, limiting the quality of data and its application to clinical practice. Randomisation of participants ensures that results are valid and reliable by preventing bias. It also ensures that each study group is homogenous. The dearth of randomised controlled trials may inhibit the recognition of MTH as a safe practice and further restrain its implementation. However, as more evidence supports the use of MTH, it becomes difficult to ethically justify the inclusion of a control group, treated at normothermia, in such studies.

Too cool for school?

There is paucity in Irish data on the subject of OHCA and no studies could be identified to date that have examined the use of MTH. Some Irish studies have examined the frequency of OHCA and its associated mortality. A recent study conducted in the Mater Misericordiae University Hospital reported the results of a cardiac arrest registry maintained in the emergency department (ED)[15]. While this hospital serves a population of 170,000 people, the ED encountered 937 OHCAs between 2003 and 2008. The mean age of the sample was 61.1 years and 69% were male. A past history of coronary heart disease was present in 13% of the sample and 73% of cardiac arrests took place in the patient's home. An initially successful resuscitation was recorded in 15% of patients, while the overall survival to discharge rate was significantly lower at 5.4% (n=51). This equates to less than 10 patients per year surviving an OHCA. A recent retrospective study by Byrne et al (2008), conducted in Galway University Hospital, reported similar results[16]. The analysis included data from 212 OHCA patients over a period of one year. It was found that 6.1% (n=13) of patients were successfully resuscitated however only 3.8% (n=8) survived to discharge. The use of MTH was not discussed in either of these two modern studies and it may be inferred that it is not routinely utilised in the nation's EDs. The Irish emergency medical services regulator, The Pre-Hospital Emergency Care Council, has demonstrated some progression in this area and recently introduced a clinical practice guideline for MTH in the care of pre-hospital ROSC patients. This may be utilised by advanced life support providers for patients who are successfully resuscitated in the pre-hospital environment and involves the administration of ice cold intravenous fluids. The introduction of this practice in the pre-hospital environment is a promising development and will hopefully be replicated in EDs.

Despite substantial evidence supporting the efficacy and safety of MTH, current research suggests it is underutilised in clinical practice[17-20].

An anonymous internet survey by Merchant et al[17] of American, British, Australian and Finnish critical care physicians (n = 2248) evaluated the implementation of MTH. It was found that 74% of American and 64% of non-American physicians had never prescribed MTH. "Not enough data" was cited by 48% of physicians as the primary reason for poor endorsement of MTH. A more recent Canadian study published in 2008 shows a slightly higher MTH implementation rate than in other jurisdictions. Kennedy et al[20], in an internet survey of ED physicians (n = 247), found 47% had utilised MTH with 40.6% having access to a local policy directing its use. The research suggests that underutilisation of MTH in clinical practice is correlated to the absence of clear protocols directing it use.

Conclusion

MTH for neuroprotection is a pioneering intervention offering OHCA patients a better chance of survival and survivors a better quality of life. While the use of MTH is being rolled out in the pre-hospital setting, no empirical data is available to quantify the use of MTH in Irish EDs. The recent data reviewed offers persuasive evidence that MTH is a valuable tool, posing minimal risk to patients. Nevertheless, the quality of data examining its safety is consistently limited by non-randomised design. It is impossible to exclude physician bias in these papers and this presents a significant limitation in the studies assessing clinical safety. The physicians involved may have subconsciously assigned study participants with a worse prognosis to a control group in order to generate favourable results. Future research should address this issue by examining MTH in a randomised controlled clinical safety trial. Further investigation is also required to elucidate the long term outcomes (>1 year) of patients who are treated with MTH. International studies indicate MTH is under implemented, but it is clear that the presence a local policy is strongly linked to its use. While several thousand people will experience an OHCA in Ireland in 2010, it is impossible to say if any will be treated with MTH. The dissemination of supporting empirical data is critical to the development of MTH as a therapeutic option for patients in Ireland and the inclusion of MTH in local resuscitation guidelines will accelerate its national implementation.

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