



Therapeutic hypothermia in the emergency department following out-of-hospital cardiac arrest

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Accepted 9 February 2010

ABSTRACT

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality and severe neurological disability. Recent literature suggests that mild therapeutic hypothermia (MTH) can improve survival and neurological outcome in some groups of comatose patients after cardiac arrest but uncertainty exists over the best way to implement this treatment. This review examines the evidence for the efficacy and mode of implementation of MTH after OHCA, particularly in the Emergency Department setting. A literature search was performed and all systematic reviews; human and animal randomised and non-randomised trials were screened for inclusion. Specific emphasis was placed on MTH being commenced in the prehospital and Emergency Department setting. Outcome measures were: time to reach target temperature, in-hospital mortality, neurological outcome at hospital discharge and complications of therapeutic hypothermia. Two systematic reviews found that MTH improved outcome after OHCA. Five human randomised controlled trials were identified. Two trials commenced cooling prehospital. One showed a favourable outcome but the other failed to show survival benefit. The other three trials only commenced cooling after the patient arrived in hospital and all showed improved survival for patients treated with MTH after OHCA. Evidence from animal and non-randomised studies suggests cooling should be commenced as early as possible after return of spontaneous circulation. Cold intravenous fluid was reported as a safe, effective means of cooling in the emergency setting. MTH improves patient outcome after OHCA. There is some evidence to suggest cooling should be commenced early. Cold intravenous crystalloid infusion may be the preferred cooling method in the Emergency Department.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of morbidity and mortality in the developed world. Resuscitation is attempted in 66 per 100 000 population across Europe every year. Of those that survive to leave hospital, >50% are left with permanent neurological sequelae.¹ The first clinical intervention in the postresuscitation phase of OHCA shown to decrease mortality and improve neurological outcome is mild therapeutic hypothermia (MTH).^{2 3} MTH was used in patients with OHCA as early as 1950, but cooling was largely abandoned due to complications. The concept of preserving the brain in the field, protecting it from hypoxia until the patient could be transported to hospital for spontaneous circulation to be restored or placed on cardiopulmonary bypass, was first suggested by Peter Safar in 1984.^{4 5} In the 1990s, a

number of encouraging animal studies showed benefit, and several pilot human studies were conducted.^{6 7} In 2002, two randomised trials demonstrated the benefit of cooling survivors of witnessed OHCA who had ventricular fibrillation (VF) as the presenting rhythm.^{2 3} This led to the International Liaison Committee on Resuscitation, the American Heart Association and the European Resuscitation Council recommending MTH in the management of unconscious patients following OHCA.^{8 9} Despite these recommendations, the use of MTH is not yet routine.¹⁰ Since 2002, further trials have explored the use of MTH for non-VF OHCA, traumatic cardiac arrests and in paediatric patients.

The optimum initiation, method and duration of cooling are unclear.¹¹ Animal research suggests that cooling early after return of spontaneous circulation (ROSC) is associated with improved neurological outcome,^{12 13} but human studies show that delayed cooling also yields favourable results.^{3 12 14}

Both invasive and non-invasive cooling methods have been developed, and whole-body and brain-only cooling methods have been trialled. The majority of cooling techniques have been trialled in critical care settings with few methods specifically evaluated in the Emergency Department (ED).¹⁵ While MTH initiated in the ED may reduce the time taken to reach target temperature, prehospital cooling poses logistical and technical challenges. Patients arriving at hospital after OHCA may require in-hospital transfer for imaging or cardiac intervention prior to ICU (intensive care unit) admission. Cooling techniques intended for early deployment must therefore combine efficacy with ease of use.

While some ambulance services and EDs have adopted MTH as a routine treatment for patients after OHCA, it is unclear whether the available evidence supports this practice.

This paper aims to review and discuss key elements of the published literature on using MTH in the emergency setting and is not intended to provide a definite statement in the form of a systematic review.

We reviewed the published literature to answer the following:

1. In comatose patients after OHCA, does MTH improve neurological outcome?
2. Is there an optimal time and place for commencing MTH?
3. In patients after OHCA considered for MTH, what methods of cooling are available for use within the ED?

METHODS

A literature review was performed by a single investigator. All short-listed studies were assessed by the other two authors for quality and to ensure the inclusion criteria were met. Search terms included 'therapeutic hypothermia', 'hypothermia', 'cardiac arrest', 'heart arrest', 'out-of-hospital cardiac arrest' and 'cardiopulmonary resuscitation'. Outcome parameters included in-hospital mortality, 6-month mortality and favourable neurological outcome (defined as independent living) within 6 months.

Inclusion criteria were studies commencing cooling early post-ROSC. For human studies we included those commencing cooling prehospital or in the ED. For animal studies we included cooling before, during or immediately after cardiac arrest. Specific exclusion criteria included non-cardiac arrest conditions—for example, myocardial infarction, cerebrovascular accident and traumatic brain injury. In contrast to previous published systematic reviews,^{16 17} this review specifically examines MTH use in the prehospital and ED setting. We found the number of randomised controlled trials (RCTs) on the use of MTH after OHCA to be small; therefore, all RCTs were screened for inclusion, regardless of the timing of initiation of cooling.

We included literature searches from Ovid Medline 1950–2009, the Cochrane Library, EMBASE 1988–2009, Google scholar and citation tracking. The search sought to identify studies that evaluated the use of MTH following OHCA using the search criteria above. Finally, a Web of Science citation search was performed on all included studies. Reference lists of all available primary studies and review articles were obtained to identify potentially relevant citations. Previously published systematic review articles were sought, looking for particular relevance to using MTH in the prehospital and ED setting. After a generalised search, limits were applied for 'trials'.

Human trials were assessed using the Jadad system¹⁸ to assess internal validity. This allows a measure of comparison of quality between trials.

RESULTS

One thousand and sixty-two papers were screened for inclusion. These were subdivided into animal studies, non-randomised studies, randomised trials and systematic reviews. Two systematic reviews and five randomised clinical trials were identified. Five animal trials comparing timing of cooling initiation were included.

Animal studies

The first animal studies using hypothermia after cardiac arrest were reported in the 1950s. In the early 1960s, Peter Safar observed that dogs that were mildly hypothermic at the initiation of experimental cardiac arrest had a better neurological outcome than dogs that were normothermic.¹⁹

A summary of selected animal studies is shown in table 1. These particularly relate to early cooling and the potential effect this may have on outcome.

The discovery of the neuroprotective effects of mild to moderate hypothermia led to the investigation of resuscitative hypothermia in several animal models. Dogs treated with immediate mild (34°C) or moderate (30°C) hypothermia showed improved functional and histological outcome. Dogs treated with deep hypothermia (15°C), however, showed no improvement in neurological function and had more severe cerebral histological changes compared with mild or moderate hypothermia groups.^{13 23} In the same model, delaying the onset of cooling until 15 min postreperfusion was not associated with the same improvement in functional outcome but did improve histological damage. MTH was not associated with any significant side effects in these studies.

More recently a trend towards better outcomes after earlier initiation of therapeutic hypothermia (<15 min post-ROSC) has been demonstrated.^{20 22} Kuboyama and colleagues demonstrated that survival without neurological deficit can still be achieved after 40 min of VF cardiac arrest in dogs when intra-arrest hypothermia is instigated using cold intravascular fluids. However, a delay in cooling after the induction of VF was

Table 1 Animal models of therapeutic hypothermia after out-of-hospital cardiac arrest

Study (year)	Animal model	Cooling method + target temperature	Duration of cooling	Outcome	Comments
Sterz ¹³	30 dogs. 10 min VF arrest model. RCT of cooling during CPR vs early post-ROSC cooling vs normothermia	Cooling externally 34°C	20 h	Improved neurological outcome when cooling started during CPR or immediately after ROSC	External CPR and resuscitation drugs used as per human practice
Kuboyama ²⁰	22 dogs, induced VF for 12.5 min. Prospective RCT of normothermia vs immediate hypothermia vs delayed (15 min after reperfusion) cooling	Cooling on bypass 34°C	1 h	Immediate cooling showed trend towards better functional outcome compared with delayed cooling and associated with lower histological damage scores	Functional outcome did not reach statistical significance
Nozari ²¹	27 dogs. VF cardiac arrest model with 40 min no-flow time. RCT of normothermia vs mild hypothermia vs moderate hypothermia	Cooling with venovenous extracorporeal shunt 34°C	12 h	Mild or moderate hypothermia during prolonged CPR improved survival and functional outcome	Invasive techniques used; not easily applicable to humans
Abella ²²	30 mice. Potassium-induced arrest. Prospective RCT of intra-arrest cooling vs delayed (20 min) postarrest cooling vs normothermia	Cooling with cooling blanket 30°C	1 h	Intra-arrest cooling showed better survival to 72 h than delayed cooling or normothermia	Results statistically significant. Only asystolic arrests.
Zhao ¹²	45 mice. Potassium-induced cardiac arrest for 8 min. Prospective RCT of normothermia vs intra-arrest cooling vs prolonged resuscitation (9.5 min) to initiate cooling	Cooling with cooling blanket 30°C	90 s	Animals treated with hypothermia, even in prolonged ischaemia group showed improved survival compared with normothermic controls. Haemodynamic variables also improved.	Results statistically significant. Early intra-arrest cooling possible only in prehospital setting. Intra-arrest cooling may be useful for haemodynamic resuscitation

CPR, cardiopulmonary resuscitation; RCT, randomised controlled trial; VF, ventricular fibrillation; ROSC, return of spontaneous circulation.

associated with an increased mortality and poorer neurological outcomes.²⁰ Nozari showed that early intra-arrest cooling in dogs with 60 min of VF resulted in a favourable neurological outcome.²¹ However, when cooling was delayed until 20 min after onset of VF, seven of eight dogs did not survive. Abella and colleagues showed that mice cooled 20 min after cardiac arrest showed a higher mortality than mice cooled just prior to resuscitation from an 8 min period of cardiac arrest.²² Zhao demonstrated in a randomised, controlled, murine model that delaying resuscitation to institute therapeutic hypothermia still resulted in a favourable neurological outcome.¹²

The animal studies reviewed suggest that cooling should commence with a minimum of delay after cardiac arrest and should continue for at least 24 h to confer lasting neuroprotection.

Non-randomised trials

The first reported human studies using therapeutic hypothermia were reported in 1958.²⁴ Since then >20 non-randomised studies have been published. The target temperature has consistently been 32–34°C using a variety of cooling techniques. Reported favourable neurological outcome rates vary from 25% to 68%. A summary of non-randomised trials is shown in table 2.

In 1997, Bernard and colleagues conducted a pilot study comparing patients treated with MTH, induced by the application of ice packs, with normothermic controls. They demonstrated improved outcome in the treatment group, without significant complications.⁶ Yanagawa cooled 13 patients who had survived initial resuscitation.⁷ Cooling to 33°C commenced on arrival at the ED (time to target temperature of 5.5 h post-ROSC) and was maintained for 48 h before slowly rewarming at 1°C per day.

Further studies adopted progressively more sophisticated means of inducing therapeutic hypothermia. A study using cold air surface cooling in the ED by Zeiner and colleagues was

successful in lowering core body temperature.²⁵ Despite non-significant results, these studies supported the evidence that MTH was a safe clinical intervention and could improve outcome after OHCA.

Cooling modalities are summarised in table 3. Methods of initiating prehospital cooling have been investigated, with cold fluids and ice packs being the modalities of choice.^{28–29} Other methods of cooling, including body surface cooling with ice and cold blankets, helmet devices, endovascular cooling catheters, haemofiltration and coronary bypass, have been studied. None of these combines efficacy with ease of use. A key finding is that infusion of up to 2 litres of cold (4°C) intravenous fluid (0.9% saline or Ringer's lactate) in the immediate post-ROSC phase is an effective and safe method of cooling and is not associated with significant complications or cardiovascular instability. Whatever the cooling technique employed the degree of hypothermia induced is important, and Merchant and colleagues have demonstrated that overcooling is a significant risk and careful core body temperature monitoring is mandatory.³⁰ The risks of overcooling include infection, coagulopathy and cardiac arrhythmias.

Randomised trials

Five randomised clinical trials of therapeutic hypothermia post-IHCA have been published.^{2–3, 32–34} These are summarised in table 4. The first clinical trial of therapeutic hypothermia, published in 2001,³² enrolled 30 patients following OHCA with asystole or pulseless electrical activity (PEA) as the initial cardiac rhythm. Sixteen patients were cooled to 34°C for a maximum of 4 h with a helmet cooling device and then allowed to rewarm passively. Two of the patients treated with MTH survived with a favourable neurological outcome compared with no patients in the normothermia group.

In 2002, two prospective, RCTs of MTH in the post-resuscitation management of witnessed OHCA were published.^{2,3}

Table 2 Non-randomised studies

Study	Year	Initial cardiac rhythm	Cooling method + target temperature	T _{targ} (min)	Duration of cooling	Outcomes
Bernard ⁶ (n=22)	1997	Any	Ice packs 33°C	74	12 h	No significant side effects. Increased survival and better neurological outcome compared with historical controls
Yanagawa ⁷ (n=13)	1998	Any	Cooling blanket 33–34°C	414	48 h	Cooling associated with increased rates of pneumonia. Higher survival and recovery rates in hypothermia group
Zeiner ²⁵ (n=27)	2000	Any	Cold air	276	>24 h	No major complications in first 24 h. Mild resuscitative hypothermia shown to be safe and feasible
Felberg ²⁶ (n=9)	2001	Any	Cooling blanket	378	24 h	No major complications. Cooling methods found to be slow and imprecise. Favourable neurological outcome demonstrated
Bernard ²⁷ (n=22)	2003	Any	Cold fluids (30 ml/kg 4°C Ringer's), ice	ASAP		Rapid drop in core body temperature from 35.5 to 33.8°C, improved BP and renal function. No cases of pulmonary oedema
Kim ²⁸ (n=17)	2005	Any	Cold fluids (2 litres of 4°C saline)	ASAP	24 h	Fluid infusion did not alter ejection fraction, central venous pressure or pulmonary pressures
Busch ²⁹ (n=27)	2006	Any	Sports ice packs and water-soaked towels placed prehospital	450	12–24 h	Cooling rates found to be slow. Higher in-hospital survival rates in cooled patients
Merchant ³⁰ (n=32)	2006	Any	Cooling blanket	360	12–24 h	Majority of cases showed unintentional overcooling to <32°C
Kliegel ³¹ (n=20)	2007	Any	Cold fluids (4°C saline 30 ml/kg/h)	60	24 h	Majority reached <34°C in <60 min

ASAP, as soon as possible; BP, blood pressure; T_{targ}, time to target temperature.

Table 3 Cooling methods

Invasive techniques	Non-invasive techniques
Cold intravenous fluid infusion	Ice packs
Extracorporeal cooling blood circuit	Cooling blankets (water/air filled)
Cardiopulmonary bypass	Cooling helmets (water/air filled)
Femoral–carotid bypass	Cold water immersion
Lavage	Self-adhesive cooling pads
Nasal/nasogastric/rectal/peritoneal	
Ice slush	
Endovascular cooling catheter	

Both of these studies recruited a highly selective cohort of patients, with 92% of patients initially assessed for eligibility excluded.

Recruitment criteria for both trials were similar and included ROSC in patients who remained intubated and ventilated after OHCA due to VF of presumed cardiac aetiology.

The European trial cooled 136 patients to a core temperature of 32–34°C using a mattress cover that delivered cold air. The aim was to reach target temperature within 4 h of ROSC, maintain it for 24 h and then allow passive rewarming to occur. The study showed the number needed to treat (NNT)=6 (RR 1.40, 95% CI 1.08 to 1.81) for a favourable neurological outcome when MTH was used. The overall mortality at 6 months was reduced from 55% in the normothermia group to 41% in the MTH group, NNT=7 (RR 40.74, 95% CI 0.58 to 0.95).

In the Australian study cooling was initiated prehospital by applying ice packs to the head and torso. The target temperature (33°C) was maintained for 12 h posthospital admission before patients were actively rewarmed after 18 h. Forty-three patients were cooled; 21 (49%) had a favourable neurological outcome of living at home or within a rehabilitation facility (RR 1.85, 95% CI 0.97 to 3.49, NNT=4). Mortality was reduced from 68% to 51% in the hypothermia group (RR 0.76, 95% CI 0.52 to 1.10, NNT=6). These findings led to the European Resuscitation Council, in association with the International Liaison Committee on Resuscitation and the American Heart Association, recommending MTH as standard treatment for OHCA victims that achieve ROSC following a VF arrest.⁸

A randomised trial³³ of inducing MTH by isovolumic haemofiltration in patients after OHCA showed an increased survival benefit, but it was unclear whether this was conferred by the hypothermic or filtration processes. This technique is not suitable for use in the emergency and prehospital environment.

A recent clinical pilot study explored the benefit of cooling patients immediately after OHCA using intravenous cold saline administered by paramedics in the field.³⁴ An infusion of 500–2000 ml of 0.9% saline at 4°C was administered. Subsequent in-hospital cooling was at the discretion of the attending physician. Sixty-three patients were treated with prehospital hypothermia. Only 78% of patients in the hypothermia group received further cooling. Prehospital cooling led to a significantly lower temperature on arrival at hospital (34.7°C vs 35.7°C, $p<0.0001$). There was no significant difference in survival to hospital discharge in the hypothermia versus normothermia groups (33% vs 29%, $p=0.70$). Subgroup analysis of patients with VF as the initial cardiac rhythm showed a trend towards increased survival to hospital discharge but there was a trend towards increased mortality in the cooling group where the initial cardiac rhythm was PEA or asystole.

Systematic reviews

Two systematic reviews matched our inclusion criteria. Cheung *et al* reviewed the combined data from four RCTs in 2006,

Table 4 Randomised clinical trials

Study (no. of patients)	Initial Year cardiac rhythm	Cooling method + target temperature	T _{target}	Duration of cooling	Patients	Survival to hospital discharge	Favourable neurological outcome	Jadad	Comments
Hachimi-Idrisi ³² (n=30)	2001 Asystole or PEA	Cooling helmet 34°C	3 h post-ROSC	4 h	16 MTH 14 normothermia	MTH: 2/16 (13%) Normothermia: 0/14	Same as survival rate	3	Results NS ($p=0.49$)
Bernard ² (n=77)	2002 VF or pulseless VT	Ice packs 33°C	2 h post-ROSC	12 h	43 MTH 34 normothermia	MTH: 21/43 (49%) Normothermia: 9/34 (26%)	Same as survival rate. OR for favourable neuro. recovery 5.25 (95% CI 1.47 to 18.79)	1	Results significant ($p=0.046$)
HACA ³ (n=275)	2002 VF or pulseless VT	Cooling mattress/ice packs 32–34°C	6 h after initiating cooling	24 h	136 MTH 137 normothermia	OR for survival 4.4 (95% CI 1.1 to 16.6)	MTH: 75/1236 (55%) NT: 54/137 (39%)	3	Trend towards high infection rate in hypothermia group but benefit deemed to outweigh risk
Laurent ³³ (n=61)	2005 VF or asystole	Cooling of the substitution fluid on haemofiltration		24 h	20 Haemofiltration 22 Haemofiltration + hypothermia		Results from haemofiltration alone were similar to haemofiltration with MTH.	2	Haemofiltration is not practical for use within ED
Kim ³⁴ (n=125)	2007 All rhythms after non-traumatic OHCA	Infusion of up to 2 litres of 4°C saline prehospital	Variable	Variable	63 cooling 62 normothermia	NS	Significantly lower ED arrival temperature (34.7 vs 35.7°C) in group treated with cold intravenous fluid.	3	Trend towards worse survival in non-VF patients treated with hypothermia. Only 78% randomised to cooling received treatment

ED, Emergency Department; MTH, mild therapeutic hypothermia; NS, non-significant; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; T_{target}, time to target temperature; VF, ventricular fibrillation; VT, ventricular tachycardia.

representing 436 patients.¹⁷ Inclusion criteria were adults with primary OHCA who remained comatose after ROSC. The clinical trials ranged from score 1 to 3 on the Jadad scale and A–C on the Cochrane grade score. The combined data showed that MTH decreased in-hospital mortality (RR 0.75, 95% CI 0.62 to 0.84). The review concluded that MTH had an NNT of 5 to improve neurological outcome and an NNT of 7 to save a life. However, the review failed to draw conclusions on the optimum cooling method, rate or duration of cooling. No evidence of treatment-limiting side effects was reported.

A meta-analysis¹⁶ of three trials has shown that patients treated with hypothermia show an increased rate of survival with favourable neurological outcome (RR 1.68, 95% CI 1.29 to 2.07). The calculated 95% CI for the NNT to result in a patient being discharged from hospital with a favourable neurological outcome ranged from 4 to 13.

DISCUSSION

There is strong evidence to support the use of MTH in comatose patients after OHCA whose initial cardiac rhythm was VF. The evidence supporting MTH use in other presenting cardiac rhythms is less clear and further studies are required. Despite animal studies demonstrating the benefit of immediate cooling, either during cardiopulmonary resuscitation (CPR) or immediately post-ROSC,^{12 20 22} the existing evidence from human studies is less clear.¹⁴ Practically, initiating cooling in the prehospital environment is challenging; however, several studies have shown that initiating cooling in the ED is feasible and effective.^{27 28 31} The different cooling modalities are shown in table 3. The use of ice packs is a simple, but relatively slow, means of cooling. A bolus of cold intravenous fluids combines efficacy with ease of use and is not associated with significant unwanted side effects. This is probably the cooling method of choice for the ED. Intravenous fluids can be stored in a refrigerator within the ED and administered to patients following OHCA shortly after arrival in hospital. Initiating cooling in the ED is likely to shorten the time to target temperature, particularly if the patient requires coronary intervention or radiological imaging prior to ICU admission. Cooling with cold intravenous fluids can continue during transfer or during clinical procedures.

The three phases of therapeutic hypothermia are induction, maintenance and rewarming. For all phases, accurate core body temperature measurement is essential to ensure accurate cooling and prevent overcooling. For rapid induction, oesophageal or central venous temperature should be measured, as probes in the bladder or rectum do not reflect core body temperature accurately.³⁵ Overcooling is common.³⁰ After induction, therapeutic hypothermia can be maintained on the ICU with body surface cooling techniques with accurate feedback mechanisms, or invasive, endovascular cooling techniques. In order to prevent shivering, paralysis and sedation are required. The optimum length of time for which MTH should be maintained remains unknown,^{11 36} but previous studies have used maintenance periods of 12–48 h.^{2 5} The optimum means, whether active or passive, and rate of warming are unknown, and further research is required to improve the induction, maintenance and rewarming phases.

Despite strong evidence suggesting benefit, uptake of therapeutic hypothermia in routine clinical practice has been slow.^{10 37} Lack of awareness, fear of a novel treatment and unknown side effects, as well as lack of equipment, have been cited as barriers to MTH implementation.³⁸

CONCLUSION

The use of MTH in patients who remain comatose after OHCA improves survival and neurological outcome. The optimal time of initiation, cooling method and target temperature have yet to be established. Cooling is feasible within the ED, and cold intravenous crystalloid infusion is effective, simple and safe. Wider awareness among ED medical staff may increase the early use of therapeutic hypothermia in patients after OHCA.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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