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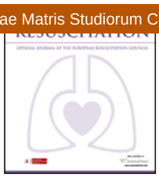

Clinical paper

Therapeutic hypothermia after cardiac arrest: A retrospective comparison of surface and endovascular cooling techniques☆

Michael A. Gillies[a,*], Rosalie Pratt[a], Craig Whiteley[a], Jamie Borg[a], Richard J. Beale[a], Shane M. Tibby[b]

[a] *Department of Intensive Care, Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, United Kingdom*
[b] *Department of Pediatric Intensive Care, Evelina Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, United Kingdom*

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ABSTRACT

Objectives: Therapeutic hypothermia (32–34 °C) is recommended for comatose survivors of cardiac arrest; however, the optimal technique for cooling is unknown. We aimed to compare therapeutic hypothermia using either surface or endovascular techniques in terms of efficacy, complications and outcome.
Design: Retrospective cohort study.
Setting: Thirty-bed teaching hospital intensive care unit (ICU).
Patients: All patients ($n = 83$) undergoing therapeutic hypothermia following cardiac arrest over a 2.5-year period. The mean age was 61 ± 16 years; 88% of arrests occurred out of hospital, and 64% were ventricular fibrillation/tachycardia.
Interventions: Therapeutic hypothermia was initiated in the ICU using iced Hartmann's solution, followed by either surface ($n = 41$) or endovascular ($n = 42$) cooling; choice of technique was based upon endovascular device availability. The target temperature was 32–34 °C for 12–24 h, followed by rewarming at a rate of $0.25\,^{\circ}\mathrm{C\,h^{-1}}$.
Measurements and main results: Endovascular cooling provided a longer time within the target temperature range ($p = 0.02$), less temperature fluctuation ($p = 0.003$), better control during rewarming (0.04), and a lower 48-h temperature load ($p = 0.008$). Endovascular cooling also produced less cooling-associated complications in terms of both overcooling ($p = 0.05$) and failure to reach the target temperature ($p = 0.04$). After adjustment for known confounders, there were no differences in outcome between the groups in terms of ICU or hospital mortality, ventilator free days and neurological outcome.
Conclusion: Endovascular cooling provides better temperature management than surface cooling, as well as a more favorable complication profile. The equivalence in outcome suggested by this small study requires confirmation in a randomized trial.

1. Introduction

Cardiovascular disease remains a leading cause of death in the developed world and survival from cardiac arrest with good neurological outcome is uncommon. In the United Kingdom less than 30% of patients admitted to the intensive care unit (ICU) following cardiac arrest survive to hospital discharge[1] and the majority of those who die do so as a result of neurological injury.[2]

Two prospective randomized controlled studies[3,4] and a meta-analysis[5] have shown benefit in survival and neurological outcome associated with a 12–24 h period of mild hypothermia (32–34 °C). Current guidance from the International Liaison Committee on Resuscitation is that therapeutic hypothermia (TH) should be instituted where possible for comatose survivors of cardiac arrest.[6] Several controversies exist concerning TH, especially with regard to the most efficient cooling technique, duration of hypothermia, and patient selection.[6]

Therapeutic hypothermia can be induced rapidly by infusion of cold (4 °C) crystalloid solution[7] following which hypothermia is maintained using either surface or endovascular techniques. Surface cooling methods are effective but can be labor intensive for the nursing staff and may prevent access to the patient. Endovascular cooling is also effective and permits precise control of body temperature, but involves insertion of a large (8.5 Fr) gauge catheter into the femoral vein, which is invasive.

We have been using TH in our 30-bedded ICU (located within a university affiliated, teaching hospital) since July 2005, employing both surface and endovascular cooling techniques. Our local policy is that all cardiac arrests receive TH, irrespective of primary rhythm or arrest location unless the patient has a contraindication. We carried out a retrospective study on all patients undergoing TH

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[*] Corresponding author. +Tel.: +44 07976609165.
E-mail address: michael.gillies@nhs.net (M.A. Gillies).

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following cardiac arrest over a 30-month period, to address two questions:

(1) Do endovascular or surface cooling techniques differ in effectiveness, in terms of time spent at target temperature, induction of cooling, re-warming and prevention of rebound hyperthermia?
(2) Does choice of cooling technique affect incidence of complications or outcome?

2. Materials and methods

A local research ethics committee reviewed the proposed study and waived the need for a full ethics submission, as the study met the national criteria for service evaluation.

2.1. Patient identification

Data were collected retrospectively on 83 patients undergoing TH between July 2005 and December 2007. Patients were identified from a prospective register of TH recipients, which was established in July 2005 prior to initiating TH within the ICU. However to ensure that no TH recipients were inadvertently missed, we searched the "Carevue" ICU Database (Philips, UK) for all patients admitted with cardiac arrest during this period and reviewed the case notes to determine if TH had been performed.

2.2. Therapeutic hypothermia techniques

Patients were cooled according to our ICU protocol (Supplementary Figure). All patients received a 15–30 ml/kg bolus of cold Hartmann's solution to induce hypothermia as soon as the decision to cool was made. One liter bags of Hartmann's solution were kept at 4 °C in fridges in the emergency department and on the ICU for this purpose. In all cases, core temperature was monitored continuously using a bladder thermistor (Covidien AG, Mansfield, MA, USA). A temperature of 32–34 °C was targeted for 12–24 h. In patients undergoing surface cooling, polythene bags filled with ice slurry were applied to both sides of the neck, axillae, groins, and under the knees. These were replaced as required until the target temperature was reached. In the surface group rewarming was allowed to occur passively with foil hats and use of warm blankets. Active rewarming (i.e. with a heating device or blanket) was not used. Two patients in the surface group underwent cooling with a cooling mattress and tent (Theracool, KCI Europe, Amstelveen, NL) and one with a cold water recirculation system (Criticool System, Charter Kontron, Milton Keynes, UK). All patients in the endovascular group had an Alsius ICY-Coolguard (Alsius Corp., Irvine, CA) inserted into the femoral artery. They were then cooled according to protocol for 12–24 h with at target temperature of 33 ± 1 °C. No other cooling device or method was used. Re-warming was at 0.25 °C h^{-1}. Once re-warmed to 36 °C the device was set to "fever" mode which attempts to prevent rebound pyrexia. There was not a specific part of the protocol relating to this; if shivering was a problem sedation was increased and neuromuscular blockers added. In the surface group the ice slurry was replaced at frequent intervals, in the Alsius group it was ensured that the power setting on the machine was at "MAX".

From July 2005 until January 2006 surface cooling only was undertaken in our institution, however from January 2006 onwards an increasing number of patients were cooled using the endovascular system. By the start of 2007, surface cooling was only employed if the ICY-Coolguard system was already in use on another patient (Fig. 1).

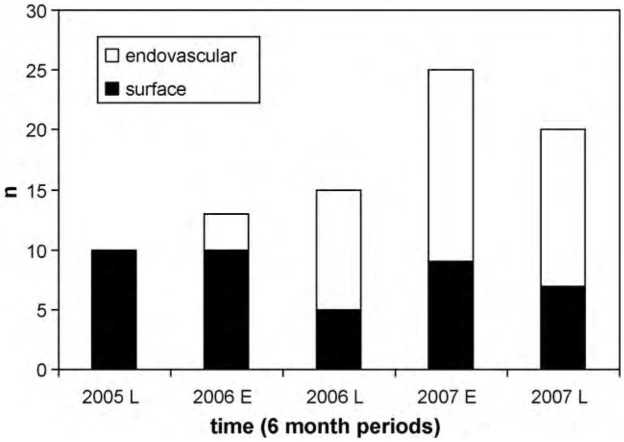

Fig. 1. Distribution of cooling methods used. E refers to the period January through June, and L to July through December.

2.3. Data collection

Patient demographic data included: age, weight, sex, and APACHE II score. Details of cardiac arrest type, location and time to return of spontaneous circulation (ROSC) were also recorded, as were duration of ICU and hospital admission, duration of mechanical ventilation, survival to ICU and hospital discharge and hospital discharge location. Discharge to home was used as a surrogate for good neurological outcome. Previous randomized controlled trials have used Pittsburgh Cerebral Performance Criteria (CPC) grades 1–2 as a measure of good neurological outcome; in CPC 2 the patient has some residual neurological impairment but can live independently.[3,4]

Hourly temperatures for the first 72 h from ICU admission were collected. Although not every patient had a temperature recorded during each hour (median number of hourly temperatures for the group was 69/83, interquartile range 65/83 to 72/83), no patient had more then 3 h of consecutive missing temperature data. Temperature during hours of missing data was estimated via linear interpolation. Area under the temperature–time graph was calculated via the trapezoid rule. Details of cooling-related complications were also collected. Cooling-related complications were defined as: symptomatic bradycardia (bradycardia requiring treatment with atropine, sympathomimetics or pacing), cooling abandoned, target not reached (i.e. less than 12 h spent below 34 °C), pancreatitis (serum amylase >500 IU/L), new diagnosis of pneumonia in first 7 days (documented chest infection requiring treatment with antibiotics), bleeding or platelet transfusion and requirement for renal replacement therapy. For the purpose of this analysis overcooling (temperature less than 32 °C), and overshoot during re-warming (temperature greater than 38 °C in the first 72 h) were regarded as complications. Phases of therapeutic hypothermia were defined as follows: cooling phase was admission temperature until 34 °C was reached, target range was 32–34 °C, and rewarming phase 34–36 °C.

Patient demographic details, dates of ICU and hospital admission and discharge, status at discharge, duration of mechanical ventilation and core temperature for the first 72 h of ICU admission were collected by querying the Carevue (Phillips) ICU database. This was undertaken by our audit and database management team. The remaining data were gathered by review of case notes and electronic patient records.

3. Statistical analysis

Between-group comparisons were made using Student's *t*-test, Fischer's Exact Test and analysis of covariance where appropriate.

Table 1
Patient demographics, cooling efficacy and outcome.

	All patients	Endovascular	Surface	p
Demographics				
N	83	42	41	
Age (years)	61.4 ± 15.7	63.1 ± 13.1	59.6 ± 17.9	0.31
Female, *n* (%)	20 (24.1)	13 (31.0)	7 (17.1)	0.20
Weight (kg)	78.9 ± 12.6	79.8 ± 12.4	78.1 ± 12.9	0.53
APACHE II	29.1 ± 5.1	28.2 ± 4.9	29.9 ± 5.2	0.14
Cardiac arrest details				
Out of hospital, *n* (%)	73 (87.5)	39 (92.9)	34 (82.9)	0.19
VF/VT, *n* (%)	53 (63.9)	32 (76.2)	21 (51.2)	0.02
Time to ROSC (min)	20.6 ± 16.4	18.9 ± 11.3	22.4 ± 20.4	0.34
Cooling efficacy				
Time to target temperature (h)		5.2 ± 3.3	6.1 ± 4.8	0.29
Time at target temperature (h)		22.4 ± 6.1	17.5 ± 12.3	0.02
Time to re-warm (h)		6.8 ± 2.6	5.5 ± 2.7	0.04
Area under 48-h temperature curve (°C h)		1661 ± 33	1687 ± 53	0.008
Average temperature fluctuation 10–20 h (°C)		1.0 ± 0.8	1.7 ± 1.3	0.003
Outcome measures				
ICU mortality, *n* (%)	37 (44.6)	16 (38.1)	21 (51.2)	0.27
Hospital mortality, *n* (%)	45 (54.2)	21 (50.0)	24 (58.5)	0.51
ICU free days	9.7 ± 10.2	9.7 ± 9.8	9.6 ± 10.7	0.97
Ventilator free days	10.6 ± 10.7	10.9 ± 10.4	10.2 ± 11.2	0.76
Neurological outcome				
N	83	42	41	
Poor neurological outcome, *n* (%)	49 (59)	24 (57.1)	25 (61.0)	0.82
PCPC	3.3 ± 1.9	3.2 ± 1.9	3.5 ± 1.9	0.55

Data are mean (±SD) or count (%).
Abbreviations: VF/VT, ventricular fibrillation/pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; ICU, intensive care unit; PCPC, Pittsburgh Cerebral Performance Criteria.

Comparison of binary outcomes (mortality, neurological outcome) was via logistic regression. The variable selection process was made *a priori*, based upon important variables identified in the literature.[6] These included: cooling technique, APACHE II score, time to ROSC, and primary arrest rhythm (ventricular fibrillation/pulseless ventricular tachycardia versus non-ventricular fibrillation/pulseless ventricular tachycardia). Multicollinearity was screened for using the variance inflation factor, with an upper acceptable limit of 2.5. The procedure for dealing with multicollinearity (if present) was variable exclusion. Interaction effects were not screened for. Routine goodness of fit tests and residual analyses were performed (examination of residual plots for delta-deviance, delta-dfitbeta, Cook's distance, and the Hosmer Lemeshow test). Because small multivariable models typically produce over-inflated odds ratios (known as shrinkage), we estimated model shrinkage using the heuristic shrinkage estimator proposed by van Houwelingen and Le Cessie.[8] This gives a global estimate of the model signal-to-noise ratio, with values $\geq$0.80 being desirable (meaning that <20% of the model is likely to be noise). Statistical analysis was carried out using SPSS version 15 (SPSS, Chicago, IL) and Stata v11 (Stata Corp., TX).

4. Results

4.1. Demographics and cardiac arrest details

A total of 83 patients receiving TH were identified, of which 42 underwent endovascular cooling and the remaining 41 underwent surface cooling. Between-group comparisons for demographics, cardiac arrest details, primary outcomes and complications are summarized in Tables 1 and 2. The two groups were comparable in terms of age, sex, weight and APACHE II scores. The majority (87.5%) of cardiac arrests was "out of hospital" and in 63.9% the primary rhythm was ventricular fibrillation or pulseless ventricular tachycardia. Of note the proportion of ventricular fibrillation/pulseless ventricular tachycardia was higher in the endovascular group (76% versus 51%, $p = 0.02$). Time to return of spontaneous circulation was similar between the groups.

4.2. Cooling efficacy

Mean temperature with 95% confidence intervals for each group from ICU admission until 72 h is shown in Fig. 1. No difference was observed in time taken to reach target temperature between the two groups (Table 1); however this may have been influenced by lead time bias as cooling was commenced in the Emergency Department and there was a higher starting temperature for the endovascular group (36.2 °C versus 35.7 °C, Fig. 1). The endovascular group spent significantly longer in the target range (22.4 h versus 17.5 h; $p = 0.02$) and re-warmed at a slower rate ($p = 0.04$).

Table 2
Cooling-associated complications.

	All patients	Endovascular	Surface	p
N	83	42	41	
Complication				
Overcooling	15 (18%)	4 (10%)	11 (27%)	0.049
Overheat	37 (45%)	18 (43%)	19 (46%)	0.83
Target not reached	13 (16%)	3 (7%)	10 (24%)	0.04
Cooling abandoned	5 (6%)	2 (5%)	3 (7%)	0.68
Bradycardia	18 (22%)	10 (24%)	8 (20%)	0.79
Pancreatitis	0 (0%)	NA	NA	NA
Pneumonia	49 (59%)	29 (69%)	20 (49%)	0.08
Bleeding	7 (8%)	6 (14%)	1 (2%)	0.11
Platelet transfusion	3 (4%)	2 (5%)	1 (2%)	1.00
Renal replacement therapy	14 (17%)	5 (12%)	9 (22%)	0.25
Any complication	73 (88%)	38 (91)	35 (85%)	0.52

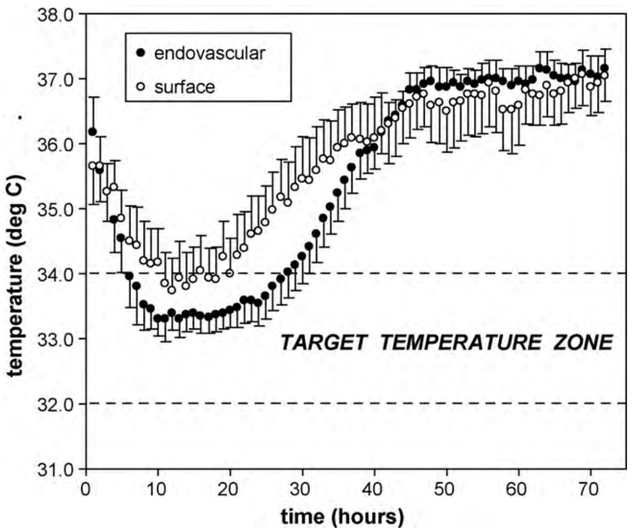

Fig. 2. Seventy-two hour profiles of temperature for the two groups. Data are mean, error bars 95% confidence interval for the mean.

The area under the temperature–time curve over 48 h was significantly less in the endovascular group (Table 1 and Fig. 2, $p = 0.008$). To exclude a learning effect (as the majority of patients in the first half of the study were treated by surface cooling), we also compared the area under the 48 h temperature–time curve for the two cooling methods after adjustment for study period (2005–2006, $n = 38$ versus 2007, $n = 45$) using analysis of covariance. This confirmed the superiority of endovascular cooling ($p = 0.003$), with no obvious time period effect ($p = 0.13$). There was also less temperature variation in the endovascular group when compared between 10 and 20 h, when cooling was most likely to have been in steady state as judged in Fig. 1 (1.0 °C versus 1.7 °C, $p = 0.003$, Table 1).

4.3. Complications

The surface cooling group had a higher incidence of overcooling (27% versus 10%, $p = 0.049$) and inability to reach the cooling target (24% versus 7%, $p = 0.04$). Therapeutic hypothermia was abandoned in 6% ($n = 5$) overall, in almost equal proportions across the two groups ($p = 0.68$, Table 2). This was for haemodynamic instability ($n = 3$), hematemesis ($n = 1$) and cardiogenic shock. Other than this there were no significant differences in complications between groups. The apparent increase in bleeding in endovascular group (14% versus 2%) did not reach statistical significance ($p = 0.11$). Of the patients in the endovascular group who suffered bleeding one was as a result of a traumatic pre-hospital intubation. The rest were ooze or minor bleeding reported around the endovascular catheter site.

4.4. Outcome measures

There was no difference in unadjusted ICU or hospital mortality, ICU-free days or ventilator-free days between groups (Table 1). The unadjusted proportion with poor neurological outcome was also similar. Multivariable analysis (Table 3) showed that two factors were consistently associated with mortality: (a) a higher APACHE II score and (b) cardiac arrests other than ventricular fibrillation/pulseless ventricular tachycardia. After adjustment for potential confounders (Table 3), there was no difference in ICU mortality, hospital mortality or neurological outcome with endovascular compared to surface cooling.

5. Discussion

The role of TH in comatose survivors of cardiac arrest is increasingly recognized,[3–5] and there is increasing evidence that a standardised approach including coronary revascularization and therapeutic hypothermia may enhance survival.[9] The optimal technique for delivering TH is debatable; the International Liaison Committee on Resuscitation identifies "optimal cooling technique – internal versus external" as a critical knowledge gap.[6] In their 2008 consensus statement, the Committee recommends that temperature maintenance is best achieved with devices that incorporate continuous temperature feedback.[6] They highlight the potential drawbacks of surface cooling using ice packs: increased labor intensity, greater temperature fluctuations, and inability to undertake controlled re-warming. This is despite the fact that, in both prospective randomized controlled trials of therapeutic hypothermia, cooling with external application of ice packs was used.[3,4] The importance of timing, especially "time to target temperature" is also controversial. Wolff et al. undertook multivariate regression analysis on a group of 49 patients successfully resuscitated from cardiac arrest and suggested that short time to target temperature was an independent predictor of a good neurological outcome,[10] however registry data from 975 patients collected between 2004 and 2008 found that factors related to the timing of TH had no apparent association to outcome.[11]

Table 3
Multivariable analysis of outcome measures.

Variable	Odds ratio	(95% CI)	p
ICU mortality (Hosmer Lemeshow $X^2 = 9.86$, $p = 0.28$, shrinkage = 0.805)			
Endovascular cooling	0.97	(0.35–2.70)	0.96
APACHE II*	1.17	(1.05–1.31)	0.004
Non-VF/VT	3.36	(1.18–9.61)	0.02
Time to ROSC**	1.01	(0.98–1.04)	0.38
Hospital mortality (Hosmer Lemeshow $X^2 = 3.46$, $p = 0.90$, shrinkage = 0.787)			
Endovascular cooling	1.24	(0.45–3.42)	0.68
APACHE II*	1.12	(1.01–1.24)	0.03
Non-VF/VT	5.46	(1.78–16.72)	0.003
Time to ROSC**	1.01	(0.98–1.04)	0.60
Poor neurological outcome (Hosmer Lemeshow $X^2 = 6.98$, $p = 0.54$, shrinkage = 0.801)			
Endovascular cooling	1.65	(0.58–4.74)	0.35
APACHE II*	1.09	(0.99–1.21)	0.10
Non-VF/VT	8.52	(2.42–30.03)	0.001
Time to ROSC**	1.01	(0.98–1.04)	0.60

Abbreviations: VF, ventricular fibrillation; VT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation.

* Odds ratio per one point increase in APACHE II score.

** Odds ratio per 1 min increase in ROSC. In all models global shrinkage was approximately 0.80, illustrating an acceptable signal-to-noise ratio.

Moreover the majority of reports to date have not involved direct comparison of endovascular versus surface methods, but rather documented the efficacy of TH using one of these two techniques in isolation. A retrospective study found that approximately two-thirds (20/32) of patients undergoing TH with ice-packs and cooling blankets demonstrated overcooling (temperatures <32 °C).[12] Conversely, endovascular temperature control has been used successfully in the neuro-ICU setting as early as 2002.[13] Holzer et al. compared 97 patients following cardiac arrest undergoing TH using an endovascular device with 941 control patients who had received standard therapy with normothermia over a 13-year period. They found temperature control with the endovascular device to be safe and effective and associated with improved survival and short term neurological recovery compared to the control group.[14]

Two studies have compared various combinations of cooling methods. Flint et al.[15] retrospectively evaluated endovascular cooling when used as an adjunct to a surface method in 42 patients over 3.5 years. The combination of endovascular and surface cooling provided better temperature control with less overcooling and a lower incidence of bradycardia compared to surface cooling alone. Hoedemaekers et al. compared five cooling methods in 50 patients (aiming for either TH or normothermia, dependent upon indication for cooling), and also found the endovascular technique more efficacious.[16]

Our study provides a large single-centre comparison of endovascular versus surface cooling following cardiac arrest. Our patient demographic is comparable to that reported by the European Resuscitation Council Hypothermia Registry, with a similar proportion of out of hospital cardiac arrest (87.5% versus 91%) and a first reported rhythm of ventricular fibrillation or pulseless ventricular tachycardia (64% versus 68%).[17] In terms of efficacy, we have shown that endovascular cooling appears superior to surface cooling, providing a greater proportion of time in the target zone (32–34 °C) and better control during rewarming. The importance of the latter finding is because rapid rewarming may negate the potential benefits of TH.[18] The cooling-associated complication rate was also more favorable for endovascular cooling, in terms of a lower proportion of patients experiencing both overcooling and failing to reach the cooling target. However this did not translate into a difference in other temperature-influenced complications (bradycardia, pancreatitis, etc.) between the groups. The efficacy and complication rate of endovascular cooling in our study is in accord with previous reports.[13–15]

After adjustment for confounders, we could not demonstrate a difference in outcome between the groups; in terms of mortality, ICU stay or neurological status at discharge. Whether this represents true equivalence or a type 2 error is unknown. Two potential sources of type 2 error in a retrospective study such as ours are failure to adjust for unknown confounders, and small sample size; both could only be addressed by a randomized control trial. One such potential confounder in the current study could be an unintended change in our entry criteria for TH as time progressed, meaning that we were offering TH to patients with different prognostic profiles in the latter half of the study when endovascular cooling was the preferred technique. This is consistent with (a) the increased number of patients receiving TH in the second half of the study (see Supplementary Figure 1), despite our overall ICU admission rate for cardiac arrest being unchanged, and (b) a higher proportion of patients with VF/VT in the endovascular group. In addition, our relatively small sample size may also have resulted in overfitting of the multivariable model; which typically gives an inflated estimate of effect size.[19] Although we attempted to account for this by quantifying shrinkage, this may not compensate fully for this phenomenon.[19] Indeed, it is conceivable that several harmful effects may be associated with endovascular cooling. Patel et al. highlighted safety concerns about catheter-related blood stream infections arising from endovascular cooling[20]; while a recent study of efficacy and safety in 40 patients noted a six-fold increase in nosocomial bacteremia compared with the general ICU population.[21] Again this is consistent with the higher (albeit non-significant) rates of endovascular nosocomial pneumonia (69% versus 49%) and bleeding (14% versus 2%) seen in our patients.

Our study has several limitations. Although the largest comparative study of its kind, it is still small, retrospective and uncontrolled. A possible source of bias is that patients undergoing surface cooling were more likely to receive this technique during our first 18 months experience with TH; following this period endovascular cooling was the preferred technique, and surface cooling was only undertaken if the Alsius Coolguard was already in use on another patient. This may have resulted in a learning curve effect for TH *per se*, thereby diminishing the apparent efficacy of surface cooling. Lastly, TH was usually initiated on admission to ICU and not at the site of cardiac arrest, which may decrease any survival benefit.

6. Conclusion

Endovascular cooling appears more efficacious than surface cooling in terms of temperature control for TH following cardiac arrest; this is also associated with a better temperature-associated complication profile. After adjustment for known confounders, we were unable to show a difference in outcome with either technique. This requires confirmation in a randomized control trial.

Conflict of interest statement

None to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.resuscitation.2010.05.001.

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