Therapeutic hypothermia after cardiac arrest in clinical practice: Review and compilation of recent experiences

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Objectives: **We sought to review findings from recent literature on the postresuscitation care of cardiac arrest patients using therapeutic hypothermia as part of nontrial treatment.**

Design: **Literature review.**

Setting: **Hospital-based environment.**

Subjects: **Patients initially resuscitated from cardiac arrest who underwent hypothermia induction as a treatment regimen or historical control patients who did not receive hypothermia therapy.**

Measurements: **We compiled protocol methodology from the various studies, as well as survival-to-hospital discharge and neurological outcomes.**

Main Results: **Although varied in their protocols and outcome reporting, results from published investigations confirmed the findings from landmark randomized controlled trials, in that the use of therapeutic hypothermia increased survival with an odds ratio of 2.5 (95% confidence interval, 1.8–3.3) and favorable outcome with an odds ratio of 2.5 (95% confidence interval, 1.9–3.4).**

Conclusions: **The survival and neurological outcomes benefit from therapeutic hypothermia are robust when compared over a wide range of studies of actual implementation. (Crit Care Med 2009; 37[Suppl.]:S223–S226)**

KEY WORDS: hypothermia; heart arrest; sudden death; adverse events; ischemia-reperfusion injury

Therapeutic hypothermia (TH) has been shown to improve survival and neurological outcomes after sudden cardiac arrest in several randomized clinical trials (1–3). Despite this body of work, and subsequent consensus recommendations by the International Liaison Committee on Resuscitation for the use of TH after sudden cardiac arrest resuscitation (4–5), adoption of this treatment option has been slow, especially in the United States (6–9). Physicians have cited the complexity of TH implementation, the relative paucity of data from actual use, concerns for adverse reactions, and the need for improved technology as barriers to implementation. Others have reported difficulty with simple cooling methods such as cold intravenous fluids or external ice packs and have questioned if other methodology or equipment may be required (7).

A number of recent publications have described implementation of TH clinical protocols within hospital systems outside of the context of clinical trials (10–22). These reports reflect a variety of hospital environments and approaches to TH, and therefore provide unique datasets with which to examine TH in actual clinical practice, outside the previously described randomized clinical trials. In this article, we will review and compare data from these studies, with attention to methods of cooling, adverse effects, and clinical outcomes from TH, such that a "real world" assessment of cooling methodology can be described.

METHODS

An electronic search of the literature (PubMed; National Library of Medicine, Washington, DC) was conducted to identify potential reports of TH after cardiac arrest. The search, conducted in November 2007, used the following strategy: (hypothermia or cooling or temperature) and (cardiac arrest or postresuscitation). No language restrictions were applied. Bibliographies of each selected study were hand-searched to identify additional pertinent literature for consideration.

Studies were considered for analysis if they evaluated adult victims of sudden cardiac arrest (>18 yrs old), if they were not randomized controlled trials, and if they were published after 2002 when the Bernard et al (2) and HACA Study Group (3) randomized controlled trials were published. Studies with and without historical controls (nonhypothermia subjects) were included. Survival outcomes, adverse effects, and cooling and rewarming methods and rates were compared when possible. Studies were excluded if they did not meet these criteria; in addition, exclusion criteria for the adverse events analysis included those articles that did not report adverse events. Animal studies and clinical case reports were excluded from analysis, as were meta-analyses or other manuscripts without the report of primary data.

Outcome was scored at hospital discharge or at various points thereafter (30 days, 6 mos, and 1 yr from discharge) among the group of publications. For uniformity of comparison, studies with survival outcomes scored after discharge were assumed to have at least the same survival rate at discharge. For subjective assessment of neurological outcomes, the assessment from each manuscript was included at the time assessed (detailed in Table 1). Therefore, all reported outcomes were compared. Neurological outcomes were scored in this publication cohort based on Glasgow–Pittsburgh Cerebral Performance Category, Overall Performance Category, Glasgow Outcome Score, or Glasgow Outcome Coma Scale, which have been validated and described elsewhere (23–26). Favorable neurological outcome was defined as survival with sufficient cerebral function to perform activities of daily life and/or return to work in some fashion (no disability or moderate disability). Therefore, a Cerebral Performance Category or Overall Performance Category score of 1 or 2, Glasgow Outcome Score of 1 or 2, and Glasgow Outcome Coma Scale of 14 or 15 were all scored together as a favorable recovery.

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Table 1. Studies included in current analysis[a]

	Arrich et al (17)	Al-Senani et al (10)	Belliard et al (21)	Busch et al (14)	Feuchtl et al (22)	Haugk et al (16)	Holzer et al (12)	Hovdenes et al (20)	Kliegel et al (11)	Laish-Farkash et al (19)	Oddo et al (13)	Scott et al (15)	Schefold et al, (30)	Sunde et al (18)
Study type														
Prospective		X				X			X	X		X	X	X
Retrospective			X	X	X		X	X			X			
Historic (nonhypothermia) controls	X		X	X			X						X	X
Location														
Teaching hospital		X	X	X	X	X	X	X	X	X	X		X	X
Community hospital												X		
Consortium	X													
Method of cooling														
Endovascular	X	X			X		X		X					X
Surface cooling														
With device	X				X	X		X		X	X	X	X	X
Simple surface cooling	X		X	X							X	X		X
Cooling duration														
24 hrs	X	X			X	X	X	X	X	X	X		X	X
12 hrs														
Other			24–48 hrs	12–24 hrs								24–36 hrs		
Outcome assessment														
Hospital discharge	X	X	X	X	X				X	X	X	X	X	X
30 days		X					X							
6 mos						X		X	X					

[a]Studies are listed by first author in alphabetical order.

Statistical analyses were performed using a statistical software package (StatXact with Cytel Studio version 6.0; Cytel, Cambridge, MA). The Breslow–Day statistic was used to test for homogeneity of odds ratios (ORs). The Mantel–Haenszel test was used to evaluate the summary ORs. Any reporting of adverse events in percentage form was converted to absolute numbers using the number of patients (n) indicated in the original article. Time to target temperature was reported using median with interquartile range (IQR), mean with range, or SD as indicated.

All rates and time to target temperatures were converted to minutes unless otherwise specified. If the original manuscript provided a rewarming rate, an active method of cooling was assumed to be in place unless otherwise mentioned, given that those studies also used a closed circuit device to control temperature during the hypothermia protocol.

Adverse events included in the analysis were defined, whenever possible, as they were in the published reports. If the investigation defined an adverse event as pneumonia or sepsis that definition was carried into this analysis. Arrhythmias were reported variously in the manuscript cohort. To compare overall arrhythmia events, any of the following, if reported in the original manuscripts, are included in this analysis: any arrhythmia, including brady- and tachyarrhythmias, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, narrow complex tachycardia, or bradycardia. "Not reported" was used if the article did not report that type of adverse event. Given concerns for reporting bias and variability of definitions, adverse event data are presented without statistical significance values.

An endovascular method of cooling was defined as any intravenous catheter used for heat exchange. External cooling with a device was defined as the use of equipment that uses skin surface contact as a means of heat exchange coupled to a temperature probe and thermostatic mechanism. Simple external cooling was defined as any method in which surface contact heat exchange was used without closed circuit temperature feedback (e.g., ice bags or cooling packs).

RESULTS

The initial electronic literature search using the terms defined in the "Methods" section resulted in 1067 hits. These were analyzed for relevance to the study topic and the inclusion/exclusion criteria defined in the "Methods" section. A total of 13 published reports were found for comparison based on these criteria, representing the clinical use of TH in adult patient cohorts outside the context of randomized controlled trials (Table 1). The majority of studies were performed at tertiary care teaching hospitals. Arrich et al (17) used a collection of data from multiple hospitals provided by the European Resuscitation Council Hypothermia After Cardiac Arrest Registry.

Outcome Comparisons. All studies with historical (nonhypothermia) controls were analyzed for survival and outcome comparisons between normothermic historical controls and TH-treated patients (Table 2). Confirming the range of survival improvements as seen in the randomized trials, the OR in each study reflects a marked mortality benefit with the use of TH, as well as improvements in neurological outcomes. Summary ORs are shown at the bottom of Table 2, and demonstrate an approximately two- to three-fold improvement in both survival and neurological outcomes with TH implementation.

The survival and favorable neurological outcomes data for the studies that did not include historical control data are shown in Table 3. Despite the limitation of lacking controls, it is worth noting that the combined survival-to-hospital discharge outcome is 59%, similar to the TH groups that were compared with historical (nonhypothermia) controls in Table 2, which suggested a 65% combined survival. Additionally, the percentage of favorable neurological outcome in the studies without historical controls was 45%, again similar to the 47% of those studies compared with controls.

Adverse Events

An analysis of adverse events from the manuscript cohort is shown in Table 4. Although a number of adverse events are evaluated in the manuscript cohort, only those

Table 2. Survival and favorable outcomes in study subset with historical controls

Author	n		Survival				"Favorable Outcome"			
	HC	TH	Historical Control n (%)[a]	Therapeutic Hypothermia n (%)	OR	95% CI	Historical Control n (%)	Therapeutic Hypothermia n (%)	OR	95% CI
Arrich et al (17)	123	462	39 (32)	267 (58)	2.9	1.9–4.6	39 (32)	212 (46)	1.8	1.2–2.8
Belliard et al (21)	36	32	13 (36)	18 (56)	2.3	0.8–6.8	6 (17)	13 (41)	3.4	0.99–12.8
Busch et al (14)	34	27	11 (32)	16 (59)	3.0	0.9–9.9	9 (26)	11 (41)	1.9	0.6–6.5
Oddo et al (13)	54	55	20 (37)	28 (51)	1.8	0.8–3.8	11 (20)	26 (47)	3.5	1.4–9.1
Schefold et al (30)	31	31	21 (70)	21 (70)	1.0	.3–2.9	6 (19)	19 (61)	6.6	2.1–20.8
Sunde et al (18)	58	61	18 (31)	34 (56)	2.8	1.2–6.4	15 (26)	34 (56)	3.6	1.6–8.5
Combined ORs					2.5	1.8–3.3			2.5	1.9–3.4

HC, historical control (nonhypothermia) group; TH, therapeutic hypothermia group; OR, odds ratio; CI, confidence interval.

[a]All percentages rounded to nearest integer. Favorable outcome is defined in the "Methods" section; generally considered favorable if Cerebral Performance Category at discharge was a 1 or 2.

Table 3. Survival and favorable outcome in studies without historical controls

Author	TH, n	Survival, n (%)[a]	Favorable Neurologic Outcome, n (%)
Al-Senani et al (10)	13	9 (69)	5 (38)
Feuchtl et al (22), endovascular	19	11 (58)	9 (47)
external	20	11 (55)	4 (20)
Haugk et al (16)	28	14 (50)	9 (32)
Hovdenes et al (20)	50	41 (82)	34 (68)
Kliegel et al (11)	26	14 (54)	13 (50)
Laish-Farkash et al (19)	51	32 (63)	31 (61)
Scott et al (15)	49	19 (39)	16 (33)

TH, therapeutic hypothermia group.

[a]All percentages rounded to nearest integer. Feuchtl et al utilized two separate cooling methods and reported data separately, as shown in the table.

Table 4. Overview of adverse events

Author	Group	n	Pneumonia (%)[a]	Sepsis (%)	Arrhythmia (%)	Bleeding (%)
Arrich et al (17)	TH	462	NR	NR	28 (6)	15 (3)
Busch et al (14)	TH	27	19 (70)	NR	7 (26)	NR
Busch et al (14)	HC	26	13 (50)	NR	9 (35)	NR
Laish-Farkash et al (19)	TH	51	27 (53)	12 (24)	5 (10)	8 (16)
Oddo et al (13)	TH	55	16 (29)	2 (4)	20 (36)	NR
Oddo et al (13)	HC	54	19 (35)	2 (4)	23 (43)	NR
Sunde et al (18)	TH	61	29 (47)	2 (8)	15 (25)	5 (8)
Sunde et al (18)	HC	58	33 (57)	1 (2)	9 (16)	NR
Total, TH	TH	656	91/194 (47)	16/167 (10)	75/656 (11)	28/574 (5)
Total, HC	HC	138	65/138 (47)	3/112 (3)	41/138 (30)	NA

TH, therapeutic hypothermia group; HC, historical control (nonhypothermia) group; NR, not reported; NA, not applicable.

[a]All percentages rounded to nearest integer. Statistical significance of combined results was not calculated, because some reports are without historical controls and others did not report specific adverse events (note differing denominators in each column total).

that are included in the majority of studies are shown. Given the variability of reporting and adverse event definitions, the data shown in Table 4 are presented without statistical assessment.

DISCUSSION

In this review of recent literature pertaining to TH application outside of randomized controlled trials, we have found that real world application of TH affords the same survival and neurological outcome benefits seen in the landmark trials, with similar adverse event profiles as well. Although TH represents a powerful evidence-based approach to treat patients after resuscitation from sudden cardiac arrest, there is no established universal methodology for reporting or quantifying the effects of TH, making comparisons between studies difficult. We sought to review the current literature with the primary goal of comparing and contrasting TH investigations on outcomes that are commonly reported.

TH has been incorporated into international consensus guidelines for resuscitation care since 2005. Despite this, survey studies have shown that uptake of the therapy has been slow, in part due to the perception of sparse data. Given that randomized controlled trials in cardiac arrest care are expensive to conduct as well as complex from regulatory and informed consent perspectives, it remains unclear whether other randomized controlled trials using TH postarrest will take place, given the positive findings of the initial trials in 2002. Therefore, case series and implementation reports are useful and important additions to the literature. It is likely that there will be additional such publications in coming years as well, as other postresuscitation care modalities—such as more careful neurological monitoring (27) and the use of specific hemodynamic goals (28)—are performed in addition to TH.

A review of the current publications reveals a fundamental problem in the field that hinders appropriate comparisons. That is, there is little standardization regarding reporting of postarrest variables such as adverse events, cooling rates, method of temperature monitoring, and other data. Similar issues in the documentation of cardiac arrest data were improved by the development of the so-called "Utstein style" template, a consensus set of data elements that encouraged uniform reporting in the literature (29). It is likely that similar tem-

plates will be required for postarrest care data collection.

It is interesting to note that the magnitude of benefit in the currently reviewed studies is similar to that seen in the randomized controlled trials by Bernard et al and the HACA group (2, 3), despite the range of hospital environments and methods of cooling used in the manuscript cohort. One may hypothesize that the findings in a randomized trial would be enhanced by the careful presence of study infrastructure and staff, as well as stricter protocol adherence; to a first approximation, we have found that the survival benefit of TH is robust and was not highly dependent on the apparatus of a clinical trial.

A limitation of this review is the narrow scope of adverse event reporting. A number of potential adverse effects of cooling have been proposed, including a range of infectious complications, shivering, coagulopathy, electrolyte derangements, and arrhythmia. We chose to include only adverse events that were reported by a number of investigations. Another limitation in the literature is that the magnitudes of adverse events are rarely reported but of great relevance for practitioners; for example, in the study by Arrich et al (17), 3% of TH-treated patients had bleeding complications, but only approximately 1% had bleeding complications actually requiring treatment. Future studies will hopefully present more expansive data on adverse effects of TH to guide future protocol development.

In summary, we have found that among publications describing TH protocol implementation, similar benefits in terms of both survival and neurological outcomes were obtained compared with prior randomized controlled trials. Adverse event reporting was widely variable, but adverse event profiles among TH cohorts did not differ widely from the non-TH groups. Further work will be required to derive a consensus set of data elements that should be reported in TH studies such that meaningful comparisons can be made. Through such work, and the extension of other postresuscitation care modalities, the ability of TH to improve patient outcomes will be enhanced in coming years.

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