Efficacy of Mild Hypothermia for the Treatment of Patients with Cardiac Arrest

Yu Gao[1], Kang-Li Hui[2], Yu-Jie Wang[1], Lin Wu[2], Man-Lin Duan[2], Jian-Guo Xu[2], De-Xin Li[2]

[1]Jinling Hospital, Medical School of Nanjing University, Nanjing, Jiangsu 210000, China

[2]Department of Anesthesiology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu 210000, China

Abstract

Background: Therapeutic hypothermia has been recommended for the treatment of cardiac arrest patients who remain comatose after the return of spontaneous circulation. The aim of this study was to evaluate the effectiveness and safety of mild hypothermia on patients with cardiac arrest by conducting a meta-analysis.

Methods: The relevant trials were searched in Cochrane Library, PubMed, Web of Science, Embase, CNKI and Wan Fang Data from the date of their establishment to October 2014. Thereafter, the studies retrieved were screened based on predefined inclusion and exclusion criteria. Data were extracted, and the quality of the included studies was evaluated. A meta-analysis was conducted using the Cochrane Collaboration Review Manager 5.2 software.

Results: Six randomized controlled trials involving 531 cases were included, among which 273 cases were assigned to the treatment group and the other 258 cases to the control group. The meta-analysis indicated that mild hypothermia therapy after cardiac arrest produced significant differences in survival rate (relative risk [*RR*] =1.23, 95% confidence interval [*CI*]: 1.02–1.48, $P = 0.03$) and neurological function (*RR* = 1.33, 95% *CI*: 1.08–1.65, $P = 0.007$) after 6 months compared with normothermia therapy. However, no significant differences were observed in the survival to the hospital discharge (*RR* = 1.35, 95% *CI*: 0.87–2.10, $P = 0.18$), favorable neurological outcome at hospital discharge (*RR* = 1.53, 95% *CI*: 0.95–2.45, $P = 0.08$) and adverse events.

Conclusions: The meta-analysis demonstrated that mild hypothermia can improve the survival rate and neurological function of patients with cardiac arrest after 6 months. On the other hand, regarding the survival to hospital discharge, favorable neurological outcome at hospital discharge, and adverse events, our meta-analysis produced nonsignificant results.

Key words: Cardiac Arrest; Cardiopulmonary Resuscitation; Mild Hypothermia; Neurological Function; Survival Rate

Introduction

Modern cardiopulmonary resuscitation (CPR) began in 1960.[1] Incremental improvements in the survivorship from CPR occurred as more and more people were trained in CPR and as defibrillators became portable and were deployed in more locations. Unfortunately, a cascade of brain injury begins within minutes after cardiac arrest.[2] Finally, most people who had suffered from cardiac arrest did not survive to leave the hospital or did so in a neurological devastated state. In the early of 21st century, the survival rate of cardiac arrest outside of the hospital remained 7–8%.[3,4] About one-quarter of patients regained pulses after CPR, and about one-third of the patients with those initial successes survived hospitalization.

The severe brain defect after CPR stimulated many investigations into the pathophysiology of, and treatments for, global brain ischemia. For the protection of patient's brain, mild hypothermia therapy has been proposed. In many animal experiments, hypothermia plays a protective role. For example, it can increase the survival rate and improve neurological function of animal.[5] Besides, it reduces metabolic rate and the expression of some pro-apoptosis proteins.[6,7] In clinical trials, the effectiveness of hypothermia also has been proved.[8,9] Hence, 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommended,[10] comatose patients with out-of-hospital ventricular fibrillation cardiac arrest were cooled to 32–34°C for 12 or 24 h. However, recent years some other clinical trials showed that mild hypothermia cannot improve the prognosis of patients after CPR.[11] Therefore, we conducted a meta-analysis of all relevant published studies to evaluate the effectiveness and safety of mild hypothermia on patients with cardiac arrest.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.157691

Address for correspondence: Dr. Man-Lin Duan, Department of Anesthesiology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu 210000, China
E-Mail: dml9001@163.com

Methods

Inclusion criteria and exclusion criteria

Studies were considered for inclusion if they met the following criteria: (1) All published randomized controlled trials (RCTs). (2) We included studies in adult patients who suffered from cardiac arrest and were successfully resuscitated. (3) The intervention was therapeutic mild hypothermia, no matter how to lower the body temperature. The temperature should remain between 32°C and 34°C. And the treatment for the control group was according to the standard treatment after cardiac arrest without hypothermia. (4) The primary outcomes were survival rate and neurological function recovery. The secondary outcomes were adverse events, such as rearrest, renal failure, pulmonary edema and so on. (5) The relative risks (*RR*s) with their corresponding 95% confidence intervals (*CI*s) were reported. Studies were considered for exclusion if they met the following criteria: (1) We excluded studies on children and pregnant women. (2) Cardiac arrest patients under the treatment of mild hypothermia received other drugs in combination therapy. (3) There was a history of central nervous system depressant drug medication prior to cardiac arrest.

Search strategy and data extraction

An extensive literature search was conducted using electronic databases, manual searching, and correspondence with authors of included studies. The Cochrane Library, PubMed, Web of Science, Embase, CNKI, and Wan Fang Data were searched from the date of their establishment to October 2014. There was no language restriction on the publications. The search strategy was based on free text words. Search terms used were "cooling," "hypothermia," "CPR," "cardiac arrest" and "RCT." Two reviewers independently reviewed the citations, abstracts, and full-text articles and determined the eligibility of all the studies identified in the initial search. When the entire process was completed, the two cross-checked with each other. In cases of disagreements, a third reviewer was consulted. The following details were extracted: Authors, year of publication, sample size, interventions, and outcomes.

Quality assessment

Assessment of the quality of the included studies was performed using the methodology recommended by Cochrane Collaboration.[12] This method comprised assessments of the risk of potential bias in six domains: Random sequence generation (correct, incorrect or unclear), allocation concealment (correct, incorrect or unclear), blinding of outcome assessment (correct, incorrect or unclear), incomplete outcome data (complete, incomplete or unclear), selective reporting (yes, no or unclear), other bias (yes, no or unclear), such as the baseline, source of funding, and academic biases. If all quality criteria were met, the trial was considered to have a low risk of bias (score: A). If one or more of the quality criteria were only partially met, the trial was considered to have moderate risk of bias (score: B), and if one or more criteria not met, the trial was considered to have high risk of bias (score: C).

Statistical analysis

Statistical analysis was performed using Review Manager Version 5.2 (Cochrane Collaboration, Oxford, UK) software. We conducted separate meta-analysis according to different subgroups. The heterogeneity of the qualitative analysis was assessed by Chi-square test, and the significant level was set to $P = 0.1$. We used I^2 to conduct quantitative analysis of heterogeneity. The significant level was set to 50%. If $P > 0.1$, $I^2 < 50\%$, the different RCTs can be regarded as homogeneous. Pooled effect estimates were assessed using a fixed effects model. If $P < 0.1$, $I^2 \geq 50\%$, the different RCTs can be regarded as heterogeneity. Pooled effect estimates were assessed using a random effects model. We used weighted mean deviation (WMD) and 95% *CI* to represent the continuous data. And the dichotomous data can be described by *RR* and 95% *CI*. A funnel plot was used to examine publication bias. An asymmetric funnel plot indicated publication bias.

Results

Study selection process

A total of 1613 potentially relevant studies were identified from the following databases in our initial articles search: Two hundred and twenty-six from PubMed, 412 from Embase, 161 from Cochrane Library, 292 from web of science, 245 from CNKI, 237 from Wan Fang Data. After screening the titles or abstracts, 1553 irrelevant or duplicate studies were excluded. The full text of the remaining 60 studies was retrieved and assessed for eligibility. Of the retrieved studies, 54 studies were excluded because of other type of publications (review, case report, retrospective studies, prospective studies). Finally, a total of six studies met the inclusion criteria[13-18] [Figure 1].

Characteristics of the studies

The six RCTs included 531 adult patients who suffered from cardiac arrest and were successfully resuscitated. The original articles compared the therapeutic effect under different conditions (hypothermia or normothermia). Outcomes included survival rate, neurological function, adverse events and so on. The basic characteristics of these studies are shown in Table 1.

Quality assessment of the included studies

(1) All of the six studies mentioned "random," but only three studies described the method of generating a random sequence correctly. The other three studies did not describe how to generate random sequences. (2) Only two studies showed us they use a sealed envelope to conduct allocation concealment. The other four studies did not mention how to do allocation concealment. (3) Six studies mentioned blinding in which five studies were double-blind. (4) All of the six studies described the case of which quit or lost to follow-up. The number of quit or lost to follow-up of each study were <20% of the total number. Hence, we considered the data integrity is good. The detail assessments are shown in Table 2.

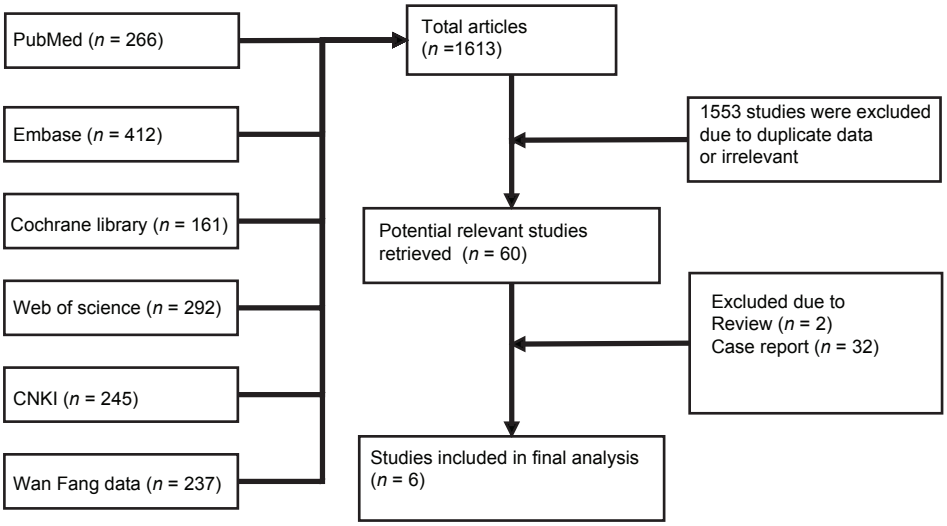

Figure 1: Flow diagram of the randomized controlled trials reviewed for this meta-analysis.

Table 1: Characteristics of the RCTs included in the meta-analysis

Studies	Sample size (treatment/control)	Rhythm	Interventions		Outcomes
			Treatment	Control	
Kämäräinen *et al.* (2009)	19/18	VF pulseless electrical activity	Cooling with 4°C intravenous infusion. Target temperature was 33°C. Duration of hypothermia was 12 h	Normothermia	Survival rate, neurological function, rearrest
Hypothermia after Cardiac Arrest Study Group (2002)	137/138	VF	Cooling with hypothermic blanket. Target temperature was 32–34°C. Duration of hypothermia was 24 h	Normothermia	Survival rate, neurological function, rearrest, renal failure
Hachimi-Idrissi *et al.* (2001)	16/14	CA	Cooling with helmet. Target temperature was 32–34°C. Duration of hypothermia was 3 h	Normothermia	Survival rate, neurological function, renal failure
Bernard *et al.* (2002)	43/34	VF	Cooling with ice packs. Target temperature was 32–34°C. Duration of hypothermia was 12 h	Normothermia	Survival rate, neurological function, rearrest
Laurent *et al.* (2005)	22/20	VF, CA	Direct external cooling of the blood. Target temperature was 32–34°C. Duration of hypothermia was 24 h	Normothermia	Survival rate, neurological function, rearrest
Tiainen *et al.* (2003)	36/34	VF	Cooling with ice packs and a cooling device. Target temperature was 32–34°C. Duration of hypothermia was 24 h	Normothermia	Survival rate, neurological function

RCTs: Randomized controlled trials, VF: Ventricular fibrillation, CA: Cardiac arrest.

Table 2: The methodological quality of the RCTs included in the meta-analysis

Studies	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias	Quality level
Kämäräinen *et al.* (2009)	Unclear	Unclear	Correct	Complete	No	No	B
Hypothermia after Cardiac Arrest Study Group (2002)	Correct	Correct	Correct	Complete	No	No	A
Hachimi-Idrissi *et al.* (2001)	Correct	Incorrect	Correct	Complete	No	No	C
Bernard *et al.* (2002)	Incorrect	Incorrect	Correct	Complete	No	No	C
Laurent *et al.* (2005)	Correct	Correct	Correct	Complete	No	No	A
Tiainen *et al.* (2003)	Unclear	Unclear	Unclear	Complete	No	No	B

RCTs: Randomized controlled trials.

Impact of mild hypothermia on survival rate of patients with cardiac arrest

The survival rate of patients who suffered from cardiac arrest and were successfully resuscitated is one of the primary outcomes which we concerned. All of the six studies reported the survival rate in which three studies[13-15] reported survival rate

at hospital discharge (subgroup 1), the other three studies[16-18] reported survival rate after 6 months (subgroup 2). There was no heterogeneity from the outcome in subgroup 1 ($P = 0.50$, $I^2 = 0$) and subgroup 2 ($P = 0.32$, $I^2 = 12\%$). A fixed effects model was used to analyze. The pooled results showed [Figure 2] no significant difference in the survival rate at hospital discharge between treatment group and control group (*RR* = 1.35, 95% *CI*: 0.87–2.10, $P = 0.18$). However, there was significant difference in the survival rate after 6 months (*RR* = 1.23, 95% *CI*: 1.02–1.48, $P = 0.03$). Summarized the above six studies, no heterogeneity among them ($P = 0.60$, $I^2 = 0$), and the pooled results showed hypothermia does improve the survival rate (*RR* = 1.25, 95% *CI*: 1.05–1.49, $P = 0.01$).

Impact of mild hypothermia on neurological function of patients with cardiac arrest

The neurological function of patients who suffered from cardiac arrest and were successfully resuscitated is another primary outcome which we concerned. In clinical, cerebral performance category (CPC) scale was often used to assess neurological function. The CPC scale ranges from 1 to 5, with 1 representing good cerebral performance (conscious, alert, capable of normal life) or minor disability which do not significantly compromise cerebral or physical function, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, dependent on others for daily life support, 4 coma or vegetative state (not conscious, unaware of surroundings, no cognition), and 5 brain death. Included studies considered CPC 1–2 as good neurological recovery and CPC 3–5 as bad neurological recovery. Hence, these data can be converted to dichotomous data. All of the six studies reported the neurological function in which three studies[13-15] reported neurological function at hospital discharge (subgroup 3), the other three studies[16-18] reported neurological function after 6 months (subgroup 4). There was no heterogeneity from the outcome in subgroup 3 ($P = 0.30$, $I^2 = 18\%$) and subgroup 4 ($P = 0.23$, $I^2 = 31\%$). A fixed effects model was used to analyze. The pooled results showed [Figure 3] no significant difference in the neurological function at hospital discharge between treatment group and control group (*RR* = 1.53, 95% *CI*: 0.95–2.45, $P = 0.08$). However, there was significant difference in the neurological function after 6 months (*RR* = 1.33, 95% *CI*: 1.08–1.65, $P = 0.007$). Summarized the above six studies, no heterogeneity among them ($P = 0.38$, $I^2 = 6\%$), the pooled results showed hypothermia does improve the neurological function (*RR* = 1.37, 95% *CI*: 1.13–1.66, $P = 0.001$).

Adverse events of mild hypothermia

In the included studies, only four studies[13,15-17] mentioned rearrest. Meta-analysis [Figure 4] demonstrated mild hypothermia does not influence the incidence of rearrest (*RR* = 1.19, 95% *CI*: 0.87–1.61, $P = 0.27$). Another two studies[14,16] mentioned the renal failure. The result [Figure 5] showed no significant difference between treatment group and control group (*RR* = 0.88, 95% *CI*: 0.48–1.61, $P = 0.68$). Other adverse events such as pulmonary edema, pneumonia, bleeding, showed the same results (data not shown). Because only a single article mentioned the above adverse events, we did not put them into meta-analysis.

Bias of publication and Sensitivity analysis

A funnel plot was used to examine publication bias. Figure 6 shows us the funnel plot is relative symmetric. And it indicated that there is almost no bias of publication. Most studies at the top of the funnel plot, it meant the studies'

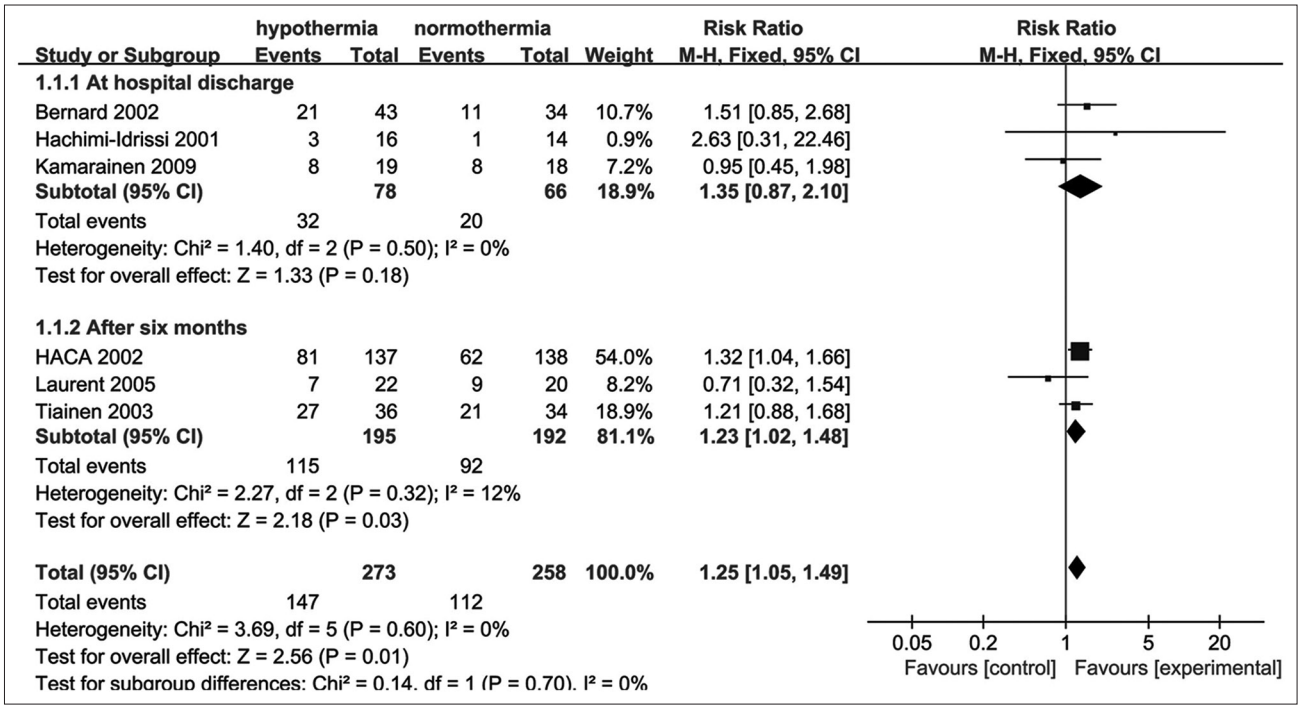

Figure 2: Summary of data on survival rate for mild hypothermia versus normothermia.

CI is narrow and their precision is high. To evaluate the influence of any single study on the pooled *RR* and *CI*, we performed a sensitivity analysis. We omitted two high-risk studies[13,14] from the overall analysis, the pooled *RR* (95% *CI*) ranged from 1.25 (1.05–1.49) to 1.21 (1.01–1.45) for studies reporting the *RR*s by survival rate and from 1.37 (1.13–1.66) to 1.30 (1.06–1.59) for studies reporting the *RR*s by neurological function. Sensitivity analysis demonstrated our results of the meta-analysis are stable.

Discussion

As the CPR technology became more and more mature, a growing number of patients with cardiac arrest were saved. And cerebral resuscitation was the key point after CPR.[19] Promotion and application of mild hypothermia therapy was a major advance in this field.[20] In the half past century especially the last 10 years, hypothermia is the only method that approved by a large amount of clinical trials[21,22] which can improve the prognosis of patients. But most trials in this field are single center and small sample size. Meta-analysis can evaluate the effectiveness and safety of hypothermia which results are quite credible. In this study, we used meta-analysis to integrate these different independent researches, in order to get more reliable analysis about the efficacy of mild hypothermia for the treatment of patients with cardiac arrest.

For patients rescued from cardiac arrest, we pay most attention to their prognosis. The survival rate and neurological function are the two most important indicators. The data of three studies[13-15] were measured at hospital discharge, the other three were measured after 6 months.[16-18] In order to avoid the heterogeneity first we analyzed the data by subgroups. The mild hypothermia therapy can not improve survival rate and neurological function at hospital discharge. However, it can improve the prognosis of patients after 6 months. We speculated the possible reasons are as follows: (1) Whole-body hypothermia influences all organ systems, and any potential benefit should be balanced against

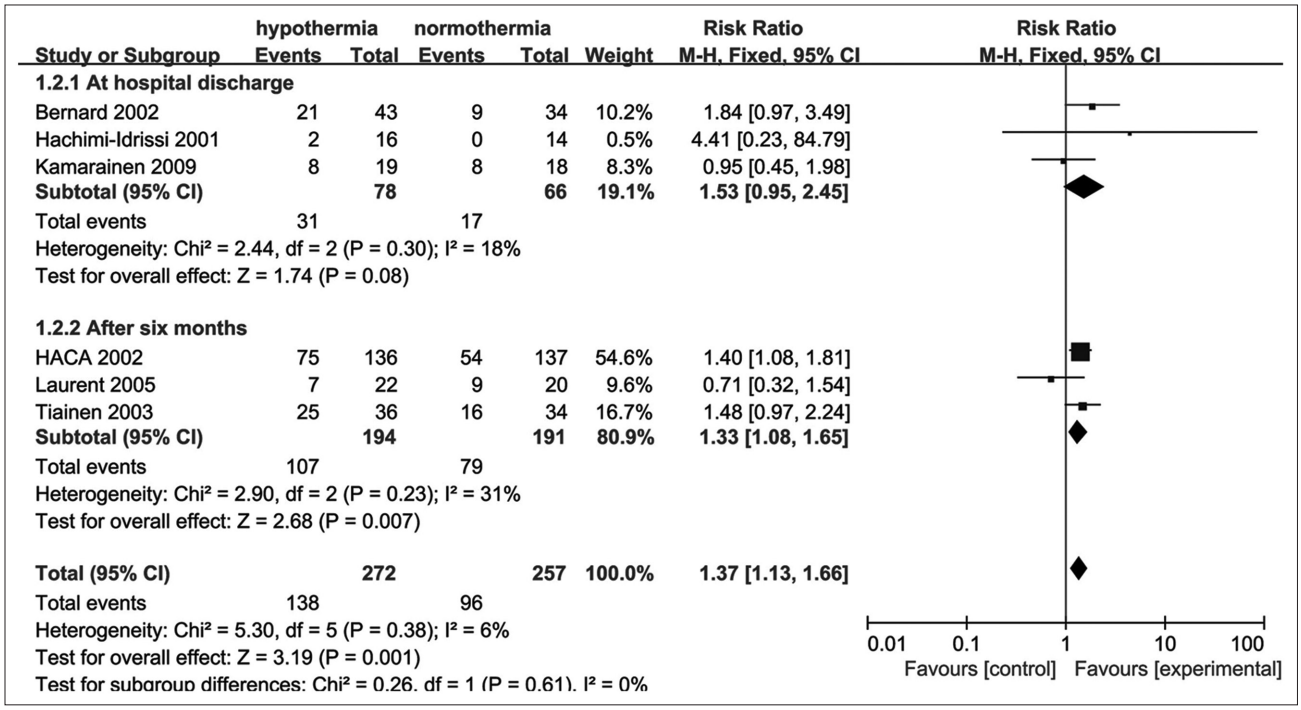

Figure 3: Summary of data on neurological function for mild hypothermia versus normothermia.

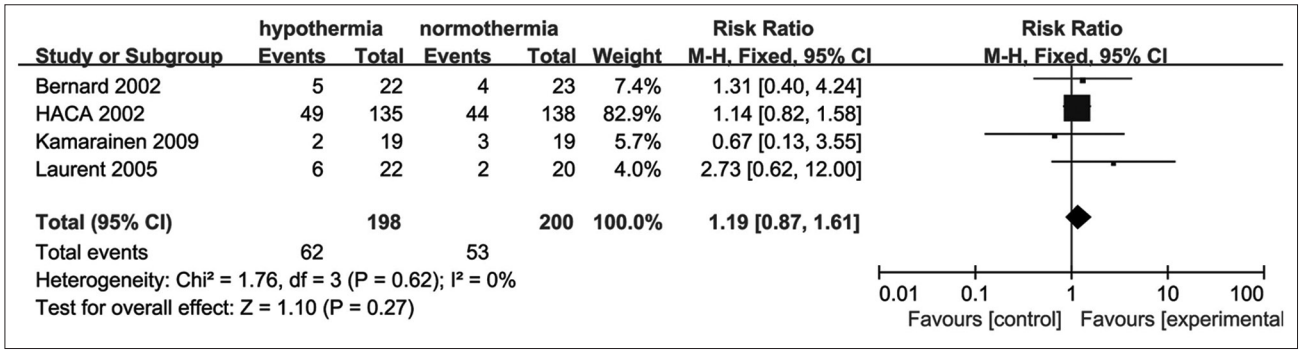

Figure 4: Summary of data on re-arrest for mild hypothermia versus normothermia.

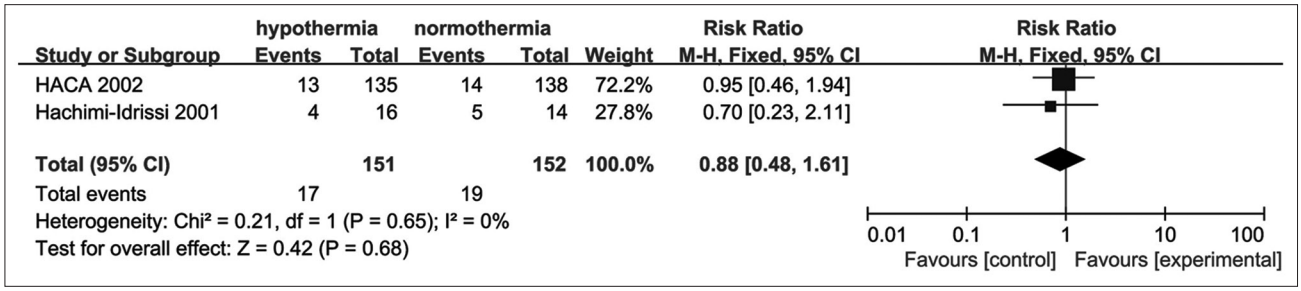

Figure 5: Summary of data on renal failure for mild hypothermia versus normothermia.

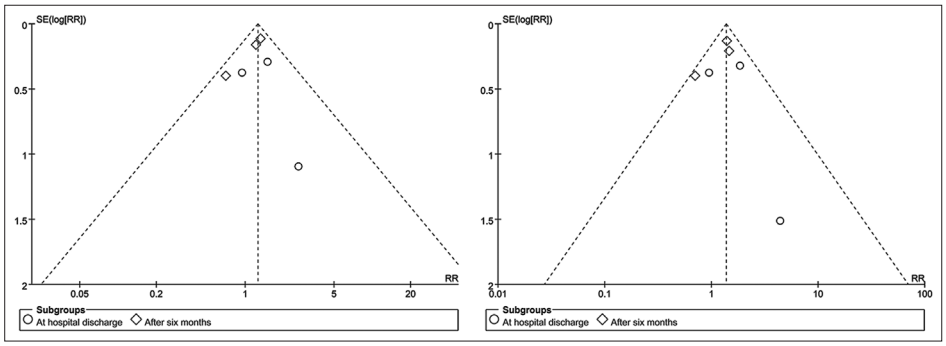

Figure 6: Funnel plot compares log relative risk (*RR*) versus the standard error of log *RR* for survival rate and neurological function (○: At hospital discharge; ◇: At 6 months).

possible side effects; (2) In clinical treatment, combination hypothermia with many other drugs may bring about some unknown influences, for example it will reduce the rate of drug metabolism and so on; (3) Hypothermia revives neurons is a long and slow process, for some other reasons patients die before neurons recovery. Then we analyzed the integrated data regardless of subgroups. Fortunately, the homogeneity among the six studies was pretty good. The pooled results showed us that mild hypothermia does improve survival rate and neurological function of patients with cardiac arrest.

Hypothermia now is widely used in clinical. There are many ways to induce hypothermia. For example: Hypothermic blanket, ice packs, cold saline intravenous infusion and so on. All of them can reach the target temperature very well. At present, there is an argument on starting of therapeutic mild hypothermia. Some studies[23,24] demonstrated the early initiation of rapid cooling gain maximum benefits. However, some other studies[25] or meta-analysis[26] hold the view that early initiation of rapid cooling cannot improve the prognosis. So when to induce hypothermia need to be further studied. Hypothermia can play a protective role of the neuron in a variety of ways. The possible mechanisms include: (1) Hypothermia can reduce cerebral oxygen consumption and energy metabolism;[27] (2) It can reduce reactive oxygen species generation and release of excitatory amino acids;[28] (3) It also can preserve the integrity of the blood-brain barrier, regulate the gene expression of inflammatory protein and apoptotic proteins and reduce cell death.[29,30] Although there are many advantages of mild hypothermia, we should not ignore the side effects. In the included six studies, the main adverse events were re-arrest, renal failure, pulmonary edema and so on. And there was no significant difference between hypothermia and normothermia. Hence, we drew a conclusion mild hypothermia therapy for cardiac arrest patients is safe.

However, the study also suffers from several limitations: (1) The number of trial and the study size may be inadequate. Therefore, the precision of the outcome parameters obtained is generally low; (2) Another potential limitation of this meta-analysis is clinical and methodological heterogeneity. According to the six studies, we knew cardiac arrest patients with different first recorded cardiac rhythm are included. Besides, the time from start of cooling to target temperature was different, the duration of keeping hypothermia was different and the methods of cooling body temperature were also different in these studies. All of the above factors would lead to inaccurate results. In this meta-analysis, we conducted a subgroup analysis according to different situations, although there was almost no heterogeneity. But in order to get more accurate results, further research should include high-quality studies to analyze the impact of different cooling measures or different hypothermia duration on the survival rate and neurological function.

In conclusions, this meta-analysis demonstrated mild hypothermia cannot improve survival rate and neurological function of patients at hospital discharge. But it can improve survival rate and neurological function after 6 months. The pooled results showed mild hypothermia does improve prognosis of patients. And it does not influence the incidence of adverse events compared with the control group.

References

1. Moss AJ, Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage 1960. Ann Noninvasive Electrocardiol 2001;6:78-80.
2. Hutchens MP, Fujiyoshi T, Koerner IP, Herson PS. Extracranial hypothermia during cardiac arrest and cardiopulmonary resuscitation is neuroprotective *in vivo*. Ther Hypothermia Temp Manag 2014;4:79-87.
3. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, *et al.* Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008;300:1423-31.
4. Boyd TS, Perina DG. Out-of-hospital cardiac arrest. Emerg Med Clin North Am 2012;30:13-23.
5. Ye S, Weng Y, Sun S, Chen W, Wu X, Li Z, *et al.* Comparison of the durations of mild therapeutic hypothermia on outcome after cardiopulmonary resuscitation in the rat. Circulation 2012;125:123-9.
6. Zou Y, Zhou Y, Gao W, Zeng Q, Hui K, Xu M, *et al.* Effects of mild hypothermia plus ifenprodil on apoptosis inducing factor translocation after global cerebral ischemia-reperfusion in rats (in Chinese). Natl Med J China 2014;94:1353-6.
7. Atkins CM, Oliva AA Jr, Alonso OF, Chen S, Bramlett HM, Hu BR, *et al.* Hypothermia treatment potentiates ERK1/2 activation after traumatic brain injury. Eur J Neurosci 2007;26:810-9.
8. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, *et al*. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: A randomized clinical trial. JAMA 2014;311:45-52.
9. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, *et al*. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. Crit Care Med 2012;40:747-53.
10. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, *et al*. Part 9: Post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S768-86.
11. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, *et al.* Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197-206.
12. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions, v.5.1. Available from: http://www.cochrane-handbook.org/2011. [Last updated on 2011 Mar 05].
13. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, *et al.* Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
14. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: A clinical feasibility study. Resuscitation 2001;51:275-81.
15. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: A randomized controlled trial. Acta Anaesthesiol Scand 2009;53:900-7.
16. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
17. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, *et al.* High-volume hemofiltration after out-of-hospital cardiac arrest: A randomized study. J Am Coll Cardiol 2005;46:432-7.
18. Tiainen M, Roine RO, Pettilä V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003;34:2881-6.
19. Weng Y, Sun S. Therapeutic hypothermia after cardiac arrest in adults: Mechanism of neuroprotection, phases of hypothermia, and methods of cooling. Crit Care Clin 2012;28:231-43.
20. Rittenberger JC, Callaway CW. Temperature management and modern post-cardiac arrest care. N Engl J Med 2013;369:2262-3.
21. Lopez-de-Sa E, Rey JR, Armada E, Salinas P, Viana-Tejedor A, Espinosa-Garcia S, *et al*. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: Pilot trial comparing 2 levels of target temperature. Circulation 2012;126:2826-33.
22. Cho JH, Ristagno G, Li Y, Sun S, Weil MH, Tang W. Early selective trans-nasal cooling during CPR improves success of resuscitation in a porcine model of prolonged pulseless electrical activity cardiac arrest. Resuscitation 2011;82:1071-5.
23. Song SS, Lyden PD. Overview of therapeutic hypothermia. Curr Treat Options Neurol 2012;14:541-8.
24. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: A preliminary report. Resuscitation 2003;56:9-13.
25. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, *et al*. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: A randomized controlled trial. Circulation 2010;122:737-42.
26. Diao M, Huang F, Guan J, Zhang Z, Xiao Y, Shan Y, *et al*. Prehospital therapeutic hypothermia after cardiac arrest: A systematic review and meta-analysis of randomized controlled trials. Resuscitation 2013;84:1021-8.
27. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci 2012;13:267-78.
28. Moore EM, Nichol AD, Bernard SA, Bellomo R. Therapeutic hypothermia: Benefits, mechanisms and potential clinical applications in neurological, cardiac and kidney injury. Injury 2011;42:843-54.
29. Bouzat P, Francony G, Oddo M, Payen JF. Therapeutic hypothermia for severe traumatic brain injury. Ann Fr Anesth Reanim 2013;32:787-91.
30. Tomura S, de Rivero Vaccari JP, Keane RW, Bramlett HM, Dietrich WD. Effects of therapeutic hypothermia on inflammasome signaling after traumatic brain injury. J Cereb Blood Flow Metab 2012;32:1939-47.

Received: 28-11-2014 **Edited by:** Yuan-Yuan Ji
How to cite this article: Gao Y, Hui KL, Wang YJ, Wu L, Duan ML, Xu JG, Li DX. Efficacy of Mild Hypothermia for the Treatment of Patients with Cardiac Arrest. Chin Med J 2015;128:1536-42.

Source of Support: Nil. **Conflict of Interest:** None declared.