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Review

Is hypothermia useful in malignant ischemic stroke? Current status and future perspectives

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Abstract

Background and aims: In acute stroke patients, mild and moderate hypothermia with a body temperature (T core) target of 32 °C to 34 °C is being tested and has shown some promising results. The feasibility of MH to control of ICP increases in patients with malignant ischemic stroke has been proven, but controversy as to its effectiveness and safety still continues. The most recent results of clinical trials and possible future applications of MH in acute stroke patients are analyzed in this review.
Design, methods and material: A search in MEDLINE/PubMed was performed. The references of selected articles were investigated and the Cochrane Library searched. Articles including severe, massive, malignant or hemispheric ischemic stroke, induced hypothermia, and animal studies with focal cerebral or brain ischemic models were considered.
Results: 196 patients with ischemic stroke treated with hypothermia have been reported in eleven small clinical studies, with a mild benefit of MH over the mortality rate and final outcome.
Conclusions: Moderate hypothermia ameliorates ischemic injury by multiple mechanisms. Treatment of acute ischemic stroke patients is feasible, and additional studies, including randomized clinical trials, are warranted.

Keywords: Stroke; Hypothermia; Acute ischemic stroke; Neuroprotection

Contents

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1. Introduction

Clinical interest in hypothermia was raised in the 1930s and 1940s after drowning victims who where exposed to hypothermia during significant periods of asphyxia were successfully resuscitated. In 1943, Fay published the first clinical report of therapeutic hypothermia in patients with severe traumatic brain injury exposed to low temperatures as 28 °C for 4–7 days, and described better-than-expected clinical outcomes [1]. However, by the early 1960s, the benefits of intraoperative hypothermia were being questioned and afterwards discouraged due to poor outcome of deep hypothermia (body temperature about 30 °C) during circulatory arrest [2]. Later, in 1987, Busto et al. [3] showed that small differences in ischemic brain temperatures were associated with the extent of neuronal injury in rats that underwent transitory cerebral ischemia. Thus, in the course of the last 15 years, a variety of experimental animal studies in global and focal cerebral ischemia indicated that mild and moderate hypothermia (MH) (about 32–34 °C) are successful for improving neurological outcome and decreasing the size of a cerebral infarct. Consequently, clinical interest was renewed, and the method was employed during open-heart surgery [4], after cardiac arrest [5–8], and in the management of traumatic brain injury [9–11] and intracranial aneurysm surgery [2].

1.1. What has happened to the use of induced hypothermia in stroke patients?

In the past 7 years, several studies were developed to evaluate the possible beneficial effects of hypothermia in acute stroke as demonstrated for MH in focal cerebral ischemia animal models [12,13]. In these animal studies MH reduced the size of brain infarct by approximately 90% and improved outcome in the animals with transient occlusion of the middle cerebral artery (MCAO). Moreover, these beneficial effects are achieved when MH is applied in the very early reperfusion period as well as in delayed reperfusion [14]. Unfortunately, such successful results have not yet been reached in patients with acute cerebral ischemia, but preliminary evidence about a possible benefit of MH in acute severe ischemic stroke (malignant infarction) has begun to emerge [15–17], instead of side effects, which can limit its application.

2. Method

2.1. Search strategy

A search in MEDLINE/PubMed was performed using key words of: acute stroke, hypothermia, microdialysis, neuroprotective drugs and malignant infarct, not restricted to any language, until January 2007. The references of selected articles were investigated and the Cochrane Library searched.

2.2. Selection criteria

Articles including (a) severe, massive, malignant or hemispheric ischemic stroke, (b) induced hypothermia, and (c) animal studies with focal cerebral or brain ischemic models were considered.

3. Review results

3.1. Concept of core temperature and subtypes of hypothermia

The normal body temperature is 37 °C, with a diurnal variation of about ±0.6 °C, usually highest at ±18:00 h [18]. Hypothermia is defined as a body-core temperature (*Tcore*) below 36.5 °C. The core corresponds to well-perfused tissues in which temperature remains relatively uniform [19] and consists of the trunk and head, comprising 50–60% of body mass. Tcore is habitually measured in tympanic membrane, esophagus, rectum, bladder, and pulmonary artery. The skin and extremities are considered "peripheral compartments", where temperature is usually 2–4 °C lower than the Tcore [20]. On the other hand, the intraparenchymatous brain temperature is slightly greater than Tcore by about 1.5±0.3 °C (range 1.0 °C to 2.1 °C) in patients with malignant ischemic stroke. However, with hypothermia induction to Tcore 33 °C, this gradient decreased by a mean of 0.3±0.4 °C [15]. Based on Tcore measurements, hypothermia has been classified into mild (35 °C to 33 °C), moderate (33 °C to 28 °C), and deep (below 28 °C), according to the temperature reached [6,7,15].

3.2. Hypothermia as a neuroprotective agent in ischemic stroke — Experimental approach

In the last decade, various animal experiments have suggested that hypothermia is neuroprotective in acute focal and global cerebral ischemia [21]. Its effectiveness mainly depends on the initiation and duration of treatment. Xue et al. showed in 1992 that after transient MCAO of 3 h under normothermic conditions (37 °C) an infarct size of 211 mm^3 had developed in rats; in contrast, intraischemic hypothermia of 32 °C for 4 h decreased the infarct size to 17 mm^3 ($P<0.001$) [12]. Maier et al. [13] investigated the influence of hypothermia duration on infarct size and found that neuroprotective effects did depend on this. Intraischemic hypothermia of 30 min did not reduce infarct volume, whereas 1 and 2 h of hypothermia directly after beginning of MCAO (120 min) led to a significant infarct reduction of between 59 and 84% compared to

normothermia. All these animal experiments in acute stroke models are summarized in Table 1. Nevertheless, early intraischemic cooling in patients is limited to elective surgery and therefore does not reflect the clinical situation of ischemic stroke. Consequently, delayed application of hypothermia represents a more realistic clinical approach for stroke treatment. Experimental data on postischemic hypothermia have been inconsistent [22,23].

The potential neuroprotective mechanisms of hypothermia contribute to multifactorial mechanisms rather than to one single one as seen in various neuroprotective drugs, these factors are summarized in Table 2. This combinatorial neuroprotective approach suggests a great potential for success, since hypothermia may act as a neuroprotective multimodal "cocktail," simultaneously blocking different processes involved in cellular death due to brain ischemia, including cellular apoptosis (Table 1) [12,14,22–33] and several oxidative DNA lesions [34]. In order to understand better the mechanisms of neuroprotection by hypothermia, future clinical investigations have to be conducted to evaluate the use of microdialysis [35–37] to confirm any neuroprotective effect of MH in patients with acute ischemic stroke.

3.3. The role of hypothermia in neurological patients

Schwab et al. [15,16] developed two non-controlled trials applying MH in acute ischemic stroke patients to evaluate its feasibility and safety as well as clinical outcome. In both studies, the patients were admitted to an ICU, none of them received thrombolytic treatment, and MH was applied using surface cooling to reach a Tcore = 33 °C for 24–72 h. The ICP was monitored using intraparenchymatous sensors placed ipsilaterally to the affected hemisphere in most of the patients. Thus, in the first study [15], 25 patients with a documented large middle cerebral artery (MCA) territory stroke were included. The baseline neurological score was 9 points in the Glasgow Coma Scale (GCS) and 24 points in the Scandinavian Scale Stroke (SSS). The National Institutes of Health Stroke Scale (NIHSS) score was not used. The mean interval between onset of stroke symptoms and initiation of hypothermia was 14 h (range 4 to 24) and the latency to achieve the target Tcore was 3.5 to 6.2 h. After 48–72 h of hypothermia, a passive rewarming to normothermia took a mean of 18 h (range 17 to 24). In all patients, ICP values decreased with initiation of MH to a mean of 14.5 ± 4 mm Hg and during steady state periods of hypothermia to 13.4 ± 8 mm Hg, which were significantly lower than initial values ($P < 0.05$). However, during the rewarming period, a significant, continuous increase in ICP values was noted, reaching a mean value of 19 ± 8 mm Hg (range 17 to 52). The ICP increase was even greater in patients who died. Side effects did not differ between the two groups of patients.

The second study [16] included 50 patients with massive hemispheric infarction treated with a MH regimen for 24 to 72 h. The method and design were very similar to the first one. The baseline means NIHSS score was 25 and the Glasgow Coma Scale (GCS) was 9. The latency to initiation of hypothermia after stroke onset was 22 ± 9 h, and the mean

Table 1
Animal studies of hypothermia in acute stroke models

	Design	Outcome
Xue et al. [12]	6 Normothermic rats (37 °C) were compared to 9 hypothermic rats (32 °C) after a bilateral internal carotid occlusion.	The main infarct volume was 211 mm^2 in the normothermic group compared to 17 mm^2 in the hypothermic group ($P < 0.001$)
Maier et al. [13]	Study design to know optimal duration of hypothermia after left MCA occlusion in a rat model. Group 1: 30 min of hypothermia ($n = 9$). Group 2: 1 h of hypothermia ($n = 8$). Group 3: 2 h of hypothermia ($n = 8$)	Group 1: No affect either the infarct size or the neutrophill accumulation. Group 2: Reduces infarct size in 59%. No effect on neutrophills. Group 3: Reduces infarct size in 84%, reduces neutrophill accumulation in 57%.
Maier et al. [22]	Study design to determine the effect of delaying induction of mild hypothermia (33 °C) after MCA occlusion. Group 1: ($n = 11$) delay MH by 0 min. Group 2: delay MH by 90 min ($n = 10$). Group 3: delay MH by 120 min ($n = 10$). Group 4: delay MH by 180 min ($n = 5$).	Mild hypothermia conferred significant degrees of neuroprotection in terms of survival, behavioral deficits, and histopathological changes, even when its induction was delayed by 120 min after onset of MCA occlusion ($P < 0.05$).
Kollmar et al. [23]	Study design to know the influence of delayed hypothermia of 180 min in a rat model of MCA occlusion ($n = 30$) followed by serial MRI studies.	Delayed hypothermia resulted in a significant increase of survival rate and a significant improvement of functional score. Moreover, a significant decrease in the extent of hyperintense volumes in T2-weighted scans was observed.
Ji et al. [34]	Rats were subjected to 2-hour MCAO and reperfusion of various durations up to 3 days. Selective brain hypothermia (33 °C) was induced at the onset of ischemia and terminated at the beginning of reperfusion.	Intraischemic MH markedly attenuated the nuclear accumulations of several oxidative DNA lesions, including 8-oxodG, AP sites, and DNA single-strand breaks, after 2-hour MCAO. Consequently, harmful DNA damage-dependent signaling events, including NAD depletion, p53 activation, and mitochondrial translocation of PUMA and NOXA, were reduced during post-ischemic reperfusion in hypothermia-treated brains.

Table 2
Beneficial effects of hypothermia

Site of action	Effects
Ischemic cascade:	Reduces release of glutamate from the nerve endings. [24,34,26,38]. Reduces lactate and piruvate concentrations [34]. Reduces free radical formation [22]. Decreases cellular metabolism by retarding ATP depletion and facilitating post-ischemic glucose utilization [22,27]. Reduces calcium influx into the cell and the secondary cytotoxic effects [24,27]. Reduces ischemic depolarization events in the peri-infarct-zone [29].
Cerebral edema:	Reduces cerebral edema formation [21,22].
Tissue perfusion:	Preserves cerebral autoregulation associated with the use of alpha-stat [23]. Reduces post-ischemic hypoperfusion and delayed post-ischemic hyperperfusion [30].
Tissue volume:	Reduces the size of infarction [12,13,20,25,29–31].
Blood brain barriers:	Suppresses disruption of the blood–brain barrier [30].
Gene expression:	Reduces gene expression associated with brain ischemia [13].

time required for cooling to Tcore = 33 °C was 6.5 h. Passive rewarming to normothermia was started after 24 to 72 h of hypothermia, and its mean duration was 17 h (range 11 to 24). The results showed that ICP values were reduced from 19.8 ± 14 mm Hg before the beginning of hypothermia to 12.4 ± 5 mm Hg when a steady state of hypothermia was reached ($P < 0.05$) and their values were sustained at constant levels in 74% of patients during the application of hypothermia. Again, a shorter rewarming period (< 16 h) was associated with a significant ICP increase as well as with higher mortality compared to longer rewarming. Although this was not an efficacy study, mortality was 38%, which is considerably lower than the 78–79% mortality described in previous studies of patients with MI infarcts without induced hypothermia [38,39]. During hypothermia mortality was 8% and during rewarming periods 30% due to an uncontrollable increases in ICP. In addition, Steiner et al. [17] observed that slow, controlled rewarming rates of 0.1 °C to 0.2 °C/2 to 4 h were associated with a significantly better control of ICP values as compared to a historic control group, in which a passive rewarming protocol had been applied for 24 h in patients affected by MI. These studies suggest that MH with a body temperature target of about 33 °C for 24–72 h combined with a slow, controlled rewarming period seems to represent adequate therapeutic conditions for achieving favorable control of increasing ICP in these patients, however, it is frequently associated with side effects (see below).

The role of a modest hypothermia regimen (Tcore target among 35 °C–36.5 °C) in awake, acute ischemic stroke patients has started to be evaluated, where a significantly fewer side effects have been described, but without any associated clinical benefit [40]. Larger clinical trials in this subject are required to determine its possible usefulness in these patients.

In conclusion, no additional evidence from larger randomized studies is available to support the routine use of induced hypothermia in acute ischemic stroke patients [41]. The feasibility of hypothermia in these patients has been proved, but the safety and efficacy needs still to be evaluated in future larger clinical trials.

3.4. MH associated with thrombolytic therapy in stroke patients

Induced hypothermia following thrombolysis therapy in stroke patients has been evaluated in a small pilot study in Cleveland, USA [42]. The COOL AID study included 10 patients with a major ischemic stroke (mean NIHSS score of 19.8 ± 3) and treated with MH with a Tcore = 32 °C for 12 to 72 h, depending on sonographic or angiographic MCA patency status. From them, 6 patients received some thrombolytic treatment associated. In the control group, 7 patients received some thrombolytic treatment and 2 none. A surface cooling system with a controlled rewarming of 0.25 °C to 0.5 °C/h was implemented. In this study, mortality was 33% in the hypothermic group and the modified Rankin Scale score was 3.1 ± 2 at 3 months. Two patients died in the hospital during the first week of admission due to severe stroke syndrome, intracerebral hemorrhage, and systemic complications in both cases. The authors concluded that hypothermia associated with thrombolysis therapy was feasible and safe. Now, the efficacy of these combined therapies needs to be tested in a phase II randomized controlled trial.

3.5. Moderate hypothermia versus surgical decompression in severe MCA infarction

To date, hemicraniectomy (CE) with duroplasty is probably the best invasive therapeutic strategy to treat intracranial hypertension and to preserve cerebral blood flow in patients who are neurologically deteriorating as a result of space-occupying hemispheric infarction. In addition, CE has been reported to improve the neurological outcome [43–46]. The efficacy of MH compared to CE to control intracranial hypertension and to reduce mortality has recently been studied in Heidelberg, Germany [47]. Here, 36 consecutive patients between 47 and 63 years of age with an infarction involving at least two-thirds of the MCA territory were treated with MH ($n = 19$) or CE ($n = 17$). Only patients with infarction in the nondominant hemisphere were included in the CE group. The age range, sex, level of consciousness, time of treatment, baseline NIHSS score (corrected for

aphasia), and cranial computed tomography (CCT) findings were similar in the two groups. The duration of MH was 71 ± 21 h (range 24 to 116) and it was induced with a surface cooling method in 12 patients and with an intravascular system in the remaining 7 patients (CoolGard, Alsius Corporation, Irvine, CA, USA). The target temperature of 33 °C was reached within 4 ± 1 h. Finally, a controlled rewarming was attempted at a rate of 1 °C/8 h and its duration adjusted to the ICP levels of each patient. The results showed that mortality between the two treatment groups constituted the major favorable finding: 2 to 17 patients in CE group (12%,) died versus 9 of 19 patients in the MH group (47%, $P<0.02$). These results with lower mortality are in good agreement with previous CE studies [48,49]. The main cause of death was uncontrollable intracranial hypertension in both the CE and MH groups. Concerning ICP, the maximal values reached were similar in the two groups: mean 22 mm Hg for the MH group versus 21 mm Hg for the CE group. More episodes of increased ICP > 20 mm Hg were detected in the MH group, but this difference was not significant ($P=0.3$). The other authors have recently published some preliminary experience about a beneficial combination approach of hypothermia and hemicraniectomy in patients with MI, with promissory results [47,50,51].

The CE emerges as the possible treatment of choice for patients with infarction localized in the nondominant hemisphere, but there is still a lack of enough evidence to support this [50]. Meanwhile, MH could be an interesting therapeutic option in patients with severe ischemic stroke who cannot be included in certain CE studies. The clinical evidence of hypothermia in acute ischemic stroke is summarized in Table 3.

3.6. Side effects of hypothermia

The appearance of side effects is closely associated with the depth and duration of hypothermia and the speed of rewarming period [6,15–17,40,42,51–56]. Some of these side effects can be serious and endanger the health of patients, even forcing hypothermia treatment to be interrupted. Based on cumulative experience, MH with a Tcore target over 33 °C is recommended to avoid severe side effects associated with lower temperatures (Fig. 1) [19]. The frequency and severity of side effects associated with induced hypothermia vary notably among different clinical studies. In MI patients treated with MH, pneumonia was described in 33%–78% of cases [15,16,42,47,54]; platelet disturbances in 37%–70%, in particular thrombocytopenia <100,000 per mm^3 [15,16]; cardiac arrhythmia with prolongation of PR and QT intervals and sinus bradycardia among 50%–62% of cases [15,16,42,54] with associated severe arterial hypotension (<50 mm Hg) in 6%–10% [16,41]; electrolytic disturbances (mainly hypokalemia) about 25% [15,54]; increase in serum levels of amylase and lipase (including pancreatitis) in 6%–28% [16,48]; and

Table 3
Clinical studies of hypothermia in acute stroke

	Design	Outcome
Schwab et al. [15]	MH was induced in 25 patients with severe ischemic stroke in the MCA territory within 14 +/− 7 h after stroke onset. Patients were kept at 33 °C for 48 to 72 h. Outcome at 4 weeks and 3 months after the stroke was analyzed with the Scandinavian Stroke Scale (SSS) and Barthel index.	14 patients survived (56%). Neurological outcome according to the SSS score was 29 (range, 25 to 37) 4 weeks after stroke and 38 (range 28 to 48) 3 months after stroke. During hypothermia, elevated ICP values could be significantly reduced. Herniation caused by a secondary rise in ICP after rewarming was the cause of death in all remaining patients. The most frequent complication of MH was pneumonia in 10 of the 25 patients (40%).
Schwab et al. [16]	Multicenter study performed to evaluate the safety and feasibility of MH and its potential to reduce intracranial hypertension in acute stroke patients. 50 prospective patients with cerebral infarction involving at least the complete middle cerebral artery territory were evaluated. Hypothermia was induced within 22 +/− 9 h after stroke onset and maintained for 24 to 72 h.	The most frequent complications of MH therapy were thrombocytopenia (70%), bradycardia (62%), and pneumonia (48%). Four patients (8%) died during hypothermia. An additional of 15 patients (30%) died during or after rewarming because of rebound increase in ICP and fatal herniation. A shorter (<16 h) rewarming period was associated with a more pronounced rise of ICP. Elevated ICP values were significantly reduced under hypothermia. Neurological outcome according to NIHSS score 4 weeks after stroke was 29, and Rankin Scale score 3 months after stroke was 2.9.
Kammersgaard et al. [40]	17 patients with stroke admitted within 12 h from stoke onset (mean 3.25 h) were compared wit 56 similar patients of a stroke registry. They were in MH for 6 h.	Mortality at 6 months after stroke was 12% in cases versus 23% in controls ($P=0.50$). Final neurological impairment (SSS score at 6 months) was mean 42.4 points in cases versus 47.9 in controls ($P=0.21$). Hypothermic therapy was not a predictor of poor outcome in the multivariate analyses.
Granberg [59]	Prospective and randomized study, 25 consecutive patients were treated after an ischemic infarction of more than two thirds of one hemisphere by hemicraniectomy alone ($n=13$ patients) or in convination with MH ($n=12$ patients). Safety parameters were compared between both treatment groups, the clinical outcome was assessed during treatment and after 6 months	Overall mortality was 12% (2/13 versus 1/12 in the two groups), but none of these 3 patients died due to treatment-related complications. There were no severe side effects of hypothermia. The clinical outcome showed a tendency for a better outcome in the hemicraniectomy plus MH group after 6 months, as assessed by the NIHSS (10 +/− 1 versus 11 +/− 3, $P<0.08$).

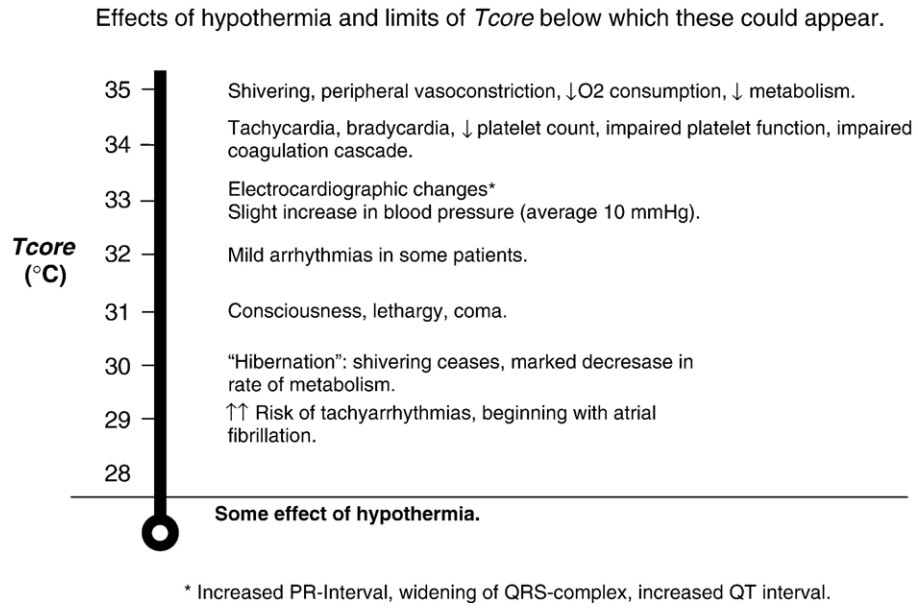

Fig. 1. Physiologic effects of hypothermia.

severe coagulopathy and bleeding disorders in 4%–5% [15,16] of cases.

3.7. Methods of hypothermia induction

Hypothermia is applied to patients according to the principles of convection (e.g., surface cooling methods such as forced air cooling via full cooling blankets or air beds) and conduction (e.g., liquid circulating in water-filled mattress) [57]. If a surface cooling method is used, it is frequently combined with other body cooling methods such as alcohol on the skin, ice bags, intravenous cold infusion, gastric lavages or cold-fluid infusion combined with ice-water cooling blanket, to achieve the programmed Tcore target [15,40,57,58]. The main surface cooling method limitations are: a) the speed at which the target temperature is achieved is lower than that of intravascular systems, b) patients who are morbidly obese cannot be treated optimally with these cooling methods, and c) these methods could require greater effort on the part of the medical and paramedical team to maintain adequate management.

New intravascular cooling systems are now being applied in stroke patients (CoolGard Alsius Corporation; Radiant Medical System) to evaluate their feasibility and safety [17,54–56]. The intravascular systems allow rapid cooling and facilitate controlled rewarming. Another advantage of the intravascular systems over surface cooling methods is the fact that they require minimal effort from the nursing staff once a catheter has been inserted.

Finally, MH is not a simple procedure. MH should be ideally done in the ICU to achieve adequate control of shivering, fluid administration, mechanical ventilation, and hemodynamic monitoring for several days. In this sense, adequate sedation, analgesia, and neuromuscular blockade must be assured. Moreover, due to the "cold-induced diuresis" from hypothermia [59], significant fluid volumes must be continuously administered to avoid arterial hypotension and dehydration, usually requiring the use of vasopressor and inotropic agents in these patients [15,16,54–56].

4. Conclusions

The IM treated with mechanical ventilation, osmotic agents, or barbiturates has a mortality of about 80% and survivors show severe disability. Limited clinical data on MH (core temperature to 32 ° C to 34 °C) in humans when applied for 48 to 72 h seems to reduce the mortality rate of patients with large ischemic stroke. But at present, no robust evidence is available to recommend induced hypothermia as a neuroprotective therapeutic strategy in these patients.

Hypothermia can cause unwanted side-effects such as hypotension, cardiac arrhythmia and pneumonia, which are closely associated with its depth and duration as well as the speed of rewarming. However, most of these side effects can be controlled or prevented in the intensive care setting. New intravascular cooling systems are promising new methods for induce and control adequate target of temperature in these patients and evidence of efficacy from clinical trials is needed. Prospective studies with larger sample size are warranted.

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References

[1] Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. Assoc Res Nerv Ment Disc Proc 1943;24:611–9.

[2] Hindman BJ, Todd MM, Gelb AW, Loftus CM, Craen RA, Schubert A, et al. Mild hypothermia as a protective therapy during intracranial aneurysm surgery: a randomized prospective pilot trial. Neurosurgery 1999;44:23–33.

[3] Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 1987;7:729–38.

[4] Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol 2002;40:1928–34.

[5] Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. N Engl J Med 2002;346:549–56.

[6] 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.

[7] Safar PJ, Kochanek PM. Therapeutic hypothermia after cardiac arrest. N Engl J Med 2002;346:612–3.

[8] Zeiner A, Holzer M, Sterz F, Behringer W, Schorkhuber W, Mullner M, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke 2000;31:86–94.

[9] Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith Jr KR, et al. Lack of effect of induction on hypothermia after acute brain injury. N Engl J Med 2001;344:556–63.

[10] Zhi D, Zhang S, Lin X. Study on the therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. Surg Neurol 2003;59:381–5.

[11] Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. Neurosurgery 2003;52:102–12.

[12] Xue D, Huang ZG, Smith KE, Buchan AM. Immediate or delayed mild hypothermia prevents focal cerebral infarction. Brain Res 1992;587:66–72.

[13] Maier CM, Ahern K, Cheng ML, Lee JE, Yenari MA, Steinberg GK. Optimal depth and duration of mild hypothermia in a focal model of transient cerebral ischemia: effects on neurologic outcome, infarct size, apoptosis, and inflammation. Stroke 1998;29:2171–80.

[14] Zausinger S, Westermaier T, Plesnila N, Steiger HJ, Schmid-Elsaesser R. Neuroprotection in transient focal cerebral ischemia by combination drug therapy and mild hypothermia. Comparison with customary therapeutic regimen. Stroke 2003;34:1526–32.

[15] Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 1998;29:2461–6.

[16] Schwab S, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. Stroke 2001;32:2033–5.

[17] Steiner T, Friede T, Aschoff A, Schellinger PD, Schwab S, Hacke W. Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery. Stroke 2001;32:2833–5.

[18] Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality—Part 2: Practical aspects and side effects. Intensive Care Med 2004;30:757–69.

[19] Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, et al. Heat flow and distribution during induction of general anesthesia. Anesthesiology 1995;82:662–73.

[20] Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality—Part 2: Practical aspects and side effects. Intensive Care Med 2004;30:757–69.

[21] Corbett D, Thornhill J. Temperature modulation (hypothermic and hyperthermic conditions) and its influence on histological and behavioral outcomes following cerebral ischemia. Brain Pathol 2000;10:145–52.

[22] Maier CM, Sun GH, Kunis D, Yenari MA, Steinberg GK. Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: neurological outcome and infarct size. J Neurosurg 2001;94:90–6.

[23] Kollmar R, Schabitz WR, Heiland S, Georgiadis D, Schellinger PD, Bardutzky J, et al. Neuroprotective effect of delayed moderate hypothermia after focal cerebral ischemia: an MRI study. Stroke 2002;33:1899–904.

[24] Feigin VL, Anderson CS, Rodgers A, Anderson NE, Gunn AJ. The emerging role of induced hypothermia in the management of acute stroke. J Clin Neurosci 2002;9:502–7.

[25] Georgiadis D, Schwarz S, Evans DH, Schwab S, Baumgartner RW. Cerebral autoregulation under moderate hypothermia in patients with acute stroke. Stroke 2002;33:3026–9.

[26] Barone FC, Feuerstein GZ, Whife RF. Brain cooling during transient focal ischemia provides complete neuroprotection. Neurosci Biobehav Rev 1997;21:31–44.

[27] Huh PW, Belayev L, Zhao W, Loch S, Busto R, Ginsberg MD. Comparative neuroprotective efficacy of prolonged moderate intraischemic and postischemic hypothermia in focal cerebral ischemia. J Neurosurg 2000;92:91–9.

[28] Winfree CJ, Backer CJ, Connolly Jr ES, Fiore AJ, Solomon RA. Mild hypothermia reduces penumbral glutamate levels in the rat permanent focal cerebral ischemia model. Neurosurgery 1996;38:1216–22.

[29] Takata T, Nabetani M, Okada Y. Effects of hypothermia on the neuronal activity, [Ca2+]i accumulation and ATP levels during oxygen and/or glucose deprivation in hippocampal slices of guinea pigs. Neurosci Lett 1997;227:41–4.

[30] Nakashima K, Todd MM. Effects of hypothermia on the rate of excitatory amino acid release after ischemic depolarization. Stroke 1996;27:913–8.

[31] Chen Q, Chopp M, Bodzin G, Chen H. Temperature modulation of cerebral depolarization during focal cerebral ischemia in rats: correlation with ischemic injury. J Cereb Blood Flow Metab 1993;13:289–394.

[32] Karibe H, Zarow GJ, Graham SH, Weinstein PR. Mild intraischemic hypothermia reduces postischemic hyperperfusion, delayed postischemic hypoperfusion, blood–brain barrier disruption, brain edema, and neuronal damage volume after temporary focal cerebral ischemia in rats. J Cereb Blood Flow Metab 1994;14:620–7.

[33] Ginsberg MD, Busto R. Combating hyperthermia in acute stroke. A significant clinical concern. Stroke 1998;29:529–34.

[34] Ji X, Luo Y, Ling F, Stetler RA, Lan J, Cao G, et al. Mild hypothermia diminishes oxidative DNA damage and pro-death signaling events after cerebral ischemia: a mechanism for neuroprotection. Front Biosci Jan 1 2007;12:1737–47.

[35] Berger C, Annecke A, Aschoff A, Spranger M, Schwab S. Neurochemical monitoring of fatal middle cerebral artery infarction. Stroke 1999;30:460–3.

[36] Berger C, Schabitz WR, Georgiadis D, Steiner T, Aschoff A, Schwab S. Effects of hypothermia on excitatory amino acids and metabolism in stroke patients: a microdialysis study. Stroke 2002;33:519–24.

[37] Schneweis S, Grond M, Staub F, Brinker G, Neveling M, Dohmen C, et al. Predictive value of neurochemical monitoring in large middle cerebral artery infarction. Stroke 2001;32:1863–7.

[38] Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. "Malignant" middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol 1996;53:309–15.

[39] Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying ("malignant") middle cerebral artery infarction under conservative intensive care. Intensive Care Med 1998;24:620–3.

[40] Kammersgaard LP, Rasmussen BH, Jorgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: a case–control study: the Copenhagen Stroke Study. Stroke 2000;31:2251–6.
[41] Correia M, Silva M, Veloso M. Cooling therapy for acute stroke. Cochrane Database Syst Rev 2000;2:CD001247.
[42] Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, et al. Cooling for acute ischemic brain damage (COOL AID): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001;32:1847–54.
[43] Kondziolka D, Fazl M. Functional recovery after decompressive craniectomy for cerebral infarction. Neurosurgery 1988;23:143–7.
[44] Rieke K, Schwab S, Krieger D, von Kummer R, Aschoff A, Schuchardt V, et al. Decompressive surgery in space-occupying hemispheric infarction: results of an open, prospective trial. Crit Care Med 1995;23:1576–87.
[45] Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, et al. Early hemicraniectomy in patients with complete middle cerebral artery infarction. Stroke 1998;29:1888–93.
[46] Hofmeijer J, van der Worp B, Kapelle LJ. Treatment of occupying cerebral infarction. Crit Care Med 2003;31:617–25.
[47] Georgiadis D, Schwarz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. Stroke 2002;22:1584–8.
[48] Carter BS, Ogilvy CS, Candia GJ, Rosas HD, Buonanno F. One-year outcome after decompressive surgery for massive nondominant hemispheric infarction. Neurosurgery 1997;40:1168–75.
[49] Mori K, Aoki A, Yamamoto T, Maeda M. Aggressive decompressive surgery in patients with massive hemispheric embolic cerebral infarction associated with severe brain swelling. Acta Neurochir (Wien) 2001;143: 438–92.
[50] Morley NC, Berge E, Cruz-Flores S, Whittle IR. Surgical decompression for cerebral edema in acute ischemic stroke. The Cochrane Corner. Stroke 2003;34:1337.
[51] Els T, Oehm E, Voigt S, Klisch J, Hetzel A, Kassubek J. Safety and therapeutical benefit of hemicraniectomy combined with mild hypothermia in comparison with hemicraniectomy alone in patients with malignant ischemic stroke. Cerebrovasc Dis 2005;21:79–85.
[52] Els T, Oehm E, Voigt S, Klisch J, Hetzel A, Kassubek J. Safety and therapeutical benefit of hemicraniectomy combined with mild hypothermia in comparison with hemicraniectomy alone in patients with malignant ischemic stroke. Cerebrovasc Dis 2006;21(1-2):79–85.
[53] Mori K, Nakao Y, Yamamoto T, Maeda M. Early external decompressive craniectomy with duroplasty improves functional recovery in patients with massive hemispheric embolic infarction. Timing and indication of decompressive surgery for malignant cerebral infarction. Surg Neurol 2004;62:420–30.
[54] Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke. First results of a novel approach. Stroke 2001;32:2550–3.
[55] Schmutzhard E, Engelhardt K, Beer R, Brossner G, Pfausler B, Spiss H, et al. Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients: a prospective pilot study. Crit Care Med 2002;30:2481–8.
[56] Hammer MD, Krieger DW. Acute ischemic stroke: is there a role for hypothermia? Cleve Clin J Med 2002;69:770–7.
[57] Theard MA, Tempelhoff R, Crowder CM, Cheng MA, Todorov A, Dacey Jr RG. Convection versus conduction cooling for induction of mild hypothermia during neurovascular procedures in adults. J Neurosurg Anesthesiol 1997;9:250–5.
[58] Polderman KH, Rijnsburger ER, Peerdeman SM, Girbes AR. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. Crit Care Med Dec 2005;33(12):2744–51.
[59] Granberg PO. Human physiology under cold exposure. Arctic Med Res 1991;50(Suppl 6):23–7.