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Clinical application of therapeutic hypothermia in stroke

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Abstract

Hypothermia has long been known to be a potent neuroprotectant. In this mini review, we highlighted clinical experience that hypothermia protects the brain from cerebral injury. We discussed the clinical practice of hypothermia in ischemic stroke. Multiple factors play a significant role in the mechanisms. Clinical application drew first from two clinical trials with comatose patients after cardiac arrest is attractive. The Australian and European study have led to renewed interest in these patients. More and more evidence bring insight into its effects on cerebral ischemia. The type of cooling technique to be used, the duration of cooling and speed of rewarming appear to be key factors in determining whether hypothermia is effective in preventing or mitigating neurological injury. Although until now, there are no clear therapeutic standards of the parameters in therapeutic hypothermia, it is well accepted that cooling should be initiated as soon as possible. By combining hypothermia with other neuroprotectants, it may be possible to enhance protective effects, reduce side effects and lengthen the maximum time. In addition to its neuroprotective properties hypothermia may extend the therapeutic window for other neuroprotective treatment. Thus, combination therapies with neuroprotective, anti-inflammatory and thrombolytic agents are likely to be investigated in the clinical setting in the future.

INTRODUCTION

Hypothermia is recognized as perhaps the most robust neuroprotectant studied in the laboratory to date. It has been shown to alter a variety of effects of cerebral injury, including reduction in metabolic and enzymatic activity, glutamate release and re-uptake, inflammation, production of reactive oxygen species, and the expression/down regulation of a host of other genes. Although stroke models vary in methodology, several laboratories have consistently shown that hypothermia reduces the extent of neurologic damage and improves neurologic function.

Two randomized clinical trials were reported using mild therapeutic hypothermia following cardiac arrest in the 2002. One is the multicenter randomized clinical trial projected by The Hypothermia after Cardiac Arrest Study Group. The other one was performed by four centers in Australia. Two trials significantly showed better outcome in the hypothermia group compared with the normothermia group. Although there were some differences between Europe study and Australia study, but their outcome was doing very well.

There is growing evidence that induced hypothermia can have neuroprotective effects in some patients with neurological injury. An association between body temperature, initial stroke severity, infarct volume, and clinical outcome has been recognized (1). Mild to moderate

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hypothermia has been found to reduce ischemic brain edema in the setting of massive ischemic strokes (2,3). Several preliminary clinical reports indicate benefits of mild to moderate hypothermia as an adjunct to thrombolytic therapy. The clinical use of hypothermia is therefore likely to increase in the near future (4).

We will discuss cooling techniques (blanket or ice pack or cold saline intravenously), selection of patients, timing of cooling (as possible as earlier or within 3 hours or 6 hours) clinical potential use and monitoring in the hypothermia group in future. In addition, clinicians including neurologists, cardiologists, intensivists and emergency physicians, should work together to practice protocols for mild hypothermia treatment.

Clinical effects of hypothermia after cardiac arrest

Our knowledge of the effects of induced hypothermia if much better for cerebral injury caused by cardiac arrest than for stroke.

After cardiac resuscitation, 80% of patients will remain comatose for more than one hour. Of those remaining comatose hours after resuscitation, only 10 to 30% of them will have a good neurological recovery at one year.

Results from two large randomized trials are now available(5,6).Two randomized clinical trials recently showed a substantial benefit of mild hypothermia after cardiac arrest on neurologic outcome, which has led to renewed interest in these patients. The Australian study was conducted at four Emergency Departments and was not blinded for treatment outcome. It had 77 total patients, 34 in the normothermic group and 43 in the hypothermic group. The inclusion criteria were: initial rhythm of ventricular fibrillation, continued coma after resuscitation, women greater than age 50 years old, and men greater then age 18 years old. Cooling began out-of-hospital using ice packs for a target temperature of 33. The cooling lasted 12 hours and was followed by passive rewarming. There was no statistically significant difference in the side effects. The primary outcome was discharge to home or rehabilitation. Poor outcome was defined as death in the hospital or discharge to a long-tern nursing home facility, conscious or unconscious. Patients in the hypothermic group had 49% (21/43) favorable outcome, while the normothermic group had a favorable outcome in 26% (9/34). ($P = 0.046$)

The European study was a randomized, blinded study conducted at nine centers in five countries. A total of 275 patients were enrolled, 138 in the normothermic group and 137 in the hypothermic group. Inclusion criteria included: a witnessed arrest secondary to ventricular fibrillation, age 18 to 75 years old, and less than 60 minutes to restoration of circulation. A target bladder temperature of 32 − 34 was achieved using surface cooling techniques, an air-cooling device and ice packs. Duration of treatment was 24 hours with passive rewarming over 8 hours. The primary endpoint was favorable neurological outcome at 6 months, as defined as a Pittsburgh Cerebral Performance scale of 1 (good recovery) or 2 (moderate disability). Fifty-five percent (75/137) of the hypothermic group had a favorable outcome, and 39% (54/138) of the normothermic group had a favorable outcome. ($P = 0.009$)

In the past few years, several preliminary studies in humans have also shown that mild postischemic hypothermia is effective in improving neurologic outcome after cardiac arrest (7-9).

Limitations to the cardiac arrest studies included: small sample sizes, one un-blinded study, and different treatment protocols – one starting out-of-hospital cooling and another inhospital. Critics have commented that the hypothermia group may not be well matched with the normothermic group. The PI's for the European study responded that the median Glasgow Coma Scales for both groups were 3. Another criticism was the subgroups of patient's with VF

cardiac arrest were a small percentage of the total number of cardiac arrest patients. The PI's from the European and Australian study responded that while their studies only represented a small subset of cardiac arrest patients, the clinical implications may apply to other groups and it warrants further investigation. Complications from hypothermia include arrhythmias, coagulopathies, and electrolyte disturbances. The lack of difference in side effects from the hypothermic group and the normothermic group, suggest that mild hypothermia may be tolerated well in a certain population of patients without significant overlay of other co-morbidities.

Clinical application of therapeutic hypothermia in stroke

The total equation for hypothermic protection includes the depth, duration, and onset. Until now there are no clear therapeutic standards except that cooling should be initiated as soon as possible. Thus further research is needed to determine optimal duration of therapeutic hypothermia, optimum target temperature, and rates of cooling and rewarming.

1. Time and temperature parameters—Different levels of hypothermia were defined: mild (> 32°C), moderate (28 − 32°C), deep (20 − 28°C), profound (5 − 20°C), and ultraprofound (< 5°C) hypothermia. Ultraprofound resuscitative hypothermia is currently under investigation for rapid cooling with very cold fluids in trauma victims. Profound resuscitative hypothermia is currently pursued under the concept of suspended animation. Deep protective hypothermia is being used in cardiac surgery with elective cardiac arrest for the duration of the operation or for brain protection during selectively reduced cerebral perfusion. The potential applications of mild to moderate hypothermia are therapeutic hypothermia for focal or global ischemia. Because of the numerous complications of deep to profound hypothermia and the difficulty in inducing these temperature reductions, beneficial effects of mild to moderate hypothermia are becoming more attractive.

The optimal duration of hypothermia after anoxic neurologic injury is unknown. Some groups used brief duration of hypothermia, and others used longer period of hypothermia. In rodent models of cerebral ischemia, hypothermia results in a significant increase in the number of surviving neurons as measured with histological examination after death. Depending on the duration of intraischemic hypothermia, studies have found between 50% and 100% preservation of rodent hippocampus. However, in clinical stroke, hypothermia may be a more effective strategy of neuroprotection if applied for a long duration after the ischemic event (10). Although a long cooling time seems attractive, the risk of complications may increase with longer duration.

From early studies, it has been clear that cooling is remarkably neuroprotective when applied during ischemia. So intraischemic hypothermia needs to be initiated as soon as possible if hypothermia is to be of beneficial effect. In contrast, the value of postischemic cooling was skeptical because of early clinical difficulties and conflicting animal data. However, even with a delay of several hours after global cerebral ischemia, hypothermia was reported to be advantageous as compared with control groups regarding loss of CA1 hippocampal cells (11). These observations were important from a treatment perspective and studies were initiated to determine the therapeutic window for postischemic hypothermia.

More recent rodent experiments have shown that a protracted reduction in temperature of only a few degrees Celsius can provide sustained behavioral and histological neuroprotection. Conversely, brief or very mild hypothermia may only delay neuronal damage. Accordingly, protracted hypothermia may be beneficial even following acute insult. In rodent models, hypothermia applied for several hours after cerebral ischemia improves neuron survival (12, 13). In clinical stroke, hypothermia may be a more effective strategy of neuroprotection if applied for a long duration after the ischemic event. The evidence from animal models of

ischemia indicates that hypothermia affects a wide range of the processes involved in ischemic brain damage, which suggests a great therapeutic potential for hypothermic therapy to alleviate the injuries even after ischemic insult. A thorough mechanistic understanding of postischemic hypothermia would lead to a more selective and effective therapy.

2. Cooling methods—Clinical interest in hypothermia began in the 1930s and 1940s with observations and case reports describing successful resuscitation of drowning victims who were hypothermic, even after prolonged periods of asphyxia. The first scientific report describing clinical application of hypothermia, a case series in patients with severe head injury, was published in 1945 [14]. Hypothermia was subsequently used in the 1950s during intracerebral aneurysm surgery [15, 16] and for cerebral protection during complete circulatory arrest, to enable intracardiac operations in a bloodless field [17,18]

Those conventional cooling techniques to induce whole body hypothermia include surface cooling using circulating cold water or fanned cold air, alcohol baths, icepacks, cold water gastric, bladder lavage, or ice-water immersion or preferential cerebral cooling, among others. These techniques are overall relatively ineffective in rapidly decreasing core temperature with the exception of ice water immersion, which can decrease core body temperature by 9.7°C/hr, but is largely impractical in the clinical setting(19) Recent clinical studies of therapeutic hypothermia have used extensive surface cooling resulting in relatively slow cooling and rewarming rates ranging between 0.3−1.7°C/hr(20,21) Furthermore surface cooling techniques are labor intensive and cumbersome to use, require neuromuscular blockade (and thus ventilatory support) to combat shivering, and provide poor temperature control(22) Typically patients are placed on a cooling blanket and bathed in ice water or alcohol until target temperature is reached after which the patient is sandwiched between 2 cooling blankets set at a fixed temperature(23) One study reported successful surface cooling to a mean body temperature of 35.5°C for 6 hours in awake stroke patients treated with pethidine to lower the shivering threshold, but it is unlikely that surface cooling methods will allow for cooling to lower target temperatures (33°C) for longer periods of time in awake patients(24) Furthermore, novel surface cooling devices have been developed in recent years [21], but their usefulness in inducing mild-moderate hypothermia in patients with cerebral ischemia has not been studied consistently to date. Some authors advocate the use of large volume (30 cc/kg) intravenous infusions of cold (4°C) crystalloid fluids as an effective, cheap, and easy-to-use strategy to rapidly decrease core temperature.(25)

Because of the apparent drawbacks of surface cooling methods, investigators have looked at alternative cooling techniques including endovascular catheters inserted via the femoral vein in the inferior vena cava. Clinical pilot studies in stroke patients show that these catheters provide rapid and precise temperature control(26,27). They also offer the advantage of providing prolonged core hypothermia to 33°C in awake patients treated with anti-shivering medications and covered with a warming blanket. These catheters are now being tested in phase II safety and feasibility studies in acute stroke patients(28,29).

Since the goal is to decrease *brain* temperature and not body temperature, the ideal cooling technique would selectively and rapidly cool the brain while avoiding the systemic side effects of full body hypothermia. Preliminary feasibility studies of cooling helmets to selectively cool the brain have reported conflicting results, and further clinical studies are on the way(30-32) It is suggested that selective head cooling combined with mild total body hypothermia during anesthesia enhances local neuroprotection while minimizing the occurrence of systemic side effects and stress associated with unsedated whole-body cooling (33).

3. Combination therapy—A number of recently published reports support the notion that combination therapy of therapeutic hypothermia with pharmacological agents may be

synergistic. In a model of cardiac arrest in dogs, the effect of mild hypothermia may be enhanced by thiopental, as well as the addition of phenytoin and methylprednisolone. The fact that mild hypothermia plus lamotrigine together were more effective in inhibiting extracellular glutamate accumulation than hypothermia or lamotrigine alone, suggests the potential for increased neuroprotection by the addition of lamotrigine to mild hypothermia (34). A study of combination of postischemic hypothermia (where protection was previously shown to be only transient) and delayed MK-801 administration indicated that the temporal therapeutic window for attenuating ischemic damage could be considerably prolonged (35). Long term neuroprotection could be observed if hypothermia were combined with IL-10, an anti-inflammatory cytokine, when neither treatment alone was effective (36). Hypothermia combined with N-tert-butyl-alpha-pheylnitrone treatment provided long-term cognitive improvement in a forebrain ischemia model, although the effect of combined treatment in this case did not appear superior to either treatment alone (37). These results collectively support promising strategies for a “cocktail” approach for therapeutic hypothermia. By combining hypothermia with other neuroprotectants, it may be possible to enhance protective effects, reduce side effects and lengthen the maximum time in which such therapies can be initiated.

Conclusions and further directions

Hypothermia has long been known to be a potent putative neuroprotectant. Experimental evidence and clinical experience show that hypothermia protects the brain from cerebral injury. Recent insights into the mechanisms of cerebral ischemia and reperfusion suggest reasons why hypothermia may be an ideal modality for stroke therapy. Hypothermia protects brain tissue in multiple ways.

There appears to be a bright future for the application of therapeutic hypothermia in acute ischemic brain injury. It is likely that benefit will be greatest when treatment is initiated very early, within several hours of symptom onset. Hypothermia may be able to extend the therapeutic window for other neuroprotective therapies, and combination therapies with neuroprotective, anti-inflammatory, and thrombolytic agents, are likely to be investigated in the clinical setting in the future.

However, many questions still need to be answered regarding the use of therapeutic hypothermia for ischemia in clinical practice, such as the optimal target temperature and duration, the therapeutic window in humans, cost-effective. Can we develop cooling techniques that can be used in the pre-hospital setting, are widely available, and have few adverse effects? Better understanding of the pathophysiology of resuscitation and the ischemic injury processes on which hypothermia acts will serve to further promote the use of this promising method to save lives. Therapeutic hypothermia is likely to undergo phase III clinical trials in various clinical settings. Novel technologies are being developed to optimize the safety and efficacy of this promising approach.

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