Hypothermia in Neuronal Protection

Nöronal Korunmada Hipotermi

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Abstract: During the last decade it has been repeatedly demonstrated that mild to moderate hypothermia (30-34°C) reduces neurological injury in animal models of focal or global ischemia, and of traumatic injury. This has led to renewed interest in the application of hypothermia for managing head injury, stroke, cardiac arrest and for undertaking aneurysm surgery. In this article, we review the relevant literature and presented our experience with cases of intracerebral hemorrhage treated under hypothermia.

Key words: Aneurysm surgery, hypothermia, intracerebral hemorrhage, neuronal protection.

Özet: Son 10 yıl içinde hafif ve orta derecede hipoterminin (30-34°C) fokal veya global iskemi ile ilgili deneysel çalışmalarda ve aynı zamanda travmatik beyin hasarı modellerinde nörolojik harabiyeti azalttığına ait yayınlar mevcuttur. Bu sonuçlar hipoterminin kafa travmaları, serebrovasküler olaylar, kardiyak arrest ve anevrizma cerrahisi esnasında kullanılmasını gündeme getirmiştir. Bu yayında hipotermi ile ilgili literatür taranmış ve hipotermi altında tedavi ettiğimiz intraserebral kanamalı hastaların sonuçları verilmiştir.

Anahtar kelimeler: Anevrizma cerrahisi, hipotermi, intraserebral kanamalar, nöronal korunma.

HISTORICAL BACKGROUND

Profound hypothermia (10-20°C) is a well established and highly effective means of protecting cerebrum from global ischemia. Bigelow et al. first described protection from global cerebral ischemia in 1950, in experiments in which they induced total cardiac arrest in dogs and maintained this state for 15 minutes at 20°C (18). This work was done before the oxygenator became available and was investigated as a strategy to permit surgical entry of the heart. By 1959, Drew and Anderson had reported clinical trials which circulation was completely halted for up to 45 minutes at 13 to 15°C using a pump but no oxygenator (51). Hypothermic perfusion without an oxygenator was then abandoned due to the high operative mortalities (91). Following it is proposal by Shumway and Lower, moderate hypothermia (30°C) came into wide clinical use in conjunction with the membrane oxygenator and selective cardiac cooling (112). From 1974 to 1980, large series reported successful total circulatory arrest at 10-20°C for up to 50 minutes during cardiac anomaly repair in children (28). Since then, total circulatory arrest at temperatures of 8 to 10°C has been used during repair of ascending aortic arch aneurysms in adults (44). In 1969, White and colleagues demonstrated that profound hypothermia (15°C) with circulatory arrest for periods of 30 minutes was well tolerated and was not associated with any neurological sequelea in primates (129).

HYPOTHERMIA

The ability to alter ischemic outcome by temperature manipulations has been used as an experimental tool for investigating mechanisms of ischemic brain injury. Elevating brain temperature during and following a focal brain injury has been shown to have detrimental effects on neurological outcome. In addition to exacerbating ischemic cell injury within selectively vulnerable brain regions, hyperthermia also leads to cell injury in brain regions normally resistant to brief periods of normothermic global ischemia (36, 49, 85)

Although neuronal protective effects of deep hypothermia (<30°C) has been attributed to reduced metabolic demand and decreased cerebral metabolic rate, the mechanisms behind moderate hypothermia (32-34°C) are different (4). Moderate hypothermia limits postischemic damage (24) either by supression of initial increase of excitatory aminoacids (EAAs) such as glutamate (8, 13, 64, 89, 101, 122, 133) by reducing of calcium influx (16), by stabilizing the blood-brain barrier (BBB) (65), by reducing the production of lipid peroxidation products (7), of by suppressing nitric oxide synthetase activity (66). Moderate hypothermia of 32°C provides neuroprotection with only a minimal decrease in the cerebral metabolic rate (94). Nakoshima et al. demonstrated a significantly longer time period to ischemic depolarization after cardiac arrest in a rat model with moderate hypothermia compared to barbiturate protection with comperable degree of metabolic supression (94). Of all the mechanisms that have been implicated in moderate hypothermia, likely the most significant is blockade of extracelluler increase of EAAs (24, 99).

BRAIN DAMAGE AND TEMPERATURE: CELLULAR AND MOLECULAR MECHANISMS

Excitotoxicity

Bruno et al. studied the effects of mild to moderate hypothermia on cortical neurons exposed to oxygen-glucose deprivation or EAAs (21). The authors showed that cooling to 30°C virtually abolished anoxia-induced glutamate release into the extracellular medium. This, and similar findings in vivo (53, 89, 104) suggest that a major mechanism by which mild to moderate hypothermia protects neurons against anoxia or ischemia attenuating endogenous glutamate release and subsequent excitotoxicity. Cooling to 30°C protected against brief ischemic periods only if hypothermia was maintained beyond the initial insult, because much of the damage occurred subsequent to the release of endogenous glutamate (21).

Work with experimental models has shown that the degree of inhibition of glutamate release after ischemia is directly dependent on the temperature and that the effect might have been a combination of a delayed initial release and reduction in the rate of EAA release (93). Postischemic glutamate levels documented by microdialysis were found to be reduced by hypothermia (32°C) but hypothermia did not influence the homeostatic release and uptake of EAAs in the nonischemic areas (97). All this beneficial effects of moderate hypothermia were also time dependent (9, 27). Nakashima and Todd suggested that the effects of hypothermia on EAA concentrations during cerebral ischemia might be due to both a delay in the time to depolarization and a direct reduction in the rate of postdepolarization EAA increase (93).

Many cellular processes are slowed down by cooling. Some are maximally attenuated at temperatures lower than those that are conventionally considered as mild to moderate hypothermia (30 to 33 °C)

Transmembrane ionic fluxes and ion homeostasis

Ionic channels are temperature sensitive. Single-channel recordings of N-metil-*D*-aspartat (NMDA) receptor activity shows that single NMDA channel conductance increases steeply at temperatures above of 20°C (52). Studies have shown that ionic currents are decreased and the mean channel open times increased at lower temperatures. Hypothermia also slows ionic pumps and exchangers. Thus, cooling may slow down the reverse operation of Na^+/Ca^{2+} exchanger during anoxia and excitotoxicity (130) that, in turn, would reduce cellular Ca^{2+} loading and resultant injury (71). The Ca^{2+}-ATPase, another important mechanism for cellular Ca^{2+} extrusion and sequestration is also temperature sensitive. Higher temperatures increase the cell membrane's Ca^{2+}-ATPase activity and cause it become more fluid (17).

Hiramatsu et al. investigated the effects of hypothermia on excitatory synaptic responses during hypoxia (59). Their study showed that hypothermia protected against hypoxic damage by prolonging the delay to hypoxic depolarization. Chen and colleaques found a significant correlation between temperature

and direct current potential deflections in a focal ischemia model (32).

Cellular energy production

Early theories of the mechanisms of protection by hypothermia focused on reductions in cerebral metabolic rate (5, 19, 76, 84). However, in vivo studies of brain ischemia under conditions of mild to moderate hypothermia have not yielded consistent evidence of report a significant salvage from ATP depletion (53, 126). In vitro studies have also indicated that mild to moderate hypothermia has variable effects on cellular ATP. Work by Bruno and colleagues showed that moderate hypothermia slightly attenuated the cellular ATP loss observed during 60 minutes of oxygen-glucose deprivation (21). Other in vitro investigations have suggested that ATP depletion is slowed by mild to moderate hypothermia only during the first few minutes after the insult (98, 138).

A recent study (67) involving the use of magnetic resonance spectroscopy has shown that moderate hypothermia increases the fraction of glucose metabolism shunted through the pentose phosphate pathway. The authours suggested that upregulation of this pathway may play an important role in maintaining cellular integrity and function during ischemia by maintaining membrane potential, stabilizing mitochondrial permeability, and countering potential oxidative damage.

Little is known currently about the effects of deeper levels of hypothermia on high-energy metabolite production during anoxia, ischemia or excitotoxicity. In one study, mitochondrial respiration and ATP synthesis were preserved in rat brain, liver and kidney under ischemic conditions (11).

The production of toxic reaction products

It has been suggested that the drop in the production of free radical species that occurs after neuronal injury is on of the possible protective mechanism of hypothermia. Experiments in vivo have shown that moderate hypothermia (30°C) is sufficient to attenuate hydroxyl radical production after brain ischemia and trauma (54, 69). Mild hypothermia (33°C) may also decrease postischemic production of nitric oxide (66). Other potential mechanisms behind the protective effects of hypothermia include cellular protein synthesis (14, 98, 131), the activity of innumerable cellular enzymes such as Ca^{+2}/calmodulin-dependent protein kinase II (61) and protein kinase C (25), cell membrane fluidity (119), action potential propagation (70), and ischemic induction of heat-shock proteins (108).

Mild to moderate hypothermia appears to be well tolerated by the brain in vivo, and by individual neurons and glial cells in vitro, as there has been no reports in the literature of toxicity connected with mild temperature reductions.

Excessive increases in intracellular Ca^{+2} are believed to participate in neuronal vulnerability to various types of brain injuries (113). Mitani and colleagues investigated the temperature dependence of hypoxia induced Ca^{+2} accumulation in a hippocampal slice (88). When hippocampal slices were superinfused with a hypothermic medium (at 35°C, 33°C or 31°C) Ca^{+2} accumulation as a consequence of anoxic depolarization was delayed in a temperature dependent manner. An in vivo study by Araki et al. also showed a significantly smaller increase in calcium signal in hypothermic conditions (3)

Protein kinase C (PKC) is part of the intracellular kinase cascade activated by growth factors and is intimately involved in regulation of protein synthesis initiation(81). PKC activity is translocated and downregulated during ischemia.

Intraischemic brain temperature has been shown to effect PKC activity after global ischemia (25, 26). In both studies, hypothermia attenuated the ischemia-induced reduction in PKC activity, and such findings suggest that PKC alterations may be an important factor involved in how temperature modulates postischemic outcome.

Obrist et al. studied severe head injury cases and measured regional cerebral blood flow (rCBF) by IV Xenon-133. They found that the initial posttraumatic reduction in blood flow was associated with depressed cerebral metabolism rate of oxygen ($CMRO_2$) and that the subsequent CBF increase exceeded O_2 requirements. The authors suggested that hypothermia retards the development of this CBF increase, possibly via inflammatory vasoactive processes (95).

The effects of temperature on the other second-messenger systems

Neuronal Ca^{2} dependent protein phosphorylation, in brain ischemia is extremely sensitive to temperature. Forebrain ischemia has been

shown to induce an early and permanent inhibition of Ca^{+2}/calmodulin-dependent protein kinase II activity (121). This protein mediates many of the second messenger effects of Ca^{+2} including neuronal excitability, synaptic modulation, cytoskeletal function and neurotransmitter release. Intraischemic hypothermia (32°C) has been shown to protect against ischemia induced inhibition of Ca^{+2} / calmodulin-dependent protein kinase II activity (36). Hypothermic protection following global ischemia may involve the maintenance of this activity.

Heat shock protein (HSP-72) and other proteins are induced in rodent models of brain injury. When induced prior to assault the induction of HSP-72 has been associated with protection in neuronal injury (34). On the other hand, in examining the role of HSP-72 in hypothermic protection (30°C) after global ischemia, Chopp and colleagues found that HSP induction was unlikely to be a potential mechanism by which hypothermia protects against ischemic cell damage (35).

Cytoskeletal proteins participate in many neuronal functions, including neurotransmitter release, axoplasmic transportation and membrane stabilisation. Miyazawa et al. reported that mild intraischemic hypothermia lessens the decrease in postsynaptic microtubule associated protein 2 (MAP-2) immunostaining that is usually seen after ischemia (90). Since MAP-2 is an important component of the neuronal cytoskeleton, these results indicate that hypothermia may protect postischemic neurons from irreversible injury by the attenuating injury induced MAP-2 loss. Ubiquitin synthesis also has been shown to increase after transient ischemia under conditions of mild hypothermia (137). Thus, the improved postischemic synthesis of spesific proteins that occurs with hypothermia may promote ischemic protection.

NEURONAL PROTECTION (EXPERIMENTAL)

In 1962, Hirsch and Muller were the first to present data that suggested that small differences in brain temperature could affect the behavioral consequences of complete global ischemia (60). In that study, postischemic survival time was linear as a function of brain temperature, and a difference of 1-2 °C was suggested to alter ischemic outcome. Busto et al. demonstrated that rectal temperature was unreliable indicator of brain temperature during global forebrain ischemia (23). They also highlighted that the importance of small differences in intraischemic brain temperature on histopathologic outcome, noting that decreasing brain temperature from 36 °C to 34°C significantly protected selectively vulnerable brain regions. Experiments on gerbils done by Clifton et al. (38) showed that a 2°C fall in body temperature provided 100% protection to the CA1 hippocampus. Minamisawa et al. studied the influence of brain and body temperature on ischemic damage using the rat two-vessel model of forebrain ischemia and confirmed that brain temperature dropped during the ischemic period when body temperature was kept constant (86, 87). Reduction of brain temperature to 35°C decreased neuronal necrosis. Another study reported that selective brain cooling during and after prolonged global ischemia also significantly protects the cerebral cortex from histopathologic damage (73). Welsh and colleagues investigated the degree of hypothermia required to diminish CA1 hypocampal injury by regulating body and head temperature (128). Reduction of head temperature to 35.5°C and 32°C diminished histologic injury in a dose-dependent manner.

The protective effect of hypothermia on reversibility of neuronal function has been investigated using the hippocampal slice (96, 124). Okada and coworkers showed that the periods of oxygen and glucose deprivation during which neurons could recover functions was extended by 21-28°C hypothermia (96). Accelerated recovery of glucose utilization at 24hr after ischemia with intraischemic hypothermia has also been reported (48).

Several studies have investigated the results of posthypothermic intervention after various periods of brain ischemia. Chopp and colleaques observed significant protection of application of hypothermia on the hippocampus 8 min after ischemia but no protection after 12 min ischemic insult (33). Another study noted partial but significant protection of CA1 neurons when 3 hr hypothermic period was initiated at 5 minutes, but not 30 minutes, into the recirculation period (22). Chen and coworkers also failed to demonstrate histopathologic protection with postischemic hypothermia after 12 minutes of forebrain ischemia (30). It is well established that short periods of ischemia (less than 3 hours) result in significantly greater variability in the infarct sizes observed, which makes it difficult to accurately define the "therapeutic window". (58).

On the basis of these studies it appears that the "therapeutic window" for postischemic hypothermia

may be relatively narrow and that ischemic duration and severity are important factors in determining whether neuroprotection is seen with postischemic hypothermia. The durations of applied hypothermia described in recent publications range from 0 to 30 hours (55, 68) and the timing for the application of hypothermia after an ischemic event ranged from 30 min before ischemia (128) to 6 hours after an ischemic event (39). Markarian and colleagues used a rat focal ischemia model to delineate the optimum parameters for postischemic hypothermia, and found the therapeutic window for this model to be no more than 30 minutes after onset of ischemia to at least 3 hours thereafter (80).

Research has also emphasized the importance of the duration of the hypothermia. While 6 hours of immediate postischemic hypothermia resulted in significant histopathologic protection there was no protection when a 1 hour hypothermic period was investigated(62). Working with a model of brief (10 minutes) transient cerebral ischemia Coimbra and Wieloch reported that, with postischemic hypothermia (28°C) hippocampal protection begun at 2 hour after the initiation of hypothermia and lasted for several hours (39). In addition to the length ischemic period, the duration of postischemic hypothermia is also critical in terms of determining beneficial effects. Zhang et al. also demonstrated that induction of hypothermia at 30°C 1 hour after focal ischemia led to significantly smaller infarct sizes (140).

Intraischemic hypothermia (30°C) has been shown to provide chronic histopathological protection for up to 2 months following transient global ischemia (56). As well Dietrich et al. documented significant protection of CA1 hippocampus at postischemic day 3, with less protection at day 7 and no protection at 2 months (47). These data indicate that intraischemic but not postischemic, brain hypothermia (30°C) provides chronic protection. It has been suggested that the main advantage of postischemic hypothermia may extension of the "therapeutic window" for delayed pharmologic treatment (46).

Using a rat model of permanent middle cerebral artery (MCA) occlusion, Morikawa et al. reported no significant differences in infarct size in hypothermic (30°C) and normothermic (36°C) rats (92); thus it appears that, in conditions of permanent focal ischemia profound degrees of hypothermia or an extended period of moderate hypothermia may be necessary to protect the brain. Moderate hypothermia is protective in several models of transient MCA occlusion (31, 92, 103, 140), and also in permanent occlusion models (31, 103, 135). Chen and colleaques reported that hypothermia (30°C) induced prior to ischemia and maintained for 2 hours following MCA occlusion decreased brain injury (31). In 1992 Morikawa et al. observed that brain hypothermia (30°C) during the 2 hour period of reversible MCA occlusion significantly reduced infarct volume (92). Many reports have described initiating of the cooling at the onset of MCA occlusion (10, 20, 55), whereas others have described starting to cooling at later time points. Xue et al. investigated rats that were subjected to 3 hours of focal ischemia and cooled to 32°C. Hypothermia lasting 3 hours and initiated at the time of MCA occlusion led to 92% reduction in cortical infarct size. Cooling for 1.5 hours was equally effective if it was started at the onset of occlusion or was deferred by 1.5 hours (45-49% cortical protection), whereas a 3-hour hypothermia delayed by 1.5 hours yielded greater protection (73% cortical protection) (135). Huh et al. investigated the effects of prolonged hypothermia. They observed cooling of the brain to 32°C for 3 hours followed by a 2 hour graded rewarming period that was initiated at the time of recirculation after 2 hour period of occlusion. This resulted in high grade histological and behavioral protection equivalent to that observed with intraischemic cooling (63).

Even mild hypothermia (31°C) extended over 6 hours reduced the volume of cortical infarction after permanent MCA occlusion(136). Ridenour et al. demonstrated that mild hypothermia (33°C) during a 1-hour ischemic period and the first hour of reperfusion reduced infarct size by 48% compared to the normothermic group(103). Zang et al. also reported that immediate or late hypothermia (32°C) also reduces infarct area (140).

Other researchers have investigated the effects of moderate hypothermia on the pharmocologic, neurobehavioral and functional consequences of global ischemia and cardiac arrest (96, 124). Using a neonatal, newborn, hypoxic-ischemic brain injury model Alkan et al. measured corpus striatal dopamine (DA) and dihydroxyphenylaceticacit (DOPAC) levels and showed that early postischemic hypothermia provides complete neural protection and reduces tissue damage (2). It has been demonstrated that intraischemic hypothermia (30°C) during 12.5-minute ischemic period attenuated the neurobehavioral consequences of global ischemia

recorded at 2 months after ischemia (56). Studies in experimental global ischemia have shown that, although shorter durations of postischemic moderate hypothermia are not permanently neuroprotective (47), prolonged reductions in body temperature confer sustained behavioral and histological neuroprotection (40, 41). In experiments using a dog cardiac arrest model, Leonov et al. reported that mild hypothermia (34°C) resulted in significant neurologic function at 96 hour post arrest than in normothermic animals (75).

NEURONAL PROTECTION (CLINICAL)

The results of experimental studies increased neurosurgical interest in hypothermia. However, by the late 1960s, neurosurgical experience involving profound hypothermia was limited to the treatment of surgically difficult intracranial aneurysms. At that time the neurosurgical literature reported over 100 patients who were operated on under profound hypothermia with circulatory arrest, using cardiopulmonary bypass to accomplish to cooling and rewarming (1, 12, 42, 50, 82, 83, 100, 107, 114, 115, 118-120, 125, 132)

In the last decade, numerous papers have appeared in the literature in support of using hypothermia for aneurysmal surgery especially in the basilar artery territory(57, 74, 106, 116, 117)

Head injury

According to Marion, the first report of the use of hypothermia appeared in 1943 in literature pertaining to the treatment of brain injury (77). In this study, Fay applied hypothermic conditions as low as 28°C to severe head injury cases for 4-7 days and claimed to record better outcomes than in cases where hypothermia was not applied. The 1960s and 1970s saw little enthusiasm for this treatment because of severe hypothermia-associated complications including cardiac arrhytmia, coagulation disorders and pneumonia. However in the 1980s, several investigators demonstrated in the experimental studies that mild or moderate hypothermia (32-34°C) effectively achieved significant improvement in neurochemical, histological and behavioral outcomes in both ischemia and brain injury model. Since 1990, many clinical studies have been conducted involving mild or moderate hypothermia for severe closed head injuries (37, 78, 79, 111).

Controlled randomized clinical studies have been published on the therapeutic use of moderate hypothermia (32-34°C) for severe closed head injuries (Glasgow Coma Scale 8 or below). Clifton et al. (37) and Marion et al. (78) continued hypothermia for 24 hours maintained temperatures of 32-33°C and Shiozaki et al. applied moderate hypothermia for 2 days (111). Tateishi et al applied titration method mild hypothermia in severely head-injured patients for whom reduction in intracranial pressure was the main goal (123). They reduce the patient's body temperature to the minimum sufficient level, titrating it according to the desired drop in intracranial pressure. The duration of hypothermia was extended if intracranial pressure remained elevated. Thus, in this study overall, the hypothermia was less intense but prolonged. Work by Xiang et al. also documented that the benefits of keeping patients hypothermic for 12 hours or more after brain injury.(134).

In these clinical studies (37, 78, 79, 111) hypothermia significantly reduced intracranial pressure (ICP) and CBF and other physiological parameters showed no significant rebound after patients were gradually rewarmed. The authors concluded that patient tolerance of therapeutic hypothermia was good and that there was associated improvement in ICP, cerebral oxygen supply, and outcome. Although the North American Multicentre prospective study sponsored by the National Institute of Health was terminated after 398 patients in 1998 because of a unfavourable outcome in the four of the seven centres involved, the study showed that moderate hypothermia to 32-33°C for 48 hours did not produce to significant neurological improvement for the group as a whole. There was evidence of benefit, however, in the group of patients who were under 45 years of age, were kept normovolaemic and had an initial GCS of 5-8 or more (77). Shiozaki et al. observed that mild hypothermia effectively prevents ICP elevations in patients who have no diffuse brain swelling and have ICP of 20-40mmHg after conventional therapy (110). Another study looked at treating severely head injured patients in whom ICP can be maintained below 20mmHg by using conventional therapies. Hypothermia did not confer any advantage over normothermia in these individuals (109).

Careful analysis of research done to date clearly indicates that certain subgroups of patients will benefit from this treatment, but the multicentre trial also raised concern that other subgroups, such as head-injured patients who are hypovolaemic, may actually be harmed by it. Thus, it would be premature to advocate this therapy as a standard treatment of

head injuried patients but should be kept in mind that some patients are likely to benefit.

Aneurysm Surgery

A 1994 survey revealed that a large majority of neuroanesthesiologists use mild to moderate hypothermia intraperativelyfor intracerebral aneurysm cases (43). Preliminary results on the use of mild hypothermia in aneurysm surgery are encouraging (57). In this study patients in the experimental group were cooled only to 33.5°C during procedures for clipping aneurysms. The results showed that, compared to the normothermic patients, there were more good outcomes in patients in the hypothermia group who had acute subarachnoid hemorrhage, and fewer of these patients had neurological deficits at discharge. However, these differences were not statistically significant.

Intracerebral hemorrhage

Our clinic ran a prospective randomized study to determine the effects of moderate hypothermia (32-34°C) on cerebral hemorrhage (72). This preliminary study was based on 14 patients, men and women age 16-65 years, who had suffered acute intracerebral hemorrhage and were admitted to intensive care. The criteria for inclusion in our study GCS score of 8 or below, computed tomography evidence of acute intracerebral hemorrhage (hematoma size>30cm^3), signs of brain swelling , such as lateral ventricle compression, midline shift more than 1cm, and neurological deterioration compared to baseline clinical status on admission to the ICU.

Angiography was performed in cases of hemispheric hematoma in which aneurysm or arteriovenous malformation were suspected. In hypothermic group, cooling of patients started during evacuation of the hematoma, and/or cliping of the aneurysm or removal of the AVM. While the most favorable hypothermia depth of 32-34°C has been well established by our experience and that of others, there is less known about optimal duration of hypothermia and optimal time to treat after ischemia. We took the approach that therapy should be started as soon as possible; therefore, a designated criterion for inclusion our study was that cooling begin within 6 hours after brain insult. Twenty-four hours was the longest duration of hypothermia, and patients were not actively rewarmed, but were left to warm to normal temperature spontaneously.

Randomly selected cases were assigned to one of two groups. Hypothermic group (n:8) was managed at 32-34°C, and the normothermic group (n:6) 36-37°C for the first 24 hours after intracerebral heomorrhagia. In the hypothermic group, ICP values fell a mean of 5.59±1.98mmHg when hypothermia was initiated. During the hypothermic period, ICP was significantly lower than it was on admission in this group ($p<0.05$). After hypothermia and during rewarming, ICP rose continuously, with the mean of the highest measured values being 16.33±2.01mmHg. Parallel testing of the two groups at given time points showed that rewarming did not cause the hypothermic group's ICP values to exceed those of the normothermic patients.

The hypothermia group required significantly less dose mannitol, narcotics, moderate hyperventilation or vecoronium than the normothermia group ($p<0.01$). Rewarming did not call for more aggressive measures to control ICP. The hypothermia patients had significant lower mortality, with patient survival in this group being 87.5%, compared to 17% in the normothermia group ($p<0,05$). There was also a significant difference between the groups with regard to Glasgow outcome score during 12 months of follow-up. The two groups had similar incidences of pneumonia, sepsis, and cardiac or other complications.

The hypothermic patients exhibited significantly greater decreases in platelet count ($p<0.05$), and their counts dropped to below their initial values. Three patients developed cardiac arrhythmias with prolonged PR and QT intervals and sinus bradycardia.

Stroke

During recent years, it has become increasingly evident that moderate hyperthermia, when present after brain ischemia or trauma exacerbated the resulting neuronal injury (102). Several recent clinical studies emphasized the importance of body temperature for stroke prognosis and severity. Azzimondi et al. showed that fever in the first 7 days after stroke was independent predictor of poor outcome (6). Higher fever was associated with a poorer prognosis and patients with high fever were more likely to die within the first 10 days after stroke that those with lower temperatures. Wang et al. retrospectively studied 509 patients with acute stroke patients and examined the relationship between admission body temperature and mortality both in-hospital and at 1-year after discharge. The found an

association between admission body temperature on admission and stroke mortality and this was independent of clinical variables of stroke severity. Hyperthermia was associated with higher mortality in 1-year mortality. Hypothermia, on the other hand, was associated with lower in-hospital mortality (127). Another investigation divided 390 patients, based on their temperature on admission, into hypothermic (36.5°C<), normothermic (>36.5°C-37.5°C), and hyperthermic (>37.5°C). The results showed strong correlations between body temperature, clinical outcome and infarct size(102). Davalos et al. observed that patients with above normal temperatures on admission were more likely to show early neurological deterioration and have significantly poorer outcome (45). The same group found increased levels of glutamate in their hyperthermic patients thus pointing to a possible mechanism for the observed changes (29). Schwab et al. studied patients with MCA infarction who were treated with moderate hypothermia. The mortality rate was only 44%, considerably lower than that noted when hypothermia was not applied and showed a favorable outcome (105). These authors also emphasized the important effects of rewarming, which consistently led to arise in ICP and increased patients mannitol requirements.

Cardiac Arrest

One recent clinical investigation examined the effect of inducing moderate hypothermia at the emergency department in patients with anoxic brain injury who had suffered out-of-hospital cardiac arrest. The result was a significantly lower mortality rate in patients who were subjected to hypothermia compared to normothermic controls (15). As well, another study showed that mild resuscitative hypothermia after cardiac arrest is a feasible and safe approach (139).

Conclusion

In summary, the investigations done to date indicate that the application of mild to moderate hypothermia in patients with head injury, cerebral hemorrhage, or stroke is a feasible method of treatment that benefits many patients. A clinical multicenter trial curently underway is expected to further support and define hypothermia as effective therapy, and may lead to its wider acceptance based on improved patient outcome. We know that mild to moderate hypothermia protects against primary or secondary ischemic injury, but the clinical strategies needed to maximize the effectiveness of hypothermia and minimize its adverse effects have yet to be determined.

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