Antiedema Therapy in Ischemic Stroke

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Abstract—Life-threatening, space-occupying brain edema occurs in up to 10% of patients with supratentorial infarcts and is traditionally associated with a high mortality rate of up to 80%. Management of these patients is currently being changed to an earlier and more aggressive treatment regimen. Early surgical decompression has recently been proven effective to reduce mortality and increase the number of patients with a favorable outcome in randomized controlled trials and is now the “antiedema” therapy of first choice for patients with large middle cerebral artery infarction aged 60 years or younger. Several medical treatment strategies have been proposed to control brain edema and reduce intracranial pressure, including different osmotherapeutics, hyperventilation, tromethamine, hypothermia, and barbiturate coma. None of these treatments is supported by level 1 evidence of efficacy in clinical trials, and some of them may even be detrimental. Preliminary results on hypothermia for space-occupying hemispheric infarction are encouraging, but far from definitive. (Stroke. 2007;38:3084-3094.)

Key Words: conventional antiedema therapy ■ edema, brain ■ hemicraniectomy ■ hypothermia ■ ischemia

Severe middle cerebral artery (MCA) or hemispheric infarctions account for ≈10% of all ischemic strokes. This type of stroke is commonly associated with variable degrees of brain edema and a high mortality rate. The clinical course in most of these patients typically follows a predictable pattern. The patients initially show a severe hemispheric syndrome with head turning, eye deviation, hemiplegia, aphasia, or severe speech disturbance. Progressive brain edema leads to neurological deterioration caused by tissue shifts compressing the midline structures, eventually leading to transtentorial and uncal herniation. Space-occupying edema usually manifests between the second and fourth day after stroke onset, although neurological deterioration within 24 hours of symptom onset has been reported in up to one-third of the patients. Outcome is fatal in the majority of patients with space-occupying hemispheric infarction, with a mortality of ≈80% in intensive care-based series, despite maximal conservative treatment.

Several treatment strategies have been proposed to reduce brain edema and control elevated intracranial pressure (ICP) for malignant MCA infarction including artificial ventilation and hyperventilation, osmotherapy, tromethamine (THAM), and barbiturate administration. There are a number of widely accepted tenets about the effects and limitations on the use of these therapies; however, only some of them appear to be substantiated. No controlled randomized trial has addressed the efficacy of these conventional therapies to improve short- or long-term clinical outcome. Thus, management of space-occupying brain edema remained controversial and poorly understood, and the value of these measures has come into question.

Today, new therapeutic options can be offered. Early surgical decompression has now been shown effective in lowering mortality and improving neurological outcome in randomized trials. Therapeutic hypothermia may represent another option, which has been demonstrated to be neuroprotective in animal models, as well as in clinical studies after cardiac arrest.

This review examines the available data on the use of conservative medical treatment modalities for antiedema therapy in ischemic stroke and discusses its value with regard to new therapeutic options that are decompression and hypothermia.

Ischemic Brain Edema

It has become customary to distinguish 2 major types of edema generation in ischemic stroke, the intracellular (cytotoxic) and the extracellular (vasogenic) edema, although this classic vasogenic and cytotoxic paradigm is probably an oversimplification. The cytotoxic edema develops within minutes in the ischemic core and is mainly caused by energy failure and anoxic membrane depolarization with subsequent energy failure and anoxic membrane depolarization with subsequent...
accumulation of intracellular Na\(^+\), leading to an influx of water and cellular swelling. The main factor for vasogenic edema is a disruption of the blood–brain barrier (BBB), leading to increased permeability and movement of proteins and fluid from the intravascular space to the interstitial and intracellular compartments. However, experimental data suggest that the early increase in brain water content is mainly caused by an abnormal Na\(^+\) transport into the extracellular space rather than structural changes of the BBB with a gross breakdown to larger molecules. The shift of ions and water into the cells during the formation of cytotoxic edema creates a new gradient for Na\(^+\) between the intravascular and the extracellular space, which probably acts as driving force for transcapillary electrolyte and water transport into the brain parenchyma.\(^7\) Breakdown of the BBB with an almost indiscriminate shift of intravascular proteins and ions into the extravascular compartments occurs later in the course of vasogenic edema. Although the exact mechanisms by which ischemia disrupts the BBB are not fully understood, several modulators and mediators have been identified in experimental investigations including aquaporins, free radicals, proteases such as matrix metalloproteinases, inflammatory cells and their mediators, bradykinin, vascular endothelial growth factor, and nitric oxide synthase.\(^7,8\)

The effect of reperfusion on edema evolution is still a matter of debate. In experimental focal ischemia, reperfusion has been reported to both reduce infarct growth and brain edema and aggravate vasogenic edema formation and hemorrhage. Whether reperfusion has beneficial or harmful effects largely depends on severity and duration of previous ischemia, and the efficacy of reperfusion.\(^9\) Interestingly, total cessation of blood flow does not cause a change in brain water and Na\(^+\) content, suggesting that brain swelling requires active cerebral blood flow.\(^7,8\) Certainly, if reperfusion is induced in already irreversibly damaged areas, the increased vascular permeability during reperfusion leads to vasogenic edema formation. In addition, late restoration of blood flow may even increase ischemic damage by inducing different pathophysiological mechanisms (e.g., increase in reactive oxygen species and excitatory amino acids, Ca\(^{2+}\) influx), with a further worsening of edema.\(^8,9\) However, the clinical significance of these experimental data should be interpreted with caution, because reperfusion was not consistently associated with aggravation of edema, and in case of human stroke, the benefits of early reperfusion by thrombolytic therapy likely outweigh the potential worsening of ischemic edema.

There is a considerable degree of variation in the timing and extend of edema formation among patients. Different clinical and radiological predictors for fatal brain edema formation have been identified, such as early nausea/vomiting, rapidly declining level of consciousness, dilated pupils, NIHSS >15, and early CT hypodensity involving >50% of the MCA territory and other vascular territories.\(^1,10,11\) Unfortunately, none of these predictors alone or in combination proved sufficient prognostic value. It seems plausible that the extent of swelling strongly depends on the extent and location of the infarcted area, but substantial individual variability exists.\(^12\)

### Medical Antiedema Therapy

An overview of the clinical studies on medical treatment strategies with proposed antiedema effects for acute ischemic stroke is shown in Table 1.

### Osmotherapy

**Mannitol**

Mannitol mainly acts as an osmotic agent, drawing water from the interstitial and intracellular spaces of the brain across the BBB. In addition, mannitol may improve microvascular cerebral blood flow by hemodilution and increased deformability of erythrocytes with a subsequent reduction of cerebral blood volume and ICP via vasoconstriction. Mannitol may also cause an increase in cerebral perfusion pressure (CPP) by augmentation of mean arterial blood pressure, which in turn may cause cerebral vasoconstriction with consequent reduction in cerebral blood volume and ICP.\(^13\)

Numerous experimental studies have investigated the effects of mannitol on focal cerebral ischemia and edema formation in various animal models, but the results have not been consistent. Most investigations found beneficial effects of intravenous mannitol with respect to infarct volume,\(^14\) edema formation,\(^14,15\) and elevated ICP.\(^15\) The effective dose used varied markedly among the studies, ranging between a single bolus of 1g/kg and repeated boluses of 2.5 g/kg every 4 hours.\(^15\) Other studies on focal ischemia failed to show a significant positive effect of mannitol therapy on infarct size or cerebral edema,\(^16\) and some studies even found detrimental effects on brain swelling and midline shift after multiple doses of mannitol.\(^17\)

Given the fact that mannitol is one of the most frequently used osmotic agent for the treatment of brain edema of various types worldwide, surprisingly few clinical trials have been performed to study the effects of mannitol in acute ischemic stroke. A recent Cochrane report\(^18\) identified a total of 5 randomized controlled trials, 4 of which were characterized as confounded, whereas the fifth\(^19\) had several methodical issues. The authors stated that no conclusion could be drawn about the effect of mannitol in acute ischemic stroke patients due to the lack of adequate controlled randomized trials.

In a more recent observational study, Bereczki et al\(^20\) analyzed the case fatality with respect to mannitol treatment in 805 stroke patients. The authors found that depending on the prognostic factors used in the multivariate analysis, mannitol had either a nonsignificant or an adverse effect on 30-day and 1-year case fatality. However, the results of this nonrandomized study should be interpreted with caution. The characteristics differed substantially between groups, the decision to give mannitol was based on the discretion of the treating physician and CT was performed in only 73% of the patients, with no lesion detected in 10%.

However, all of these clinical trials were not primarily aimed at reducing edema formation in large ischemic stroke. Randomized controlled studies on this subject are lacking, although ICP-lowering properties of mannitol have been reported in some case series on space-occupying hemispheric infarction. Single doses of 40-g mannitol in 8 patients with
Table 1. Summary of Clinical Studies Evaluating Medical Treatment Strategies With Proposed Antiedema Effect in Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>No. Treated</th>
<th>Interventions</th>
<th>Treatment Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santambrogio 1978</td>
<td>Ran-con</td>
<td>36</td>
<td>0.8–0.9g/kg daily</td>
<td>No effect on outcome and 10-day survival</td>
</tr>
<tr>
<td>Schwarz 1998</td>
<td>Prospec</td>
<td>8</td>
<td>~0.5g/kg</td>
<td>Reduced ICP in 10/14 crises</td>
</tr>
<tr>
<td>Manno 1999</td>
<td>Prospec</td>
<td>7</td>
<td>1.5 mg/kg</td>
<td>No effect on tissue shift</td>
</tr>
<tr>
<td>Videen 2001</td>
<td>Prospec</td>
<td>6</td>
<td>1.5 mg/kg</td>
<td>Preferential shrinkage of normal hemisphere</td>
</tr>
<tr>
<td>Bereczki 2003</td>
<td>Prospec</td>
<td>546</td>
<td>47±22 g/d for 6±3 d</td>
<td>No or adverse effect on 1-yr mortality</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwarz 1998</td>
<td>Prospec</td>
<td>8</td>
<td>100 mL 7.5%+60 g/L HES</td>
<td>Reduced ICP in 16/16 crises</td>
</tr>
<tr>
<td>Schwarz 2002</td>
<td>Prospec</td>
<td>6</td>
<td>75 mL 10%</td>
<td>Reduced ICP in 22/22 crises after mannitol failed</td>
</tr>
<tr>
<td>Glycerol (only ran-con studies34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew 1972</td>
<td>Ran-con</td>
<td>34</td>
<td>500 mL 10% for 4–6 d</td>
<td>No effect on mortality</td>
</tr>
<tr>
<td>Frieth 1975</td>
<td>Ran-con</td>
<td>50</td>
<td>500 mL 10% for 6 d</td>
<td>No effect on mortality, neurological improvement in intermediately disabled patients</td>
</tr>
<tr>
<td>Larsson 1976</td>
<td>Ran-con</td>
<td>12</td>
<td>500 mL 10% for 6 d</td>
<td>No effect on mortality and outcome</td>
</tr>
<tr>
<td>Fawer 1978</td>
<td>Ran-con</td>
<td>26</td>
<td>2×250 mL 10% for 6 d</td>
<td>No effect on mortality, transient improvement of neurological recovery improvement in intermediately disabled patients</td>
</tr>
<tr>
<td>Friedli 1979</td>
<td>Ran-con</td>
<td>32</td>
<td>500 mL 10% for 6 d</td>
<td>No effect on mortality, neurological</td>
</tr>
<tr>
<td>Frei 1987</td>
<td>Ran-con</td>
<td>18</td>
<td>500 mL 10% for 7 d</td>
<td>No effect on mortality and outcome</td>
</tr>
<tr>
<td>Bayer 1987</td>
<td>Ran-con</td>
<td>85</td>
<td>500 mL 10% for 6 d</td>
<td>Reduced mortality, no effect on outcome</td>
</tr>
<tr>
<td>Yu 1993</td>
<td>Ran-con</td>
<td>56</td>
<td>500 mL 10% for 6 d</td>
<td>No effect on mortality, trend toward better Barthel Index</td>
</tr>
<tr>
<td>Sakamaki 2003</td>
<td>Prospec</td>
<td>6</td>
<td>300 mL 10%</td>
<td>No effect on tissue shift</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christensen 1972</td>
<td>Ran-con</td>
<td>24</td>
<td>CO₂ ~25 mm Hg for 72 hr</td>
<td>No effect on outcome and mortality</td>
</tr>
<tr>
<td>Simard 1973</td>
<td>Ran-con</td>
<td>50</td>
<td>CO₂ ~22 mm Hg for 72 hr</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>THAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No study published</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rockhoff 1979</td>
<td>Retrospec</td>
<td>4</td>
<td>Pentobarbital (dose?) for 5 d</td>
<td>All patients died</td>
</tr>
<tr>
<td>Woodcock 1982</td>
<td>Prospec</td>
<td>5</td>
<td>Pentobarbital 50–300 mg/hr for 2–5 d</td>
<td>4 of 5 patients died</td>
</tr>
<tr>
<td>Schwab 1997</td>
<td>Prospec</td>
<td>60</td>
<td>Thiopental titrated for burst suppression</td>
<td>Reduced ICP in 50 of 60 patients after failure of conventional therapy, significant CPP decline, only 5 patients survived</td>
</tr>
<tr>
<td>Steiner 2001</td>
<td>Prospec</td>
<td>21</td>
<td>300–500 mg thiopental</td>
<td>Reduced ICP in every case, but reduced cerebral oxygenation and CPP</td>
</tr>
</tbody>
</table>

Furosemid
No study published

(Continued)
hemispheric stroke and massive edema were effective in temporarily (up to 4 hours) reducing elevated ICP in 10 of 14 episodes. Effects on long-term outcome were not investigated. Similarly, in another observational study with 21 patients with severe MCA infarction, mannitol was effective in reducing ICP in most patients. This was associated with substantial increase in CPP and brain tissue oxygen pressure in both the ischemic and the nonischemic hemisphere. Several concerns have to be considered when using mannitol in stroke patients. Theoretically, the effectiveness of osmotherapy depends on an intact BBB and hypertonic solutions may cause a preferential shrinkage of normal hemisphere where BBB is still intact, with a subsequent worsening of tissue shifts. The clinical significance of this phenomenon remains unclear and the few available data in humans are inconsistent. Moreover, accumulation of mannitol in damaged brain tissue has been reported after repeated doses in one animal study, causing a reversal of the osmotic gradient and aggravation of brain edema. Again, quantifying and demonstrating these differences between compartments after multiple mannitol doses have been proven difficult. It should be noted that the same presumed theoretical concerns apply to other osmotic agents such as glycerol and hypertonic saline.

Given the lack of systematic clinical trial in stroke patients, there is no clear information on optimal timing, dosing, and application schedule of mannitol. A range between 310 and 320 mOsm/L has been commonly recommended as target serum osmolality, and the maximum tolerable threshold is generally believed to be 320 mOsm/L. However, this practice is not supported by systemic experimental or clinical studies. Crossing this threshold is not necessarily dangerous as long as the patient is not volume-depleted.

Summing up these results, surprisingly few clinical studies exist testing mannitol in the setting of acute ischemic stroke. In a systemic Cochrane review, outcome analysis could not be performed because of lack of appropriate trials and a few retrospective and observational studies found no or even a tendency toward harmful effects in patients with acute stroke. Similarly, no randomized clinical trial has addressed the effect of mannitol treatment on clinical outcome in patients with space-occupying edema after large MCA infarction. Thus, the use of mannitol in these patients is solely founded by the results of experimental studies, or observations in small nonrandomized case series in humans.

**Hypertonic Saline**

Over the past few years, hypertonic saline solutions have increasingly been used as an alternative to mannitol to control brain edema of various types. As is the case with mannitol, several mechanisms may be responsible for the reduction of brain edema achieved with hypertonic saline. Because sodium chloride is completely excluded from an intact BBB, it has been proposed that hypertonic saline may be a more favorable osmotic agent compared with mannitol. Furthermore, hypertonic saline has the effect of expanding the intravascular volume with increasing mean arterial blood pressure leading to improved CPP, whereas mannitol is an osmotic diuretic that secondary leads to volume depletion. Other proposed mechanisms of action include modulation of inflammatory response and neuron excitation, and improved oxygenation.

Experimental studies comparing hypertonic saline with mannitol in different brain lesion models others than ischemia have provided somewhat conflicting results with respect to antiedema and ICP-lowering properties. In a few small

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>No. Treated</th>
<th>Interventions</th>
<th>Treatment Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids (only ran-con studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patten 1972</td>
<td>Ran-con</td>
<td>17</td>
<td>Dexamethasone</td>
<td>Improved 2-wk neurological outcome</td>
</tr>
<tr>
<td>Bauer 1973</td>
<td>Ran-con</td>
<td>28</td>
<td>Dexamethasone</td>
<td>No effect on outcome and 2-wk mortality</td>
</tr>
<tr>
<td>Norris 1976</td>
<td>Ran-con</td>
<td>26</td>
<td>Dexamethasone</td>
<td>Impaired 4-wk neurological outcome</td>
</tr>
<tr>
<td>Mulley 1978</td>
<td>Ran-con</td>
<td>61</td>
<td>Dexamethasone</td>
<td>No effect on outcome and 1-yr mortality</td>
</tr>
<tr>
<td>Santambrogio 1978</td>
<td>Ran-con</td>
<td>48</td>
<td>Dexamethasone</td>
<td>No effect on outcome and 10-d mortality</td>
</tr>
<tr>
<td>Gupta 1978</td>
<td>Ran-con</td>
<td>13</td>
<td>Betamethasone</td>
<td>No effect on outcome and 3-wk mortality</td>
</tr>
<tr>
<td>McQueen 1978</td>
<td>Ran-con</td>
<td>24</td>
<td>Betamethasone</td>
<td>No effect on outcome and 12-wk mortality</td>
</tr>
<tr>
<td>Norris 1986</td>
<td>Ran-con</td>
<td>54</td>
<td>Dexamethasone</td>
<td>No effect on outcome and 3-wk mortality</td>
</tr>
<tr>
<td>Indomethacine</td>
<td>Case</td>
<td>1</td>
<td>50-g bolus</td>
<td>Reduced ICP after failure of conventional therapy</td>
</tr>
</tbody>
</table>

Pros, indicates prospective; ran-con, randomized controlled; retrospect, retrospective.
randomized studies on patients with head injury, there is some support that hypertonic saline may be more effective in lowering ICP compared with mannitol. However, no definitive conclusion can be drawn at present because the experimental and clinical studies used a wide range of saline concentrations and equiosmotic solutions were not consistently used.

In stroke animal models, results have also been ambiguous; 7.5% saline worsened infarct volume when given as a bolus immediately after reperfusion followed by continuous infusion in rats. In contrast, using the same stroke model, the authors found a significant reduction of water content in both hemispheres when infusion was started 6 hours or 24 hours after ischemia induction. Of note, these positive effects were seen after prolonged continuous infusion (1 to 4 days), with a subsequent serum osmolality clearly exceeding 350 mOsm/L. Lower saline concentration (3%), however, had no effect on infarct volume and water content of ischemic brain regions. Somewhat surprisingly, the effects of repeated boluses instead of continuous infusion have not yet been systematically investigated.

Data on the clinical use of hypertonic saline in ischemic stroke are derived from only 2 small case series. In 9 patients with elevated ICP caused by massive edema after hemispheric stroke, a bolus of 100 mL of 7.5% saline plus hydroxethyl starch solution significantly lowered ICP in 16 of 16 episodes. Hypertonic saline solution appeared to decrease ICP more rapidly and effectively than equimolar doses of mannitol, and was still successful after mannitol had failed. Similarly, in 8 severe stroke patients with 22 episodes of ICP crisis, a 75-mL bolus of 10% saline led to a significant reduction of ICP in all episodes after failure of other medical therapies including mannitol. This was associated with a significant increase in CPP, whereas mean arterial blood pressure remained essentially unchanged. At present, there is no clear information on the optimum form of application of hypertonic saline. Multiple concentrations ranging from 3% to 23.4% have been tested in continuous and bolus infusion with different application schedules for the treatment of traumatic brain injury, and the results are controversial. For the use of hypertonic saline in ischemic stroke, almost no evidence exists for any one formula because of the lack of systemic trials.

A frequently emphasized argument against the nonrestrictive use of hypertonic saline is the fear of complications attributable to severe hypernatremia and to inducing pontine myelinolysis, although these concerns are more hypothetical and such complications have been rarely observed in clinical studies. Other potential side effects of hypertonic saline include congestive heart failure and pulmonary edema, hyperchloremic acidosis, hypokalemia, and hypomagnesemia.

In summary, although data on the use of hypertonic saline for the treatment of brain edema and elevated ICP are promising in various conditions, it is far away from definitive. Only 2 small case series investigated hypertonic saline solutions in the setting of brain edema after large MCA infarction. No clinical trial addressed its effect in the acute stage of ischemia or its impact on functional outcome. Thus, whereas hypertonic saline may ameliorate elevated ICP over a short period of observation, its long-term effects in patients with ischemic stroke are largely unknown.

Glycerol

The sugar glycerol is another osmotic agent that may also have neuroprotective properties. In human stroke, increase of blood flow to ischemic territories and improvement in ischemic brain energy metabolism after glycerol administration have also been postulated. The occurrence of a rebound phenomenon has been controversial, but glycerol has the theoretical advantage over other osmotics in being metabolized by the brain on crossing BBB, thus reducing the risk of rebound edema. Using MRI before and after glycerol administration in 6 patients with large hemispheric infarction, no effect on tissue shift and noninfarcted hemisphere volume has been observed. In addition, glycerol has almost no major side effects.

Glycerol has been evaluated in numerous randomized and nonrandomized clinical trials of acute stroke, either ischemic or hemorrhagic. A systemic (Cochrane) review identified 10 randomized studies in which a total of 482 glycerol-treated patients were compared with 463 control patients. Glycerol was associated with a nonsignificant reduction in odds of death within the scheduled treatment period (OR, 0.78; CI, 0.58 to 1.06), which was significant for definite or probable ischemic stroke (OR, 0.65; CI, 0.44 to 0.97). However, there was no evidence of any effect of glycerol on mortality at the end of scheduled follow-up. Functional outcome was comparable only in 2 trials, and there was a nonsignificant reduction in odds of being death or dependent (OR, 0.73; CI, 0.37 to 1.42). However, these results should be interpreted with caution because most trials were performed in the pre-CT era, and only a few patients had their stroke confirmed by brain imaging. Furthermore, in only 1 study the clinical suspicion of brain edema was considered in the inclusion criteria. Therefore, the review does not provide reliable evidence on the efficacy of glycerol in patients with established brain edema.

Summarizing these results, glycerol is one of the most frequently tested treatments for acute human stroke. Glycerol therapy seems to have a beneficial effect on short-term survival in patients with acute ischemic stroke, but no long-term efficacy. The lack of proven benefit on long-term clinical outcome does not support its routine use in patients with acute ischemic stroke. No randomized trial specifically addressed its effect on outcome in patients with massive edema secondary to large hemispheric infarction.

Barbiturates

The main effect of barbiturates consists of a decrease in cerebral metabolism. Reduced metabolic rate and subsequent reduction of cerebral blood volume and cerebral blood flow may theoretically reduce edema formation and lower ICP. Case series suggest that barbiturate therapy may be effective to reduce elevated ICP in various conditions, although ICP-lowering effect appears to be relatively inconsistent. A prospective comparative study with 95 severely head-injured patients reported that barbiturate coma was less effective than mannitol for control of raised ICP, and may be even harmful
in the subgroup of patients without hematoma.41 The use of high-dose barbiturates is frequently associated with severe complications, including hypotension, hepatic dysfunction, and increased risk of infections.

There are only very limited data on the use of barbiturates for brain edema after severe infarction. Some case studies in the 1970s and 1980s on ICP-lowering effects of barbiturates included a few patients with brain swelling secondary to ischemic infarction, and the observations were disappointing.38,39 In a more recent case series with 21 patients with elevated ICP after large MCA infarction, barbiturate treatment was persistently associated with a reduction in cerebral oxygen pressure and reduced CPP, although ICP was temporarily decreased in every case.22 In the only prospective, but uncontrolled study on this subject, 60 consecutive patients with elevated ICP caused by severe MCA infarction were treated with barbiturates, after failure of osmotherapy and hyperventilation. Only 5 patients survived. Although barbiturates were initially effective in lowering ICP in 50 patients, sustained ICP control was only achieved in the 5 survivors. Moreover, a significant decline in CPP was observed during barbiturate infusion.42 Randomized controlled trials are lacking.

Thus, in patients with large MCA infarctions, barbiturates only seem to offer limited and short-lasting benefits that may be counterbalanced by severe adverse effects, especially if hypotension occurs with a subsequent critical decline in CPP.

Hyperventilation

Hyperventilation decreases ICP by the induction of cerebral vasoconstriction, with a subsequent decrease of cerebral blood volume and cerebral blood flow. The ICP-lowering capacity of hyperventilation has been shown in numerous case series in traumatic brain-injured patients, with duration of hyperventilation mostly ranging between 10 and 30 minutes.43 However, some studies suggest that the effect of hyperventilation may diminish within a few hours.43,44 Despite the wide use of hyperventilation in the treatment of elevated ICP after head trauma, its effect on clinical outcome was evaluated in only 1 randomized clinical trial. Depending on subgroup analysis, prolonged hyperventilation had no or even harmful effect on functional outcome at 3 and 6 months.44

The major drawback of hyperventilation is that cerebral vasocnstriction may decrease cerebral blood flow to ischemic levels.45 In addition, various clinical studies on head injury suggested deleterious effects of hyperventilation on cerebral oxygenation46 and cerebral metabolism.45 Moreover, rebound vasodilation may occur along with the risk of increasing ICP after discontinuation of hyperventilation.44

Data on the use of hyperventilation in stroke patients are rare and were derived from clinical studies in the early 1970s. In these trials, no effect of hyperventilation (CO2 22 to 25 mm Hg) on clinical outcome and mortality was observed.57,48 More recent clinical studies on this subject are lacking.

With regard to the large body of evidence indicating the possible deleterious effects of hyperventilation on cerebral oxygenation, metabolism and blood flow, and the lack of evidence of any beneficial effect on outcome, hyperventilation cannot be recommended in stroke patients.

THAM

THAM is supposed to act by entering the cerebrospinal fluid compartment and neutralizing the acidosis-induced vasodilation, thereby reducing ICP. ICP-lowering properties as well as beneficial effects on edema formation and cerebral energy disturbance of THAM have been demonstrated in animal models of head injury.49 In animal models of focal cerebral ischemia, THAM infusion was associated with a significant reduction of infarct size, brain edema and lactate concentration.50

There are only a few data published on the clinical use of THAM treatment for brain edema and elevated ICP. In the only prospective randomized trial in 149 patients with severe head injury assigned to receive THAM or placebo for 5 days, THAM treatment was associated with significantly fewer episode of ICP elevation and a significantly lower incidence of requiring barbiturate coma. However, no difference in outcome was observed.51

There are no controlled studies on the use of THAM in acute stroke patients. Nevertheless, some authors consider THAM administration as an option for treating brain edema and elevated ICP secondary to large MCA infarction.2,12,26

Elevated Head Position

Elevation of the head is thought to decrease ICP via increasing the venous outflow and reducing venous hydrostatic pressure and volume at the cranial level. Thus, patients with massive hemispheric stroke are traditionally nursed with the head moderately (15° to 45°) elevated. These recommendations for stroke patients are largely derived from pathophysiological considerations and the results from head-injured patients. In addition, elevated backrest position may reduce the risk of ventilator-associated pneumonia.52 Head elevation, however, may also cause marked decrease in CPP because of decrease in mean arterial blood pressure,53 and sustained CPP declines can result in further ischemic damage. Despite this concern, only 1 study systematically investigated the effects of body position in 12 patients with large supratentorial stroke.54 Mean ICP decreased only slightly from 13 mm Hg in horizontal position to 11.4 mm Hg at 30° backrest elevation, whereas CPP markedly declined from 77 mm Hg to 64 mm Hg. These findings and our own experience give little support for the routine use of 30° head elevation, because the increase in ICP in the horizontal position is likely not clinically significant, but the decrease in CPP may be harmful for patients with massive stroke. Instead, optimal body position should be established individually: the flat position may probably be preferable to achieve sufficient CPP; moderate head elevation appears reasonable as long as CPP is adequately maintained (>70 mm Hg) and in those patients in whom ICP increases substantially in a horizontal position.

Indomethacin

Indomethacin is a potent cerebral vasoconstrictor that also may exhibit antiedema and anti-inflammatory effects. ICP-lowering capacity of indomethacin has been described in few
A systematic (Cochrane) review identified only 7 of 22 published trials of acute steroid treatment in acute presumed ischemic stroke acceptable for further analysis, and these comprised only 453 patients in total with no uniformity of evaluation and assessment. Only 1 study performed CT to exclude hemorrhagic stroke. The authors concluded that these trials of steroids do not provide any evidence of a beneficial effect on mortality or functional outcome after presumed ischemic stroke. Clinical studies on intracerebral hemorrhage also failed to show beneficial effects, whereas the rate of complications significantly increased. Given the lack of systemic clinical trials, indomethacin for the treatment of postischemic swelling remains experimental.

Steroids

A systematic (Cochrane) review identified only 7 of 22 published trials of acute steroid treatment in acute presumed ischemic stroke acceptable for further analysis, and these comprised only 453 patients in total with no uniformity of evaluation and assessment. Only 1 study performed CT to exclude hemorrhagic stroke. The authors concluded that these trials of steroids do not provide any evidence of a beneficial effect on mortality or functional outcome after presumed ischemic stroke. Clinical studies on intracerebral hemorrhage also failed to show beneficial effects, whereas the rate of complications significantly increased. Given the lack of systemic clinical trials, indomethacin for the treatment of postischemic swelling remains experimental.

Furosemide

Loop diuretics like furosemide may act by decreasing total body water and increasing blood osmolality, thereby removing water from the brain. Only a few experimental studies addressed the use of furosemide for treating brain edema after focal cerebral ischemia, and results are inconsistent. No clinical trials have been published evaluating the effects of furosemide on outcome after ischemic stroke. As a note of caution, the risk of substantial volume depletion with subsequent decrease in mean arterial blood pressure and CPP to ischemic levels may outweigh any potential benefit on brain edema and ICP.

New Therapeutic Approaches

Hypothermia

Most likely, hypothermia exerts multiple and synergistic neuroprotective effects. Hypothermia reduces the cerebral metabolic rate, stabilizes BBB, reduces brain edema, free radical formation, and the release of excitatory neurotransmitters, and attenuates postischemic inflammatory response and apoptosis.

In animal models of transient focal ischemia, hypothermia consistently decreased infarct volume when initiated before or at the onset of ischemia, and to a less extend with increasing delay of cooling. A longer cooling period results in better neuroprotective effects when initiation of cooling is delayed. Another crucial factor for its neuroprotective potential is the depth of hypothermia. A recent study systematically evaluating temperatures between 32°C and 37°C found the smallest infarct volumes with a body temperature of 33°C and 34°C.

Although early intervention to protect the ischemic penumbra until restoration of blood flow may be seen as the ultimate goal of therapeutic hypothermia for ischemic stroke, most of the initial human studies were designed to address the effects of hypothermia on space-occupying edema after infarction was completed.

In the 5 observational case series on this subject published to date, a total of 112 patients has been investigated, all of them with space-occupying infarction involving at least two-thirds of the MCA territory (Table 2). All trials used 33°C as target temperature and treatment entailed deep sedation, relaxation, and mechanical ventilation. The delay from stroke onset to induction of hypothermia was relatively long in all trials, with a mean ranging between 10 and 28 hours. Duration of cooling also varied, ranging between 55 and 71 hours in the first 4 studies. In the study by Milhaud et al testing more prolonged hypothermia, mean cooling period was 19 days. A significant and rapid decrease in ICP was described in the first 2 studies by Schwab et al. Mortality was relatively consistent among trials, being 44% and 38% in the studies reported by Schwab et al, 47% in the study described by Georgiadis et al, and 42% in the study by Milhaud et al. The rewarming period seems to be crucial, because rebound intracranial hypertension during rewarming was a common occurrence and a major contributor to mortality. A shorter rewarming period (<16 hours) was associated with a more pronounced increase in ICP. Though all patients fulfilled the criteria for malignant MCA infarction, the survivors reached a fairly favorable outcome at 3

Table 2. Summary of Clinical Studies on Hypothermia (33°C) for Antiedema Therapy After Severe (More Than Two-Thirds) MCA Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Induction Latency (h)</th>
<th>Hypothermia Duration</th>
<th>Mortality, %</th>
<th>Outcome of Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwab 1998</td>
<td>25</td>
<td>14±7</td>
<td>65 (48–72) hr</td>
<td>44</td>
<td>BI 70 (60–85), mRS 2.6 (2–4)</td>
</tr>
<tr>
<td>Schwab 2001</td>
<td>50</td>
<td>22±9</td>
<td>55 (24–72) hr</td>
<td>38</td>
<td>BI 65 (10–85), mRS 2.9 (2–5)</td>
</tr>
<tr>
<td>Georgiadis 2001</td>
<td>6</td>
<td>28±17</td>
<td>48–78 hr</td>
<td>17</td>
<td>Not given</td>
</tr>
<tr>
<td>Georgiadis 2002</td>
<td>19</td>
<td>24 (18–24)</td>
<td>71±21 hr</td>
<td>42</td>
<td>Not given</td>
</tr>
<tr>
<td>Milhaud 2005</td>
<td>12</td>
<td>10±7</td>
<td>19±4 d</td>
<td>42</td>
<td>BI 75 (50–95), mRS 3 (1–5)</td>
</tr>
</tbody>
</table>

BI indicates Barthel Index.
months (Barthel Index 65 and 70, respectively) by 60% to 80% or at 6 months (Barthel Index 75). The most common complications were arterial hypotension (40% to 100%), thrombocytopenia (37% to 76%), pneumonia (11% to 48%), and bradycardia (30% to 60%). Randomized controlled clinical trials on hypothermia for the treatment of space-occupying MCA infarction are still lacking.

Other clinical trials focused on the feasibility of the early (<6 to 9 hours) use of therapeutic hypothermia. Two recent studies reported early cooling to be safe and feasible in awake stroke patients, even when combined with thrombolysis. Overall, no significant differences were observed between hypothermic and normothermic patients, but studies were not powered to evaluate the efficacy of early cooling.

In summary, although numerous experimental studies consistently demonstrated robust neuroprotection when cooling was initiated during ischemia evolution, its effect on space-occupying edema after established large infarction has barely been tested in animal studies. Five observational case series specifically addressed the effect of hypothermia on massive brain edema after severe MCA infarction. Hypothermia seems to reduce mortality, with a good outcome of survivors when compared with historical controls with malignant MCA infarction. Although these results are encouraging, they are preliminary and far from firm. The interpretation is strongly limited by confounding bias of such comparisons, the highly selective nature of nonrandomized trials, and the low number of patients included. Evidence from randomized trials on cooling for the treatment of space-occupying infarction is lacking. Thus, the use of hypothermia in these patients remains experimental and no evidence-based recommendation can currently be given.

Future Directions

Further investigations should define the optimal methodical approach for inducing hypothermia in stroke including patient selection, onset timing, depth and duration of hypothermia, and rewarming. One oft the most pressing issues is the optimal timing of hypothermia. All studies on hypothermia for antiedema therapy awaited clinical worsening before deciding for hypothermia treatment. The long delay in cooling induction surely precluded any significant neuroprotective effect.

Optimal duration of cooling represents another important issue that also should be addressed. Most of studies for massive edema applied cooling for 48 to 72 hours. However, given the natural time course of edema evolution in which swelling is usually maximal on days 2 to 5, cerebral edema is still present even after 72 hours, and the patient’s condition frequently worsens during rewarming. Thus, from a pathophysiological point of view, it seems reasonable that hypothermia might be more effective in controlling ICP when cooling period exceeds the natural peak of brain swelling, ie, >120 hours. Prolonged (8 days) hypothermia has been shown to be safe and feasible in a trial on severe head injury and, more recently, in 1 study on space-occupying MCA infarction, with a complication rate comparable to previous studies using shorter cooling times and a fairly good functional outcome of survivors.

Thus, with regard to neuroprotection and the natural course of edema evolution, early induced (<6 hours) and more prolonged (>120 hours) hypothermia may achieve increased benefit in patients with evolving space-occupying hemispheric infarction.

Decompressive Surgery

Over the past decades, decompressive hemicraniectomy for malignant MCA infarction has been reported to lower mortality without increasing the number of severely disabled survivors in several uncontrolled case series. However, given the highly selected nature of such uncontrolled studies, and the lack of prospective randomized trials, there was as yet substantial concern about allowing survival at the cost of a high degree of disability with this aggressive therapy.

Fortunately, the results of a pooled analysis of 3 European randomized controlled trials (DECEMAL, DESTINY, HAMLET) assessing the effect of decompressive surgery in patients with space-occupying MCA infarction are now available. Inclusion criteria for the pooled analysis were age 18 to 60 years, NIHSS >15, decreased level of consciousness, infarct volume >50% of the MCA territory on CT or >145 cm³ on diffusion-weighted MRI, and surgery initiated within 48 hours after stroke onset. A total of 93 patients were included. Survival rate was significantly higher in patients treated with decompressive surgery compared with patients without surgery (78% vs 29%; Figure 1). Significantly more patients in the surgery group had a favorable outcome with a modified Ranking scale (mRS) score ≤4 (75% vs 24%) and mRS ≤3 (42% vs 21%; Figure 2). Number needed to treat was 2 for survival with mRS ≤4, 4 for survival with mRS ≤3, and 2 for survival irrespective of functional outcome. Further analysis suggested that age older than 50 years, time window to treatment >24 hours, and the presence of aphasia did not alter the beneficial effects of surgery, although subgroups were small and not powered to detect small differences in treatment effects.

It must be noted that this study design is an unconventional approach in which a pooled analysis from 3 independent trials was planned in advance while these trials were still ongoing. The obvious advantage of such an approach is to keep the number of patients included to a minimum and to report the results much earlier than would have been possible based on individual trials alone. However, this study design certainly has limitations that are strongly related to the nature of pooled analysis of independent trials. Eligibility criteria such as age, time to randomization, and neuroimaging criteria were not identical, resulting in differences in baseline characteristics, infarct morphology, and in timing of surgery between individual trials. Nevertheless, there was no significant heterogeneity between the three trials with regard to all outcome measures and adjusted analysis did not make any differences to the results. More importantly, 2 of the 3 trials (DESTINY and DECEMAL) stopped recruitment in 2006 and the results of both trials are consistent to those of the pooled analysis, confirming the significance of the pooled analysis. The results will be published soon in Stroke.

Thus, based on these findings, early (<48 hours) decompressive surgery can now be recommended as the treatment
of choice for patients aged 60 years or younger, with severe infarction of at least 50% of the MCA territory, to reduce mortality and increase the number of patients with favorable functional outcome, independent of laterality. However, some aspects must be considered when offering this treatment.

First, although surgery doubles the probability to survive in a favorable condition (mRS ≤ 3), and the risk of severe disability (mRS 5) is not increased, the chance of surviving in a condition requiring assistance from others (mRS 4) increases >10 times. Thus, the decision to perform decompressive surgery in patients with space-occupying infarction should always be based on the wishes of the patient and their families in light of the potential to survive with long-term moderate disability.

Second, several nonrandomized trials suggest that decompressive surgery is less effective in elderly patients.\textsuperscript{73} The 3 randomized trials excluded patients older than 55 or 60 years, and the results of the pooled data probably cannot be extrapolated to patients who are older. Thus, to date, it remains unclear whether decompressive surgery is also beneficial in patients older than 60 years. A randomized controlled trial addressing this subject is underway.

Third, whether decompressive hemicraniectomy is still beneficial if performed after the first 48 hours remains also unclear and is currently being tested in HAMLET.\textsuperscript{77}

Fourth, several complications of surgical decompression have been reported, including wound infection, subdural...
hygroma and hematoma, tissue shearing from inadequately large craniotomy, brain sagging, and hydrocephalus that should not be shunted when skull remains open.

Conclusions

Several medical treatment strategies have been proposed to be effective in controlling cerebral edema and reducing elevated ICP after severe hemispheric stroke. However, conservative antiedema therapy, as exists today, is disappointing. None of these treatments is supported by adequate evidence of efficacy from experimental studies or clinical trials, and some interventions may even be detrimental.42,44 Thus, at present, no evidence-based recommendation on the use of any of these conventional strategies for space-occupying postischemic edema can be made. Earlier and more aggressive therapeutic approaches are strongly needed for these patients. Immediate access to reperfusion therapy remains the cornerstone of stroke therapy and also the first step of antiedema treatment, because limiting final infarct size by restoration of blood flow may likely reduce the chance of developing massive postischemic edema. In cases of evolving large MCA infarction, early surgical decompression is now the “antiedema” therapy of first choice for patients younger than 60 years independent of affected hemisphere. Whether this aggressive treatment is beneficial for elderly patients or when performed after 48 hours is currently being tested.

Disclosures

None.

References

Antiedema Therapy in Ischemic Stroke
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