Multimodal Neuroprotective Therapy With Induced Hypothermia After Ischemic Stroke

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Abstract—Neuroprotective therapies have so far failed to provide improved neurological function and outcome after stroke. A recent focus on multimodal therapies, including the combination of neuroprotective medications with hypothermia, opens a promising new treatment strategy. Advances in hypothermia administration make it one of the most promising neuroprotective therapies available and an ideal candidate for combination with other neuroprotective approaches. (Stroke. 2009;40[suppl 1]:S126-S128.)

Key Words: hypothermia • ischemia • neuroprotection

Multiple attempts at achieving neuroprotection after stroke have failed,1 and possibly no single therapeutic may sufficiently provide neuroprotection within a reasonable therapeutic window without intolerable toxicity in humans.2 Hypothermia has long been regarded as one of the most active modes of neuroprotection.1,3 Clinical applications of hypothermia have been limited by logistical and patient comfort issues, but recent advances in endovascular cooling and better antishivering regimens now make the clinical use of induced hypothermia after stroke feasible.4

Hypothermia
Smaller Phase 1 studies established that rapid and well-controlled cooling after ischemic stroke is feasible.5–8 In animal models, hypothermia was more effective after temporary occlusion than after permanent ischemia.9–11 Earlier cooling after ischemia and longer cooling duration show greater efficacy.12–16 In stroke models, infarct size was more reduced at lower target temperature (below 28°C),17 but animals showed better recovery when temperature did not fall below 28°C.18 This may, in part, be caused by reduction of regional cerebral blood flow at low temperatures.19 Clinical trials of endovascular hypothermia after stroke targeted temperatures around 33°C,5,6,20 whereas the temperatures achieved with surface cooling methods and acetaminophen are between 34°C and 36°C.21–23 Further details about the pros and cons of surface or endovascular cooling have been previously discussed.4

Multimodal Neuroprotective Therapy
Over many years, attempts at finding neuroprotective agents after ischemic stroke have failed for a variety of reasons.24 In many cases, the tolerated plasma level was not sufficient or the treatment effect too small for each single compound to show neuroprotection within clinical trial cohorts.25,26 To increase the treatment effect, it seems reasonable to combine neuroprotective strategies.7 Finding synergistically active neuroprotective therapies could produce a more potent effect after ischemia. Hypothermia is an ideal candidate to combine with neuroprotective compounds and such combinations have been studied in animal models. Zausinger et al showed that the combination of hypothermia with tirilazad and magnesium was effective in reducing infarct size.27 Aronowski et al used the combination of ethanol, caffeine (Cafenol), and hypothermia in animal models of ischemic stroke.28 The infarct volume was significantly reduced after 180 minutes of transient occlusion when combination therapy began within 60 minutes of ischemia onset. The combination of hypothermia, caffeine, and ethanol (Cafenol) is currently being tested for safety and efficacy in clinical use.29

Thrombolysis and Neuroprotective Therapy
Most neuroprotective therapies are more effective in models of transient ischemia.30 Combining recombinant tissue plasminogen activator-mediated revascularization with neuroprotective therapy is most promising.31 Thrombolysis and neuroprotective therapies have shown synergistic effects in studies of citicoline and AMPA and NMDA antagonists.32–34 Other interventions such as the administration of antileukocytic adhesion antibodies have been shown to extend the therapeutic window for thrombolysis.35 In addition to improved neuroprotection, tissue plasminogen activator (tPA)-induced hemorrhage may be reduced in certain neuroprotective regimens. Topiramate reduced urokinase-induced hemorrhage and improved neuroprotection.36 Cafenol showed a trend in reducing tPA-induced hemorrhages after experimental stroke.28 In early human studies, no adverse events were reported due to Cafenol and...
no increased hemorrhage risk was seen in patients treated with Cafergot and tPA.29 Preliminary data from the SAINT trials indicated that NXY-059 may reduce tPA-induced hemorrhages.37 This finding, however, was not confirmed in a second trial.38 As seen with other neuroprotective therapies, hypothermia is more effective in models of transient ischemia.10,39 Although reperfusion is important after ischemic stroke, it is of concern that the activity of tPA may be reduced in hypothermia. In vitro analysis shows that cooling to 30°C to 33°C decreases tPA activity by 2% to 4%.40 In addition to tPA, however, plasminogen activator inhibitor 1 activity is also reduced during hypothermia, making the net effect of hypothermia in vivo on thrombolysis difficult to predict.

Wolberg et al reported that tPA activity declined to 50% when the clot temperature decreased from 40°C to 30°C. Although thrombolysis is reduced by low temperature, platelet function decreases when temperature is lowered from 37°C to 33°C.41 and in trauma patients, platelet function and coagulation activity are decreased at temperature below 34°C.42

Another mechanism by which hypothermia may affect hemorrhagic complications after stroke is its potential to reduce the activities of matrix metalloproteinases after ischemia.33 Matrix metalloproteinases play a major role in blood-brain barrier dysfunction and subsequent hemorrhagic transformation after stroke.43,44

Preliminary findings in the ICTuS-L study did not show an increased risk of bleeding after tPA use for ischemic stroke.8,20

**Conclusion**

Neuroprotection after ischemic stroke remains a promising field for therapeutic interventions. Combination therapy using synergistically active neuroprotective strategies increases therapeutic effects in preclinical studies. Hypothermia is one of the strongest neuroprotective strategies and an ideal intervention with which one can combine neuroprotective medications. Future studies will also include the combination with thrombolysis and other neuroprotective strategies.

**Disclosures**

None.

**References**


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