Current Status of Hemodilution in Acute Cerebral Ischemia

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"Thinning the blood" is such an intuitively reasonable and understandable treatment for ischemic stroke that most clinicians have invoked this phrase to explain to families one of the ways of possibly treating their recently hemiplegic relative. The Scandinavian Stroke Study Group reports in this issue of Stroke, however, that hemodilution (or probably any treatment) does not work when applied by general physicians seeing patients several days after a stroke. This is a clinically important finding but it should not be a surprising one considering the conservative design of the study. In their thoughtful discussion, the authors address many of the questions raised by their results, but in addition, it should be emphasized that while it is necessary to validate any therapy in the "real world" and not in just the specialized confines of tertiary referral centers, the delay in treatment and relatively indiscriminate selection of patients characteristic of this study contradicts the emerging concept, based on modern studies of cerebral blood flow (CBF) and metabolism, that therapy of cerebral ischemia should be instituted early and tailored to subgroups of patients.

The concept of hemodilution has been extensively reviewed in this journal and it is based on the close correlation of hematocrit and whole blood viscosity. Lowering hematocrit results in reduced viscosity and less resistance to blood flow, especially in regions of relative stasis. Arguments in favor of hemodilution therapy for cerebral ischemia are based on observations that hemodilution increases CBF and has improved clinical outcome in animal and preliminary human studies. Hypervolemic hemodilution is so popular for treating ischemic complications of vasospasm after subarachnoid hemorrhage that most clinicians dealing with this condition are reluctant to perform controlled trials including untreated patients. Arguments against hemodilution are based on the poor correlation of CBF and outcome after stroke and the generally negative results obtained with other therapies aimed at raising CBF. Furthermore, improved perfusion after hemodilution may be offset by (and in fact may be a response to) reduced oxygen delivery to ischemic tissue caused by the lowered oxygen-carrying capacity of the blood. Finally, determinants of viscosity in the microcirculation are not well understood. There is evidence that the cerebral microcirculation is already autoregulated to changes in viscosity. In addition, capillary flow may depend more on red cell deformability and plasma viscosity than on hematocrit. These concerns, coupled with the relative complexity of hemodilution protocols, have dampened enthusiasm for hemodilution among the neurologic community.

The Scandinavian study does little to increase support for hemodilution but, because of its design, should not terminate interest in this therapeutic modality but rather encourage investigators to answer 4 important questions in future studies. These are as follows:

1. Is there a brief interval after stroke when raising CBF can be effective? In the Scandinavian study, only 28% of patients were entered within 12 hours of their stroke, and optimal hemodilution was not achieved for 3 days in the average patient or for 5 days in those who were entered 24—48 hours after their stroke. It is likely that, to improve outcome, CBF must be raised within the first few hours after stroke and, indeed, may be harmful after 3 days when cerebral edema is most prevalent.

2. Is hypervolemia a useful adjunct to hemodilution? Hemodilution can be achieved isovolemically by equal amounts of phlebotomy and volume administration, hypervolemically by administration of a volume expander, or by a combination of both. The Scandinavian study employed a slightly hypervolemic algorithm, but when insensible fluid losses are considered, the therapy was probably isovolemic. Both isovolemic and hypervolemic hemodilution result in increased cardiac output by lowering viscosity and resistance to flow, but hypervolemic therapy raises cardiac output further by improving left ventricular filling pressure and moving the heart up the Starling curve. Some investigators believe that raising cardiac output even without hemodilution will improve CBF. Recent studies have shown that hypervolemic therapy would be tolerated and may even be indicated to correct volume depletion on admission in some stroke patients.
To perform aggressive hypervolemic hemodilution in stroke patients with associated cardiovascular disease, however, makes close hemodynamic monitoring necessary, introducing a complexity and risk unacceptable to most neurologists. The challenge is to find a safe and relatively simple hypervolemic algorithm that can be employed in selected patients without invasive monitoring. It is hoped that ongoing studies will provide the data necessary to design such a protocol and will help establish the clinical profile of patients in whom it might be most successfully applied.

3. What is the optimal reduction of hematocrit? Experimental studies have suggested that a hematocrit of 33% provides an optimal trade-off between viscosity and oxygen carrying capacity, but this value has yet to be established in patients with acute stroke. Hematocrit was lowered from 44% to 37% in the Scandinavian study, but future studies of oxygen availability by positron emission tomography (PET) scanning before and after hemodilution may provide more scientifically based guidelines. Until then, hemodilution should not be employed in patients with impaired pulmonary gas exchange or low hematocrit on admission.

4. What subgroups of patients might benefit most from hemodilution? Obviously patients with reduced CBF would be the logical choice for this therapy, and it would not be expected to help those with luxury perfusion or total absence of collateral flow. Unfortunately, easily administered bedside studies such as carotid or transcranial Doppler do not provide information about microcirculatory flow, and we cannot predict a patient’s cerebral perfusion from the clinical profile on admission. In the Scandinavian study, therefore, all ischemic stroke patients were included, but future studies may refine patient selection by employing newer methods of CBF measurement (single photon emission tomography, xenon-133 inhalation, PET, etc.).

As stated by the authors, the Scandinavian study should be "regarded as a challenge to the concept of hemorheologic therapy in brain infarction" and not the final word. This study has shown that relatively isovolemic hemodilution will not dramatically reverse the neurologic deficit in unselected stroke patients when employed in customary practice. Whether hemorheologic therapy is useful when applied more acutely and when using information gained from modern physiologic studies to select patients and to guide fluid management must be answered by future studies.

References

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