Hemodilution for Cerebral Ischemia

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Although hemodilution has received considerable experimental and clinical attention as a potential therapy for cerebral ischemia, its role in the management of patients with stroke is not yet defined.

Background and Rationale

If irreversible cerebral infarction from stroke occurred immediately at the time of arterial occlusion, there would be little hope of intervening therapeutically. However, even though there may be a central "core" of severe ischemia where brain tissue dies after a period of several minutes, in most situations there is a surrounding "ischemic penumbra" where blood flow is reduced enough to result in physiological loss of function but not so much as to cause irreversible loss of cellular integrity. This "penumbra" may persist for days and offers a window of time during which therapeutic intervention to improve the delivery of oxygen and metabolites and the removal of carbon dioxide and products of metabolism may be effective in preventing irreversible damage to this area. Such damage may occur if marginal levels of perfusion persist for hours or days since the development of infarction is related not only to the severity of ischemia but also to its duration. Even a slight improvement in perfusion may be capable of preventing irreversible damage to the "penumbra" until reperfusion occurs, either by clot dissolution in cases of embolic stroke, by increased collateralization in cases of more proximal thrombosis, by resolution of vasospasm in patients with subarachnoid hemorrhage, or by surgical revascularization in some carefully selected cases.

There is considerable evidence that hemodilution is an effective way to increase perfusion of ischemic brain. The rationale for using hemodilution in the treatment of cerebral ischemia is based on the well-known Hagen-Poiseuille equation, which states that, other factors remaining constant, blood flow is inversely proportional to blood viscosity. Hematocrit (Hct) is a major factor influencing blood viscosity, and it is a particularly important determinant of flow at the low velocity gradients (shear rates) present in the microcirculation. With ischemia these velocity gradients decrease further, and Hct becomes an even more important factor.

The available data have not clearly defined the optimal Hct for cerebral tissue. Although hemodilution increases perfusion to ischemic brain, it also decreases the oxygen carrying capacity of blood. There is a highly significant relationship between cerebral blood flow (CBF) and arterial oxygen content, with CBF changing as necessary to maintain the rate of transport of oxygen to the brain within certain limits. In other words, oxygen delivery remains constant over the entire normal Hct range in normal brain. However, in ischemic brain, which has lost the capacity for flow autoregulation and where vessels are already maximally dilated, hemorheological factors assume great importance in the determination of blood flow. Thus, a favorable inverse correlation between regional oxygen transport and Hct in ischemic brain has been demonstrated.

Hemodilution can be hypovolemic, achieved by phlebotomy alone; isovolemic, by phlebotomy and fluid replacement; or hypervolemic, by volume expansion with asanguineous fluids. There is no compelling rationale for hypovolemic hemodilution except in patients in cardiac failure or in markedly hypertensive patients. Hypervolemic hemodilution can result in significant cardiac overload and increased intracranial pressure (ICP), particularly in the presence of ischemia. Therefore, it should be used with caution in patients with compromised cardiovascular reserve and in stroke patients where an increase in ICP may be detrimental. This form of therapy seems ideal for younger patients with an intact cardiovascular system such as those with subarachnoid hemorrhage and vasospasm. Isovolemic hemodilution does not result in cardiac overload or intracranial hypertension and, therefore, can be used more safely in older patients, in patients with impaired cardiovascular reserve, and in most stroke patients who are at risk of increased ICP.

Experimental Studies

Hypervolemic Hemodilution

The earliest studies of hemodilution by volume expansion with dextran in cats with middle cerebral artery (MCA) occlusion indicated that this therapy resulted in a significant decrease in infarct size as well as an increase in the velocity of flow, a decrease in red blood cell and platelet clumping,
dilation of arteries in spasm, and a reversal of cortical pallor as observed directly through a cranial window. More recently, a series of studies with infusions of low molecular weight dextran (LMD) to reduce the Hct in dogs to a level of about 30–32% after occlusion of the distal internal carotid artery (ICA) and proximal MCA showed that 1) regional cerebral blood flow (rCBF) increased significantly throughout the brain but particularly in ischemic areas after hemodilution, 2) the cardiac output increased markedly as a result of hemodilution, 3) there was a significant increase in ICP after hemodilution, and 4) the size of infarction was reduced from approximately 10% of the total hemispheric volume in the control animals to 4% in the treated animals. In a study of cats with MCA occlusion in another laboratory, hemodilution with mannitol, which reduced viscosity markedly, increased CBF only in areas of disturbed autoregulation. These investigators postulated that there is a mechanism of autoregulation to viscosity that is independent of the autoregulation to perfusion pressure, although the two types of autoregulation may share the same vasogenic mechanism. In another study of 20 cats with MCA occlusion for 6 hours, hypervolemic hemodilution with human albumin to a Hct of approximately 23% was compared with no treatment. There was no improvement in rCBF with hemodilution, and although there was some electroencephalographic (EEG) improvement in the treatment group, there was no difference in the area of impairment of carbon perfusion when the cats were killed 6 hours after occlusion. Since this was only an acute study, no statement can be made about the efficacy of treatment in ameliorating the eventual development of infarction.

**Isovolemic Hemodilution**

We have recently completed a study involving 76 dogs where the effect of isovolemic hemodilution by phlebotomy and replacement with LMD was compared with no therapy in dogs subjected to a 6-hour period of occlusion of the distal ICA and proximal MCA on one side. In addition, the effects of isovolemic hemodilution were compared with no therapy in sham-operated animals in order to study the effects of hemodilution per se. Half of the animals were kept alive for a week for daily neurological grading and final histopathological confirmation of the size of infarction. Isovolemic hemodilution in these studies was accomplished 1 hour after arterial occlusion and was adjusted to bring the Hct down to the 30–32% level. Hemodilution resulted in a significant reduction in viscosity and fibrinogen levels. The decrease in Hct lasted through 1 week in the chronic animals without need for repeated hemodilution. The reduction in viscosity correlated almost linearly with the decrease in Hct. There were no significant changes in systemic arterial pressure, central venous pressure, or pulmonary wedge pressure. Cardiac output did not increase as a result of hemodilution. ICP likewise did not increase as a result of hemodilution.

The rCBF decreased significantly in the ischemic MCA territory after arterial occlusion, and this decrease was partially reversed by hemodilution in the treated animals. The neurological condition of the hemodiluted animals was significantly better than that of the control animals, and the size of infarction was reduced from approximately 10% of the total hemispheric volume in the control animals to approximately 1% in the hemodiluted animals. Although a markedly significant protection against infarction was observed in our studies (p<0.001), caution should be exercised in extrapolating these results to the clinical situation since the study was designed in an optimal fashion to show whether there was any benefit from hemodilution, slight as it might be. To this end, a model of only moderate ischemia, which resulted in a relatively small infarct, was used and hemodilution was accomplished within 1 hour of arterial occlusion and to a rather marked degree. These ideal conditions often cannot be achieved in the clinical situation.

**Choice of Hemodiluting Agent**

Generally, colloid solutions have been used as the hemodiluting agent in both experimental and clinical studies under the assumption that in the injured or ischemic brain, where autoregulation is impaired and the blood–brain barrier may be damaged, crystalloids will result in an increase in brain edema and intracranial hypertension. This assumption remains unproven. Colloid solutions have the disadvantage of being very expensive and, depending on the type, can result in disease transmission (human plasma) or in anaphylactic reactions and coagulation disorders (dextrans and starches). A large body of literature suggests that crystalloids, particularly balanced salt solutions, are as effective as colloids in restoring normal circulatory dynamics after severe loss of blood and fluids such as occurs with trauma and burns in the clinical setting and hemorrhagic shock in the experimental setting. However, none of the studies comparing colloids with crystalloids has concerned patients or animals with primary brain injury.

With this background, we have conducted an as-yet unpublished study in 44 dogs comparing the effects of isovolemic hemodilution with Ringer’s lactate versus LMD in the setting of focal cerebral ischemia. In brief, we found that although the Hct could be lowered to the same level (30–32%) with a crystalloid solution, the volume required was approximately four times that required when a colloid solution was used. There was no significant change in hemodynamic parameters, including cardiac output, whether hemodilution was carried out with the crystalloid or with the colloid solution. The crystalloid solution was as effective in improving rCBF in areas of ischemia. However, hemodilution with Ringer’s lactate resulted in increased cerebral edema, reflected indirectly by a decrease in specific gravity.
in the ischemic regions of the brain. This resulted in a significant increase in ICP that was not observed when the animals were hemodiluted with LMD. The assessment of efficacy by comparing neurological status and size of infarction is currently under study, but preliminary results indicate that hemodilution with Ringer’s lactate is ineffective and possibly detrimental, whereas the beneficial results obtained in the previously described studies with LMD appear to be confirmed.

Another colloid solution that has received considerable attention is hydroxyethyl starch (HES). This compound, when used in a 10% solution, appears to have similar rheological effects to dextran-40 with probably fewer adverse effects on the coagulation cascade, a lower incidence of allergic reactions, and less frequent renal complications. In addition, when repeated infusions are necessary, as in volume expansion without phlebotomy (hypervolemic hemodilution), the large molecules of dextran tend to accumulate in the plasma, resulting in increased plasma viscosity and red blood cell aggregability. HES, on the other hand, is broken down into smaller molecules, and therefore, repeated infusions of this substance actually appear to decrease plasma viscosity and red blood cell aggregability. As a note of caution, it should be pointed out that there is much less clinical experience with the starches than with dextran or plasma.

Another approach has been to use hypertonic crystalloid solutions for hemodilution. In an acute study with rabbits, hypertonic Ringer’s lactate solution resulted in an increase in rCBF and no change in ICP, whereas isotonic normal saline resulted in a significant decrease in brain specific gravity and increase in brain water content and ICP. Dextrose solutions have also been suggested for hemodilution, but in view of their adverse metabolic effect during ischemic conditions, they should probably be avoided in the setting of stroke.

The ideal agent for hemodilution would not only have the desired effect of reducing blood viscosity but would also result in an increase in oxygen carrying capacity. Fluorocarbon solutions were suggested as an ideal agent, and initial results in acute studies were very encouraging. However, chronic studies in our laboratory have indicated that at least one of these substances, fluosol-DA, is not beneficial and may, in fact, be detrimental. On the other hand, in our studies the infarction from MCA occlusion in cats was so large that there was a very high early mortality observed, and it is unlikely that a marginal therapeutic effect could have been noted.

Clinical Studies

The beneficial clinical effects and ability of hemodilution by LMD to increase rCBF and improve metabolism were initially demonstrated almost 20 years ago. Subsequently, several studies of simple volume expansion in the treatment of stroke were reported. In most of these studies, LMD was used not specifically to achieve hemodilution but rather to expand the intravascular volume and secondarily to increase cardiac output and presumably rCBF, although the latter were not measured in the majority of the studies. Suffice it to say that the results of these studies were contradictory, with some showing benefit and others no benefit.

More recently, the ability of isovolemic hemodilution to improve rCBF and the EEG in patients with stroke or after extracranial to intracranial bypass procedures has been demonstrated. Another study of 24 patients in whom the Hct was brought down to an average of 32% confirmed the ability of hemodilution with LMD to improve rCBF. In a pilot study with nine patients that were very carefully monitored physiologically, hypervolemic hemodilution with 6% hetastarch solution to bring the Hct to an average of 32.9% was well tolerated hemodynamically and resulted in no complications.

There has been abundant clinical evidence of the value of hypervolemic hemodilution by volume expansion with colloids in patients with symptomatic vasospasm secondary to subarachnoid hemorrhage. Volume expansion with or without induced hypertension is the only therapy that has been proven to be effective under these circumstances.

The first prospective controlled trial of isovolemic hemodilution was conducted in Scandinavia. In this careful preliminary study 52 treated patients were compared with 51 randomly chosen control patients, all of whom were cared for in a specialized intensive care stroke unit. The Hct was brought down from an average of 43% to 37% over a 2-day period by venesection and infusions of LMD. Of the hemodiluted patients 85% improved compared with 64% of the controls (p<0.025). Among the survivors, 8% of the hemodiluted and 31% of the control patients were unable to walk at 3 months, and 13% of the hemodiluted versus 39% of the controls were still hospitalized at 3 months. However, when this trial was enlarged to involve 15 centers, including several community hospitals with no specialized stroke units, a similar protocol of hemodilution appeared to offer no advantage when the 183 hemodiluted patients were compared with the 180 controls. Even when these results were analyzed by subsets according to clinical criteria such as delay of treatment, Hct at entry, volume of venesection, neurological score at entry, location of lesion by CT scan, etc., no subset was found in which hemodilution appeared to be of benefit. The authors were careful to point out, however, that the sample sizes were too small to refute the possibility of a modest clinical effect of hemodilution. This trial has been criticized because of the heterogeneity of the patients studied, the setting in which they were cared for, the delay in entry to the study (only 28% of the patients were entered within 12 hours of the onset of the stroke), the slowness with which hemodilution was achieved (over a 3–5 day period), and the relatively moderate
degree of hemodilution achieved (37% Hct on average).26

In a more recent multicenter Italian trial, 1266 patients with acute hemispheric stroke were randomized to a protocol of hemodilution by venesection and dextran infusion or to a control group within 12 hours of onset of the stroke.27 Eighty-six percent of the patients had infarcts, and 14% had hemorages. The Hct was decreased from an average of 43% to an average of 37% after 48 hours. Mortality and disability after 6 months were no different in the two groups. Again, even though patients were entered early in this trial, hemodilution was carried out slowly and only to a modest degree.

One of us carried out a study of 35 patients in Japan who were treated rapidly with isovolemic hemodilution by venesection and replacement with fresh plasma.28 There were 21 patients with ICA occlusion and 14 patients with MCA occlusion, and all of the patients were cared for and monitored physiologically in a specialized unit. The Hct was brought down to an average of 33% within 72 hours of the onset of stroke. The cardiac output increased by an average of 33% and the rCBF by an average of 23% in the affected MCA territory. The cerebrospinal fluid pressure increased by 16%, but there were no clinical symptoms of increased ICP. There was significant improvement in somatosensory evoked potentials and in neurological scores, and there were no complications from the therapy.

Present Role and Future Directions

The value of hemodilution by volume expansion with colloid solutions in the treatment of vasospasm is well established. These patients are usually young and in good general condition, and they can tolerate the volume expansion and consequent increase in cardiac output. However, to maintain a state of hemodilution by volume expansion alone requires repeated infusions of rather large amounts of colloid. With phlebotomy, a relatively anemic state is created that cannot be compensated for rapidly since erythropoiesis is a relatively slow process. Therefore, the addition of phlebotomy to the regime of volume expansion, particularly in patients with a high Hct, may also be beneficial before carotid endarterectomy or intracranial to extracranial bypass procedures, particularly in patients with a high Hct. Patients with crescendo TIAs and stroke-in-evolution would appear to be ideal candidates for rapid institution of hemodilution to optimize hemorheological conditions and prevent a major stroke although this clinical use has not been thoroughly investigated.

References

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