Experimental Cerebral Infarction: Modification by Treatment with Hemodiluting, Hemoconcentrating, and Dehydrating Agents\textsuperscript{\textdagger}\textdaggerdbl

Thoralf M. Sundt, Jr., M.D.,\textsuperscript{\dagger} Arthur G. Waltz, M.D., and George P. Sayre, M.D.

Section of Neurology, and Section of Experimental and Anatomic Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Recent attempts to treat peripheral vascular obstruction by using agents designed to alter the rheologic characteristics of the blood\textsuperscript{1, 2} have met with some success in humans and in experimental models in animals.\textsuperscript{1, 2} Such agents, including low-molecular-weight dextran (dextran-40, Rheomacrodex), also have been used as plasma expanders\textsuperscript{3} and during cardiac surgery with extracorporeal circulation.\textsuperscript{4} The apparent success of these agents in favorably influencing the clinical response to peripheral vascular obstruction has suggested that they might be used in the treatment of acute cerebral infarction.

Our studies,\textsuperscript{1} and those of others,\textsuperscript{5, 10} of the superficial microvasculature and microcirculation of the cerebral cortex of animals after occlusion of the middle cerebral artery have shown that definite changes result from ischemia. These changes can be modified by the intravenous administration of certain hemodiluting agents.\textsuperscript{2, 11} Similar changes in the superficial vessels of the cortex have been observed, in dogs undergoing hypothermic perfusion, as the temperature of the brain approached 17°C. Hemodilution with saline and low-molecular-weight dextran alters the changes which occur with hypothermia (Nofzinger and Sundt, unpublished data). Thus, there are several reasons for investigating the effect of various hemodiluting, hemoconcentrating, and dehydrating agents on cerebral infarction in animals. One of these agents, low-molecular-weight dex-}

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\textsuperscript{\ddagger} Special National Institutes of Health Fellow in Basic Neurologic Sciences, Mayo Graduate School of Medicine, University of Minnesota, Rochester, Minn.

\textsuperscript{1} In this paper we shall report the results of the modification of cerebral infarction in cats by a variety of agents. The agents include: hyperoncotic solutions of low-molecular-weight dextran, serum albumin, and urea, individually and in combination; homologous serum; physiologic saline; and packed erythrocytes.

\textbf{Materials and Methods}

\textit{Occlusion of Middle Cerebral Artery.} In 64 cats, a middle cerebral artery was occluded under sterile conditions by a technique developed and standardized prior to this study.\textsuperscript{11} Briefly, by using a Zeiss operation microscope and microsurgical technique, the artery was approached extradurally through the retro-orbital space after removal of the greater wing of the sphenoid bone. The dura was incised over the optic nerve, and the delicate arachnoidal tissue, which forms a web around the major vessels of the circle of Willis, was dissected free. The loop of the middle cerebral artery was elevated at its origin at the circle of Willis without damage to small collateral or perforating vessels, and a small Mayfield clip was applied to it. Adequacy of the occlusion of the artery was verified by observing a decrease in the velocity of the flow of the formed elements of blood through the superficial vessels of the cortex (seen through the transparent dura with the operation microscope) and by noting that the entire width of the artery was in the jaws of the clip. The dura over the surface of the brain was left intact. The wound was irrigated and closed in three layers.

There was very little trauma to the brain in this procedure, and no hypotension was produced.\textsuperscript{11}
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_Treatments._ Sixteen cats, a control group, received no treatment.

Five cats were given physiologic saline, 25 to 30 ml/kg, intravenously through a polyethylene catheter in a superficial vein of a hind limb during a 12-hour period beginning 15 to 30 minutes prior to the occlusion of the middle cerebral artery.

Five cats were given a single intravenous injection of homologous serum, 10 ml/kg, at 15 to 30 minutes prior to occlusion of the artery.

Five cats were given low-molecular-weight dextran (10% solution in physiologic saline) intravenously according to the following schedule: 15 to 30 minutes before occlusion of the artery, 10 ml/kg; 6 and 12 hours postoperatively, 4 ml/kg; 18 hours postoperatively, 10 ml/kg; 24 hours postoperatively, 4 ml/kg; and 30 hours postoperatively, 10 ml/kg.

Ten cats were given salt-poor human serum albumin. A 25% solution of albumin was mixed with an equal amount of Ringer's solution and the mixture (12.5% albumin) was given intravenously as follows: 15 to 30 minutes before occlusion of the middle cerebral artery, 8 ml/kg; 6 and 12 hours postoperatively, 3 ml/kg; 18 hours postoperatively, 8 ml/kg; and 24 and 30 hours postoperatively, 3 ml/kg.

Six cats were given a concentrated urea solution (30% in 5% dextrose solution) intravenously: 6 hours postoperatively, 1 gm/kg; 24 and 36 hours postoperatively, 0.5 gm/kg.

Five cats were given packed erythrocytes, 10 ml/kg. The cells, obtained from heparinized donor animals, were infused 15 to 30 minutes after occlusion of the middle cerebral artery.

Two cats were given a combination of homologous serum and low-molecular-weight dextran in the amounts described above.

Ten cats were treated with a combination of albumin, low-molecular-weight dextran, and urea. The regimen in these animals was: albumin solution, 4 ml/kg., and low-molecular-weight dextran solution, 5 ml/kg, given intravenously 15 to 30 minutes before occlusion of the middle cerebral artery, followed by urea, 1 gm/kg, 6 hours postoperatively; albumin and low-molecular-weight dextran, 4 ml/kg each, 12 and 18 hours postoperatively; urea, 0.5 gm/kg, 24 hours postoperatively; albumin and low-molecular-weight dextran, 4 ml/kg each, 30 hours postoperatively; and urea, 0.5 gm/kg, 36 hours postoperatively.

_Evaluations._ Clinical evaluation. Each animal was examined daily for level of consciousness, ability to walk, tendency to circle while walking, weakness of the extremities, differences in posture of the forelimbs and hind limbs (such as doubling of the front paw and extension of the hind limb), and visual field defects.

_Observation of the cortex._ Five to 7 days after occlusion of the middle cerebral artery each animal was anesthetized with pentobarbital (25 mg/kg injected intraperitoneally). An endotracheal tube was inserted, and the scalp wound was opened. The site of craniectomy was enlarged with rongeurs, the dura overlying the convexity of the cerebral hemisphere on the side of the occlusion was removed, and the brain was covered with plastic film (Saran). The superficial microvasculature and microcirculation of the cortex were examined with the operation microscope for degree of apparent increase or decrease in numbers of small cortical vessels and for velocity of the flow of formed elements of blood. In certain animals, photographs were made.

_Evaluation of infarcts._ The brain was perfused, through the brachiocephalic artery, with 10% formalin and removed. After fixation, each brain was sectioned in a contoured miter box, and the individual sections of brain were photographed. The volume of the cerebral infarct was computed by the average end-area method and corrected to a standard as described previously.11 Histologic sections of the infarct were prepared, compared with the photographs, and evaluated for histologic changes.

The means of the corrected volumes of the cerebral infarcts of each of the eight groups of animals to which agents were administered were compared statistically with the mean of the corrected volumes of the untreated control group. Confidence intervals at the 95% level were computed for the comparisons.4

_Results_ 

_Immediate Effect of Occlusion of Middle Cerebral Artery._ Immediately after occlusion
of the middle cerebral artery, the velocity of flow of formed elements of blood through the superficial vessels of the ipsilateral cerebral cortex decreased. In the five cats given packed erythrocytes intravenously, there was a further decrease in the velocity of flow in the superficial vessels after the injection.

**Neurologic Deficit.** No animals died as a result of the surgical procedure. Hemiparesis developed in all cats except for three which had been given serum albumin and five which had been given the mixture of albumin, low-molecular-weight dextran, and urea. It was not always possible to predict the size of the cerebral infarct from the findings on examination. In general, the degree of neurologic deficit was related to the degree of involvement of the internal capsule rather than to the absolute size of the infarct as determined from later inspection of the brain. However, the level of consciousness or alertness of the animal was more closely related to the absolute size of the infarct.

The neurological status of the animals seldom deteriorated after the first 24 hours. Treated animals which had no abnormalities on clinical examination were later found to have no cerebral infarct.

**Superficial Microvasculature.** When the surface of the brain was inspected 5 to 7 days postoperatively, in all animals the pattern of the superficial cortical vessels was found to be distinctly different from that of the exposed cortex of normal brain. If the cerebral infarct was deep and did not extend to the cortex or if, as happened in five treated animals, no cerebral infarct developed, there was a considerable increase in the number of small cortical vessels which could be seen with the operation microscope. In addition, the vessels were somewhat more tortuous than usual (Fig. 1 left). It could not be determined whether the additional vessels seen were newly formed as the result of vascular proliferation or whether they had been present previously and were now made visible because of dilatation. Nearly all of these newly visible vessels were veins or venules.

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**Fig. 1.** Superficial microvasculature of the brains of cats after occlusion of the ipsilateral middle cerebral artery. **Left.** This animal had been given concentrated serum albumin intravenously. At 7 days postoperatively, the infarct resulting from the occlusion did not extend to the cortical area shown in the photograph. Note the markedly increased vascularity of the cortex and the tortuosity of the small vessels. (Magnification, X 16.) **Right.** This animal had been given packed erythrocytes intravenously. At 5 days postoperatively there was reduction in number of visible vessels in the area of infarcted cortex; regions of stasis in venous channels were seen. (Magnification, X12).
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### TABLE 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean vol. (cm$^3$)</th>
<th>$\Delta$ (cm$^3$)*</th>
<th>95% CI (cm$^3$)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>16</td>
<td>3.3</td>
<td>$\ldots$</td>
<td>$\ldots$</td>
</tr>
<tr>
<td>Albumin, dextran, and urea</td>
<td>10</td>
<td>0.5</td>
<td>2.8</td>
<td>$-0.7 \text{ to } -4.9$</td>
</tr>
<tr>
<td>Albumin</td>
<td>10</td>
<td>1.8</td>
<td>1.5</td>
<td>$+0.7 \text{ to } -3.6$</td>
</tr>
<tr>
<td>Dextran and serum</td>
<td>2</td>
<td>2.0</td>
<td>1.3</td>
<td>$+2.8 \text{ to } -5.5$</td>
</tr>
<tr>
<td>Dextran</td>
<td>5</td>
<td>3.3</td>
<td>0.8</td>
<td>$+2.3 \text{ to } -3.8$</td>
</tr>
<tr>
<td>Serum</td>
<td>4</td>
<td>2.5</td>
<td>0.7</td>
<td>$+1.9 \text{ to } -3.2$</td>
</tr>
<tr>
<td>Urea</td>
<td>6</td>
<td>2.6</td>
<td>0.7</td>
<td>$+1.9 \text{ to } -3.2$</td>
</tr>
<tr>
<td>Saline</td>
<td>5</td>
<td>4.9</td>
<td>$-1.6$</td>
<td>$+4.4 \text{ to } -1.1$</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>5</td>
<td>4.4</td>
<td>$-1.1$</td>
<td>$+3.8 \text{ to } -1.6$</td>
</tr>
</tbody>
</table>

* $\Delta$ = control volume minus volume in treated group.
† 95% CI = expected range, at 95% level of confidence, of deviations from control value.

If the cerebral infarct extended to the surface of the brain, it could be seen as an extremely pale area with very few vessels (Fig. 1 right). Nearer the margins of the infarct, more vessels were visible. Around the infarct, more small vessels could be seen than in the normal brain; the appearance was similar to that of the surface of the brain overlying a deep infarct as described above.

In the infarcted area there was stasis of blood in veins, with aggregation and clumping of formed elements of the blood (Fig. 1 right). The clumps appeared to be chiefly of erythrocytes. In the marginal zones there was a considerable reduction in the velocity of the flow of formed blood elements through veins and venules. There was no apparent reduction in the velocity of flow in arterial vessels, although occasionally a pulsating interface was noted where there was an equilibration of the pressures of columns of blood entering a vessel from two directions simultaneously.

In the margins of the infarct, and occasionally in the center as well, venous blood was frequently noted to be more red than usual. This redder blood, presumably with a high oxygen content, was nearly the same color as arterial blood and contrasted sharply with the usual blue color of the blood seen in veins elsewhere on the surface of the brain. Red blood was noted in a single vein or venule, in all branches of a particular venous tree, or, occasionally, in all veins exposed by the craniectomy. Occasionally, a vein containing red blood would join with another vein containing blue blood to form a larger vessel, and the two streams of differently colored blood could be seen flowing side by side.

At 5 to 7 days after occlusion of the middle cerebral artery, no white thrombi or emboli were seen in vessels.

Cerebral edema was usually present on the side of the infarct, and occasionally this was so severe that the brain extruded when an incision was made in the dura for observation of the surface vessels.

With respect to the changes in the superficial cortical microvasculature and microcirculation, there was no apparent difference between the untreated cats and the cats given any of the modifying agents. The changes were not dependent on a reduction in blood pressure because the blood pressure remained at normotensive levels in all animals. Differences from animal to animal were due to the size and location (superficial or deep) of the infarct.

**Size of the Infarct.** In untreated animals, the size and location of the infarct resulting from occlusion of the middle cerebral artery varied. The mean corrected infarct volume in the 16 untreated cats was 3.3 cm$^3$ (Table 1), but the individual volumes ranged from 0.53 to 8.60 cm$^3$. The infarct sometimes was located laterally and superficially (Fig. 2), but more commonly it was deep, near the thalamus and basal ganglia (Fig. 3).

Figure 4 shows the distribution of the volumes of the infarcts in the untreated and treated groups. The mean corrected infarct volume in the group of animals treated with the combination of albumin, low-molecular-weight dextran, and urea was 0.5 cm$^3$; three animals had no infarct detected by gross or
Fig. 2. Sections of the brain of a cat killed 6 days after occlusion of the left middle cerebral artery. This animal had no treatment. The infarct is located laterally and superficially.

Fig. 3. Sections of the brain of a cat killed 6 days after occlusion of the left middle cerebral artery. No. treatment had been given. The infarct is deep, near the basal ganglia.
FIG. 4. Distribution of volumes of infarcts in the untreated (control) and treated groups of cats. Open bars represent cats killed 5 to 7 days postoperatively; hatched bars represent animals dying before 72 hours postoperatively.

Fig. 4. Distribution of volumes of infarcts in the untreated (control) and treated groups of cats. Open bars represent cats killed 5 to 7 days postoperatively; hatched bars represent animals dying before 72 hours postoperatively.

Microscopic inspection of the brain sections (Fig. 5). The largest infarct in this group was 3.47 cm³. The difference between the mean volume of the infarcts in this group and that of the untreated group (Table 1) was statistically significant at the 95% level of confidence; therefore, use of this combination of agents before arterial occlusion provided partial protection from cerebral infarction.

For the group of animals treated with albumin, the mean corrected infarct volume ranged from 0 to 7.7 cm³ (mean, 1.8 cm³). The difference between the means of this group and the untreated group was not statistically significant, but it is possible
that, with a larger series of animals, in the group treated with albumin the mean infarct volume would be significantly smaller than in the untreated group.

In animals given saline in an attempt to modify the infarct, considerable cerebral edema developed (Fig. 6). Four of five animals in this group died as a result of this edema before 72 hours postoperatively. The volumes of the infarcts, corrected for the regions of edema, ranged from 0.25 to 8.1 cm$^3$ (mean, 4.9 cm$^3$). The difference from the untreated group was not statistically significant at the 95% level, but with a larger sample a significant difference might well have been shown.

Animals which were given packed erythrocytes also appeared to have somewhat larger infarcts than did those in the untreated group; all infarcts exceeded 3.7 cm$^3$. However, the difference did not approach statistical significance as closely as it did with the group given saline.

The means of the infarct volumes in the groups given low-molecular-weight dextran and homologous serum, low-molecular-weight dextran alone, homologous serum alone, or urea were not significantly different from the mean volume of the infarcts in the untreated group.

Discussion

We have shown in this study that the size of an experimental cerebral infarct may be modified, either increased or decreased, by hemodilution, hemoconcentration, or dehydration. Although the use of a combination of three agents (albumin, low-molecular-weight dextran, and urea) was necessary for the best results, it appeared that albumin was the most effective single agent.

**Effects on Process of Cerebral Infarction. Effects of hemodilution.** Part of the favorable response to treatment may have been the result of a modification of the rheologic properties of the blood. For example, low-molecular-weight dextran tends to decrease the viscosity and the aggregation of formed elements of blood.$^{6,14}$ Thus, aggregation of erythrocytes and stasis in veins, which are seen in the superficial vessels of the cortex immediately after occlusion of the middle cerebral artery and 5 to 7 days later, may have been reduced, and flow through capillary and venous channels may have been improved. It is in the capillary and venous systems, where flow rates are slower and shearing forces are less, that aggregation of
formed elements of blood is most likely to occur and to be of the greatest significance in the development of an infarct. It is here that hemodilution, by decreasing blood viscosity and influencing the surface charges of the erythrocytes, might have produced a beneficial effect.

However, simple dilution of the blood was not enough to protect against cerebral infarction. In fact, hemodilution with saline produced unfavorable effects because of increased cerebral edema. Although we have found that the immediate result of the infusion of physiologic saline after occlusion of a middle cerebral artery in a cat was a seemingly improved circulatory state, in the present study the ultimate result was severe cerebral edema. This edema almost certainly accounted for the deaths of four of the five cats given saline.

Thus, the solution to the problem of the treatment of acute cerebral infarction is more complex than one of simple hemodilution. If a hemodiluting agent is to be used, it must be one which remains within blood vessels. Albumin satisfies this requirement, if there is no pathologic alteration in capillary permeability. Low-molecular-weight dextran may also be satisfactory but it is not retained for as long a time in the intravascular space. In the present study, low-molecular-weight dextran had a less significant effect, compared to albumin, in protection against infarction.

The lack of response to homologous serum may have reflected the presence of clotting factors in serum, which tend to enhance the aggregation of erythrocytes.

Effects of hemoconcentration. Increasing the viscosity of the blood by hemoconcentration with erythrocytes had an unfavorable influence on experimental cerebral infarction. A more severe infarct developed in animals given packed erythrocytes. When the cells were infused, there was a decrease in the velocity of the flow of formed elements of the blood through the superficial cortical vessels in addition to the decrease caused by the occlusion of the middle cerebral artery. This was most likely the result of increased blood viscosity and cellular aggregation.

Effects of dehydration on edema and infarction. In addition to producing hemodilution, concentrated solutions of albumin, urea, and low-molecular-weight dextran have the very important effect of acting as dehydrating agents for the extravascular cerebral tissues. When these agents are used (again...
assuming there is no pathologic alteration in capillary permeability), there is a net flow of water from tissue to blood because of oncotic pressure. Cerebral edema may be prevented or significantly reduced.

Protection against cerebral edema may provide definite protection against cerebral infarction. In the presence of cerebral edema, there is almost certainly an increased vascular back pressure and, thus, an increased resistance to the entrance of blood into an infarcted zone. There may be secondary collapse of some vessels. In addition, there may be interference with the exit of blood from venous channels. This would be particularly true if the intracranial pressure were high, as it undoubtedly was in many of the animals.

In addition to influencing the final absolute size of an infarct, edema probably also influences the clinical state. A greater degree of neurologic deficit, or even death, may be caused by the edema itself.

Changes in superficial microvasculature. The most striking feature of the surface of the brain 5 to 7 days after occlusion of the middle cerebral artery was the presence of an increased number of small blood vessels. We noticed this in animals in which an infarct did not develop and also outside of areas of cerebral infarction in other animals. Although there may have been some vascular proliferation with the formation of new vessels, we believe that the observed phenomenon was due chiefly to dilatation of smaller vessels not visible in the exposed normal brain. We interpret this to mean that the cerebrovascular system responds to anoxia with dilatation; in those animals in which infarcts did not develop, the response was at least partially successful. Dilatation was not influenced by the various treatments, indicating that it is a process inherent within the vascular system of the animal.

In other animals not included in this study, we have seen microvascular dilatation as early as 24 hours after occlusion of the middle cerebral artery. This compensatory dilatation is the probable explanation for the finding that the animals seldom deteriorated after the first 24 hours after arterial occlusion. Treatment may be ineffective after arterial dilatation has developed.

We do not believe that red blood in the veins was due to the presence of arteriovenous shunts. We have seen no arteriovenous anastomoses in any of the many animals in which we have observed the superficial vessels of the cortex. Lassen has suggested that the presence of red blood in veins indicates a disturbance of the mechanisms of autoregulation of cerebral blood flow. More oxygen is supplied to the tissue than can be utilized, and the oxygen tension of the draining venous blood is increased.

Effect of time of administration of agents. Extravascular dehydration, with reduction of local cerebral edema, is probably as important as hemodilution and modification of rheologic factors in protection against cerebral infarction. But, for these agents to retard the development of edema during infarction and not to cause an increase in edema later, there must be no pathologic increase in capillary permeability. Such increased permeability may occur, from endothelial anoxia, at some time during the process of infarction.

In this study, to simulate a possible clinical application to neurovascular surgery, the hemodiluting agents were given before occlusion of the middle cerebral artery; presumably, capillary permeability was normal then. In one cat, not included in this study, low-molecular-weight dextran and albumin were given 12 hours after the occlusion of a middle cerebral artery, after the development of a well-formed cerebral infarct. There was a definite increase in edema in the infarcted area, with a worsening of the infarct. Perhaps sufficient time had elapsed for vascular anoxia to occur and to result in transudation of the agents into the tissue.

Other observations in our laboratory have indicated that the development of pallor of the cortex, which we believe to be one of the earliest significant events in the process of cerebral infarction, does not occur immediately after the occlusion of a middle cerebral artery. Early after arterial occlusion, before the development of cortical pallor, there appears to be a disturbance of function of cerebral tissue, manifested by electroencephalographic changes. If hemodiluting agents can be given at this time, before an infarct has become established, the effects of the agents may be favorable. Later, such agents may be harmful.
Application to Clinical Treatment of Strokes. It should be emphasized that the favorable effect of hemodiluting and dehydrating agents on the cerebral infarct occurring after acute occlusion of a middle cerebral artery in the cat does not imply that similar treatment will be effective on patients with acute or chronic cerebral ischemia. The clinical situation is much different from the situation in these experiments. For example, in human cases there is usually atherosclerotic obstruction of many vessels; this is not present in cats. In man, an occlusion may develop gradually, or an infarct may result from ischemia in an area of stenosis without complete occlusion of a vessel; in our experimental studies, occlusion was abrupt and involved a major vessel. Moreover, in cases of stroke the flow of blood through collateral channels may increase gradually over a prolonged period, during which there is also a gradual development of stenosis or occlusion.

But perhaps the most important difference between the clinical and experimental situations is that experimentally the agents used for treatment were given before and immediately after occlusion of the artery, before infarction had occurred. If these agents are to be effective at all in the treatment of patients with strokes, we think that they must be given very shortly after the onset of the neurologic deficit. Once an infarct has stabilized, hemodiluting agents may be harmful rather than helpful. The exact interval during which benefit may be expected from this type of treatment will have to be established by clinical studies; it may be too short for this treatment to have any practical clinical application.

Application to Neurovascular Surgery. The beneficial effects of the agents used in this study in protecting against cerebral infarction may have more relevance to neurovascular surgery than to treatment of strokes. Perhaps, by giving these agents before arterial manipulation, suturing, or grafting, the postoperative complication of cerebral infarction can be prevented or the size of a developing infarct can be reduced. However, we caution against the indiscriminate use of hemodiluting agents in attempts to maintain patency of small intracranial vessels. The agents used probably should be hyperoncotic to prevent the development of cerebral edema.

Summary

Acute cerebral infarcts were produced by intracranial, extradural occlusion of a middle cerebral artery in cats. Vascular dilatation occurred as early as 24 hours after occlusion in areas surrounding the infarct and was thought to be an inherent protective mechanism. Autoregulation of cerebral blood flow in the ischemic zone frequently was impaired.

The development of the infarct could be modified, favorably or unfavorably, by the intravenous administration of agents which influence blood viscosity, aggregation of formed blood elements, or intravascular oncotic pressure. Intravenous injection of a combination of concentrated serum albumin and low-molecular-weight dextran before the occlusion and of concentrated urea after the occlusion resulted in a significantly smaller mean infarct volume when compared to that in untreated cats. The use of albumin alone resulted in a slightly smaller mean infarct volume, but protection against infarction was less than with the combination of agents. Groups of cats given physiologic saline or packed erythrocytes had larger mean infarct volumes than the untreated group.

Cerebral edema was of considerable importance. Agents which favorably influenced the size of the infarct probably did so both by reducing cerebral edema and by changing rheologic factors. The detrimental effect of physiologic saline was due chiefly to an increase in cerebral edema.

It would be premature to infer that there would be any beneficial effect from these agents in the treatment of human strokes. Separate clinical studies, with particular emphasis on the time of treatment and the production of edema, will be necessary to assess the practical clinical application of hemodiluting agents in the treatment of strokes. However, these agents may prove to be useful in neurovascular surgery.

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References


