Low Molecular Weight Dextran
In Experimental Embolectomy

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SUMMARY The canine middle cerebral artery (MCA) was embolized with a pliable cylinder 8 mm long by 1.6 mm in diameter via the internal carotid artery. Both control and experimental embolectomies were performed 6 hours following embolization. The experimental animals were treated with low molecular weight dextran (LMD). In the control animals, the average volume of infarction in the brain was 1.45 cm$^3$. In the experimental animals the average volume of infarction was 0.13 cm$^3$.

THE TREATMENT of cerebral thromboembolism is controversial. Anticoagulants, steroids, anti-edema agents, and hyperventilation are used in the management of cerebral ischemia, despite controversy over their benefits in clinical and experimental situations. 1-4 Administration of barbiturates and dimethyl sulfoxide (DMSO) in experimental models has been encouraging. 5-10 Operative treatment, such as middle cerebral artery (MCA) embolectomy, has been sporadically reported with variable success. 11 It has been shown in experimental models that canine MCA embolectomy is safe within 5 hours of embolism, while embolectomy beyond 5 hours results in massive hemorrhagic brain infarction. 12 As it is usually not feasible to perform embolectomy in humans within such a short period, several pharmacological agents have been employed experimentally to extend the "grace period." 11-14

Low molecular weight dextran (LMD) has been used in the management of acute stroke with conflicting results. 13, 14 In the present study, the effect of LMD was evaluated in dogs subjected to embolization followed by MCA embolectomy.

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0.9% normal saline, and injected using moderate pressure until back bleeding indicated it was lodged intracranially beyond the junction of the internal carotid and maxillary arteries. EEG, ECG, and BP were continually monitored prior to and immediately following embolus injection. Since the embolus is radiopaque, its position was checked with lateral and AP skull roentgenograms. The cannula was then withdrawn from the internal carotid artery and the needle hole repaired with 2 or 3 6-0 polypropylene stitches. The neck incision was closed in layers.

In both the control and experimental animals, MCA embolectomy was performed at 6 hours postembolism. Immediately following MCA embolization, however, the experimental group also received an intravenous infusion of 10 ml/kg dextran§ for 2 hours. The dose of dextran was repeated for 3 days postembolectomy.

A temporal craniectomy was performed, and the MCA was microsurgically exposed. The location and state of the MCA embolus was noted and it was then removed via an 0.5 mm arteriotomy over the distal portion of the embolus by a small, manually adjusted suction cannula developed in our laboratory.¶ The arteriotomy site was closed with 10-0 nylon sutures and the rest of the incision closed in layers. Animals in which the embolus was fragmented or lodged distal to its position was checked with lateral and AP skull roentgenograms. The cannula was then withdrawn from the internal carotid artery and the needle hole repaired with 2 or 3 6-0 polypropylene stitches. The neck incision was closed in layers.

In both the control and experimental animals, MCA embolectomy was performed at 6 hours postembolism. Immediately following MCA embolization, however, the experimental group also received an intravenous infusion of 10 ml/kg dextran§ for 2 hours. The dose of dextran was repeated for 3 days postembolectomy.

Animals surviving for 3 weeks postoperatively were killed by hemodilution with normal saline (cannulas in both carotids and jugulars), followed by 10% formalin. The brain was removed and studied grossly, weighed, and immersed in 10% formalin. The MCA was examined macroscopically for possible stenosis or thrombosis. The excised segment of the MCA was later examined histopathologically.

The brain was serially sectioned coronally, and photographic enlargements (7X) of both sides of each section made. A planimeter was used to compute the infarct areas on each side of the coronal sections. The infarct volume in each section was determined by adding the 2 infarcted areas from each side, dividing by 2, and multiplying this average area by the thickness (generally 0.8 mm) of the coronal slice. The coronal slice infarction volumes were added to obtain the total infarction volume for a given brain. As a base for comparing the groups, a statistical analysis of the volume of the infarction was done by the Mann-Whitney U-Test.

Results

In 6 of the 9 control and 4 of the 5 experimental animals, the EEG voltage decreased immediately following embolization. In 3 of the controls and 2 of these experimental animals the low voltage was quickly followed by several episodes of sharp, high and fast waves. The remaining 3 controls and one experimental animal developed EEG low voltages between 15 and 30 min postembolization. In none of these animals was there any episode of sharp, high, and fast waves. There were also no significant differences in hematocrit or serum osmolarity between control and experimental groups.

Three of the 9 control animals embolectomized 6 hours following embolization died within 48 hours. These 3 animals were extremely ill during the postoperative period with impaired consciousness and contralateral hemiplegia. Autopsy revealed massive hemorrhagic infarction of the ipsilateral cerebral hemisphere in each of the animals (fig. 1). The MCA was patent in all 3.

Six control animals survived for 21 days. Three were hemiplegic with diminished consciousness, and intermittent intravenous fluid had to be administered for nourishment. Large infarctions of the thalamus, internal capsule, pyriform, and ectosylvian lobe were observed at autopsy. The other three control animals also had persistent hemiparesis, although their level of consciousness improved 24 to 48 hours postoperatively. At autopsy, areas of hemorrhagic infarction in the pyriform lobe and amygdala were noted. The average volume of infarction in the control group was 1.45 cm³ (table).

Four experimental animals survived the embolectomy and were killed 21 days postoperatively. One was normal neurologically and showed no brain lesion at autopsy. Three developed contralateral hemiparesis, but recovered by the fifth postoperative day. At autopsy, there were no brain lesions in 2 of the animals (fig. 2A), while the brain of the third showed an area of hemorrhagic infarction (fig. 2B). The volume of infarction was 0.22 cm³. The fifth experimental animal remained comatose and died within 24 h of embolectomy. Autopsy revealed hemorrhagic infarction involving the basal ganglia and thalamus. The volume of infarction in this animal was 0.42 cm³. Gross and microscopic examination of the arteriotomy site was performed on all animals at

§Dextran 40 (Rheomacrodex) 10% W/V, Pharmacia Laboratory, Piscataway, NJ 08854.
¶Codman and Shurtleff, Randolph, MA 02368.
TABLE Middle Cerebral Artery Embolectomy Performed 6 Hours After Embolism: Infarct Volume (cm³)

<table>
<thead>
<tr>
<th>Group</th>
<th>Infarct Volume (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>1.42</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>2.30*</td>
</tr>
<tr>
<td></td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>1.64*</td>
</tr>
<tr>
<td></td>
<td>1.96*</td>
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<td>1.16</td>
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<td>0.13</td>
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<tr>
<td></td>
<td>0.19</td>
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<td>0.08</td>
</tr>
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* Died within 72 hours.

Discussion

Despite recent advances in understanding the pathophysiology of cerebral ischemia, the management of cerebral embolism is still not adequately defined. It is well recognized that the heart and extracranial carotid arteries are the 2 major sources of cerebral emboli, the majority of which lodge in the area of the MCA. Technical improvements and EEG monitoring during extracranial carotid surgery have produced satisfactory results. However, a definitive treatment for acute stroke due to cerebral embolism, and the relative safety of acute reperfusion of the brain are not well established.

Experimental guidelines for MCA embolectomy have been used with some success. A critical safe period for MCA embolectomy or STA-MCA anastomosis has been outlined.

Canine MCA embolic occlusion and embolectomy performed within 5 hours of embolization did not produce neurological deficit or histopathological changes in the brain. However, restoration of blood flow 6 hours and beyond after embolic occlusion consistently resulted in edema and hemorrhagic infarction of the ipsilateral cerebral hemisphere. Similar observations were made when STA-MCA anastomosis were performed in dogs 6 hours after embolization.

Initially used as a plasma volume expander, LMD has been used in the treatment of acute cerebral infarction. In experimental temporary occlusion of the canine MCA, Cyrus et al. noted that animals treated with LMD immediately prior to occlusion showed much smaller areas of infarction and minimal neurological damage compared to the control animals. Similarly, Crowell and Olsson noted that monkeys treated with LMD after temporary occlusion of the MCA showed improved microvascular filling. In a controlled clinical trial of 100 patients with acute cerebral infarction due to thromboembolism, Gilroy et al. found that patients treated with LMD showed lower mortality and a better quality of survival. Matthews et al. also observed a significant reduction of mortality in the acute stage of stroke, although residual neurological impairment and disability among the survivors were disappointing. In a recent double blind study of acute brain infarction, a combination of dexamethasone and LMD failed to show any improvement in either mortality or morbidity of the treated patients.

A potential complication of acute reperfusion of the brain after a certain period is the development of hemorrhagic infarction, presumably due to intraparenchymal hemorrhage through the damaged vessel wall. In the early period of ischemia, structural evidence of progressive irreversible injury occurs in a portion of the neurons with alternations and changes in the microcirculation as ischemia con-
Slight impairment of filling in the microcirculation with ischemia of less than 3 hours duration has been noted in squirrel monkeys. When ischemia continued, severe microcirculatory obstruction was found. Electron microscopic studies have shown that obstruction at the capillary level is due to swelling of the endothelial and perivascular glial cells with formation of intravascular blebs. Such impairment of flow may lead to the "no-reflow phenomenon" with consequent irreversible tissue damage.

It is apparent from our results that LMD can be helpful in extending the critical period for embolism. LMD has been found to alter the rheologic characteristics of the blood, and has been used to prevent microcirculatory changes in traumatic shock, to maintain capillary flow in hypothermia, in vascular surgery, and in thrombophlebitis. Infusion of dextrans in humans can increase the bleeding time, decrease platelet aggregation, and inhibit development of platelet procoagulant activity. The mechanisms of action are not clear, but may be due to alternations in the platelet membrane, or LMD's interaction with plasma proteins essential for platelet aggregation.

The salutary effect of dextran is probably related to lowered blood viscosity and diminished stasis and sludging. The hemodiluting effect may help to improve collateral circulation and diffusion of catabolites. Improved cortical flow in pial vessels of cats and increased blood flow in the cerebral region after infusion of LMD in humans have been demonstrated. An early recovery of electrical response has also been recorded in animals receiving dextran in the posts ischemic period.

Low molecular weight dextran was not as effective as dimethyl sulfoxide or low-dose methyl prednisolone in our experimental model, which may be related to the anti-anoxic, anti-edema, stabilization of lysosomal membranes and the diuretic effect of these drugs. However, dextran's ability to prevent or reduce infarction appeared to be a useful adjunct in experimental acute reperfusion of the brain.

Acknowledgment

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Does Size Matter?

LOUIS R. CAPLAN, M.D. AND RICHARD BAKER, M.D.

SUMMARY A 47-year-old patient had lesser development of her left limbs and face, smaller left vascular structures, and severe occlusive disease of the left internal carotid, left subclavian, left vertebral and left iliac arteries. In 12 examples of occlusion of a carotid artery, 10/11 with unequal vascular luminal size had the occlusion on the smaller side. Of 20 patients with severe asymmetrical carotid stenosis, 13/17 with unequal size had more stenosis on the smaller side. These preliminary observations suggest that a small vessel may be more likely to occlude than its larger counterpart.

Extracranial Occlusive Vascular Disease: Does Size Matter?

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E. Garrod, Inborn Errors of Metabolism

THE NATURAL SIZE of arteries is usually given scant attention in discussion of factors promoting thrombosis. In fact, the degree of acquired stenosis of a vessel is generally reported as percentage occlusion, a measure which completely disregards (by cancellation in the numerator and denominator) the pre-existing size of the vascular lumen. We report an unusual "natural experiment" in which lesser development of the left limbs and left systemic and extracranial vascular systems of a patient was associated with stenosis or occlusion of the smaller left-sided vessels. Her right-sided vasculature was relatively unaffected.

This unusual case stimulated closer scrutiny of the relationship between carotid size and occlusive disease. Accordingly, angiographic examinations of 32 consecutive patients with stenosis of the internal or common carotid artery lumen to 2 mm or less were evaluated.

Case Report

S.W., a 47-year-old female, was referred for evaluation in December 1973 after a routine visual examination after low molecular weight dextran infusion in sheep. Med J Aust 18: 539-541, 1967


As a girl, she had undergone surgery for a "wry neck." At age 40, she had attacks of a "black shade descending over vision in the left eye." These brief episodes recurred approximately 5 times over a matter of months, but were always transient. At age 42, her rheumatic heart disease was diagnosed when congestive heart failure prompted cardiac evaluation and catheterization.

Despite rheumatic heart disease, she had 11 normal pregnancies and living children, one born subsequent to her cardiac catheterization. For several years, she suffered from pain in her left calf while walking. She had no visual or other neurological complaints.

On examination, the patient's right face, right sternocleidomastoid muscle and right neck were clearly more prominent than her comparable left-sided structures. Her right-sided vasculature was relatively unaffected.

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