Treatment of Acute Focal Ischemia with Continuous CSF Drainage and Mannitol

JOHN R. LITTLE, M.D. AND DONALD O'SHAUGHNESSY, M.Sc.

SUMMARY A simple implanted device was used to occlude acutely the left middle cerebral artery (MCA) of 32 conscious cats. Groups of 8 cats each were treated with continuous cerebrospinal fluid (CSF) drainage, mannitol (1 gm/kg i.v.), or a combination of continuous CSF drainage and mannitol (1 gm/kg i.v.). Eight cats served as a control group. The neurological status of cats treated with mannitol improved transiently. Perfusion with a mixture of colloidal carbon and buffered paraformaldehyde was carried out 12 hours following MCA occlusion. Gross swelling of cerebral tissue, distribution of colloidal carbon, and breakdown of the blood-brain barrier to fluorescein were similar in the 4 groups. Reduction of mean capillary luminal diameter to 4.5 ± 1.0 μ (control 6.5 ± 1.0 μ) in the left Sylvian cortex was unaltered by treatment. A significant difference in the distribution of severe neuronal alterations was not demonstrated.

THE ROLE OF continuous cerebrospinal fluid (CSF) drainage in the treatment of acute cerebral ischemia has not been defined. A recent report by Smialek et al. suggests that CSF drainage substantially reduces mortality in gerbils following bilateral carotid artery occlusion. The effect, if any, on acute focal ischemia has not been studied.

Hyperosmolar agents, including mannitol, glycerol, and low molecular weight dextran, have a beneficial effect when administered shortly following the onset of ischemia. However, previous studies suggest that protection is limited to the period of elevated plasma osmolality. Consequently, the use of hyperosmolar agents alone may not constitute a definitive form of therapy.

The object of this investigation was to study the effect of continuous CSF drainage, alone and in combination with mannitol, upon the development of cerebral infarction in conscious cats following MCA occlusion.

Methods

Implantation of Occluding Device

Details of the implantation of the device used to occlude the MCA have been described previously. Thirty-two adult cats with a mean weight of 3,200 gms were anesthetized with sodium pentobarbital (30 mgm/kg) injected intraperitoneally. The left MCA of each cat was exposed through a transorbital approach and the slotted housing of the occluding device, with the short stylet inserted, was applied to its proximal segment. The orbit was briefly sprayed with neosporin aerosol. The small craniectomy was packed with small pieces of gelfoam and covered with a piece of thin silastic sheeting. The orbit then was filled completely with rapidly hardening epoxy cement. The incision was closed with 4-0 silk suture and a dressing applied.

A 20-gauge polyethylene catheter was inserted into the left femoral vein through a small incision in the groin. The injection nozzle of the catheter was brought out through another small incision on the flank. The wounds were closed with 4-0 silk suture and dressings applied. Each animal was given 30 ml of isotonic saline by intravenous injection.

Oclusion of the MCA

The left MCA of the 32 conscious, unanesthetized...
cats was occluded on the third or fourth postoperative day by inserting the occluding stylet.

Treatment Groups

The 32 cats were divided into 4 groups of 8 cats each: 1) Control group. No treatment was given. 2) CSF drainage group. The left MCA was occluded with a special occluding stylet which allowed continuous CSF drainage (fig. 1). Only the distal 1 mm of the stylet, made from thin-walled, 18-gauge stainless steel tubing, was filled with solder. A small opening was made in the side of the stylet near its distal end. The proximal end was not closed. 3) Mannitol group. Each cat received 20% mannitol (1 gm/kg i.v.) in a divided dose, half during a 10-minute period before and half during a 10-minute period after MCA occlusion. 4) CSF drainage — mannitol group. The hollow occluding stylet was used for MCA occlusion. As well, each cat received 20% mannitol (1 gm/kg i.v.) as in group 3.

Perfusion Technique

The 32 cats were perfused 12 hours following MCA occlusion. Each cat was anesthetized with sodium pentobarbital (30 mgm/kg i.p.) 20 minutes before perfusion. A tracheostomy was performed and the animals were ventilated mechanically. Fifteen minutes before perfusion, each cat received an intravenous injection of 10% sodium fluorescein (1 ml). Two cats in each group also were given an intravenous injection of 10% Evans blue (1 ml).

A midline thoracotomy was performed. Immediately prior to commencing perfusion the occluding stylet was withdrawn. A large cannula was passed through a left ventriculostomy incision into the ascending aorta and secured with a ligature. The descending aorta was clamped and the right atrium incised. The animals were perfused initially with 50 ml of isotonic saline followed by a mixture of colloidal carbon (250 ml) and phosphate-buffered (pH 7.3) 4% paraformaldehyde (250 ml) at a constant pressure of 120 mm Hg.

The brain of each cat was removed carefully one hour following completion of perfusion and placed in 50 ml phosphate-buffered 4% paraformaldehyde at 4°C for 48 hours.

Tissue Preparation

The brains were cut into 5 mm coronal slices. These slices were photographed and examined under ultraviolet light using a Kodak-Wratton #21 barrier filter. Thin semi-serial coronal sections (10 and 25μ) were prepared from paraaffin-embedded slices of both hemispheres, stained with hematoxylin and eosin, cresyl violet and periodic acid Schiff, and examined with a light microscope.

Analysis of Tissue

The distribution of carbon staining in the left cerebral hemispheres was graded: grade "0" indicated normal vascular filling; grade 1 referred to a few circumscribed foci of poor filling not more than 3 mm in diameter; grade 2 indicated a large area of improper subcortical filling; and grade 3 referred to an extensive cortical and subcortical region of impaired filling. The intensity of the zones of pallor also was classified.

The cross-sectional area of gray matter, where severe ischemic neuronal alterations (i.e., grades 2 and 3) predominated, were determined with a Keuffel and Esser planimeter in coronal sections of the left cerebral hemispheres 3 mm posterior to the temporal lobe tip. Comparisons were made using the Student t-test.

Photomicrographs of anterior and posterior Sylvian cortex were taken and enlargements made. Capillary luminal diameters were measured (500 measurements per section) and the mean capillary luminal diameter calculated.

Results

Neurological Findings

The initial response of the cats in the 4 groups was similar, that is, agitation, circling to the left, and right hemiparesis. Transient improvement in the neurological deficit was seen during the initial 6 hours of MCA occlusion in most cats receiving mannitol (i.e., groups 2 and 3); however, findings were essentially the same in the four groups immediately before perfusion.

CSF Drainage

Leakage of CSF from the special occluding stylet used in group 2 and 4 cats was observed immediately following its insertion. It occurred at an approximate rate of one drop (0.04 ml) every minute. CSF continued to drip from the stylet throughout each experiment.
Macroscopic Findings

A. Brain Swelling. Gross swelling of cerebral tissue in the left MCA territory was observed in 6 cats in group 1, 7 cats in group 2, 6 cats in group 3, and 7 cats in group 4. Mean left to right shift of midline structures ranged from 1.2 mm in group 1 to 1.4 mm in group 4.

B. Distribution of Vital Dyes. The distribution of fluorescein in the left cerebral hemispheres of the 32 cat brains is listed in table 1. Blue staining was not observed in the brains of cats receiving Evans blue dye, but yellow staining of fluorescein was present in each cat receiving both dyes (fig. 2).

C. Distribution of Colloidal Carbon. The major branches of both MCA's were filled with the carbon solution. The presence of carbon in the trunk of the left MCA indicated reopening of this artery. The distribution and intensity of carbon staining in the left cerebral hemispheres are listed in table 2.

Light Microscopic Findings

The ischemic changes observed were similar to previous detailed descriptions. Severe neuronal alterations (i.e., grades 2 and 3) consistently were present in the caudate nucleus and cortex supplied by the left MCA. There appeared to be general correlation between the extent of neuronal damage and the neurological deficit, brain swelling, and degree of impaired carbon filling. No abnormalities were seen in the right cerebral hemispheres.

The size of the resulting cerebral infarct was not altered by treatment with CSF drainage and/or mannitol. The percentage of gray matter cross-sectional area where severe neuronal alterations predominated was 43 ± 14 % in the control group; 45 ± 11 % in the CSF drainage group; 41 ± 12 % in the mannitol group; and 44 ± 14 % in the CSF drainage-mannitol group. A significant difference among the 4 groups was not demonstrated.

Considerable reduction of capillary luminal diameters in ischemic gray matter was observed. Mean capillary luminal diameter in the left Sylvian cortex was 4.5 ± 1.0 μ in all groups compared with 6.5 ± 1.0 μ in the non-ischemic right Sylvian cortex. Many capillaries, particularly those in the core area of ischemia, contained numerous erythrocytes and did not fill with carbon. Despite the substantial narrowing, few capillaries appeared collapsed. The distribution and severity of capillary narrowing correlated with the amount of astrocytic swelling in the adjacent neuropil.

Discussion

Occlusion of the MCA in conscious cats with a sealed craniectomy has been shown to result in a large

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**Table 1 Distribution of Fluorescein in L. Cerebral Hemispheres**

<table>
<thead>
<tr>
<th>Distribution of fluorescein</th>
<th>Treatment groups (8 cats/group)</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Gray only</td>
<td>1</td>
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<tr>
<td>White only</td>
<td>3</td>
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<tr>
<td>Gray &amp; white</td>
<td>3</td>
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Abbreviation: dr. = drainage.

**Table 2 Distribution of Colloidal Carbon in L. Cerebral Hemispheres**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment groups (8 cats/group)</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1x</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1x;3x;1x</td>
</tr>
</tbody>
</table>

(mild = x; moderate = y; intense = i; dr. = drainage).
cerebral infarct involving caudate nucleus and cortex. The amount of irreversible tissue injury is considerable at 6 hours and only slight extension occurs with longer periods of occlusion. This is in contrast to studies by Sundt et al. and others in cats under barbiturate anesthesia with an open dura and craniectomy where infarcts usually were small and frequently restricted to subcortical structures. The use of barbiturates likely was a modifying factor; however, the effect of concomitant CSF drainage was not defined.

The findings of this study failed to demonstrate a significant difference in the distribution and severity of ischemic neuronal alterations following 12 hours of MCA occlusion despite treatment with continuous CSF drainage alone and in combination with mannitol. Therefore, it is unlikely that CSF drainage was an important factor in reducing infarct size in previous studies using this experimental model.

Mannitol (1.2 gm/kg) previously was reported to suppress the development of ischemic cerebral edema, capillary narrowing, and severe neuronal alterations during the initial 6 hours of MCA occlusion in cats. This corresponded to the period of plasma osmolality elevation produced by this hyperosmolar agent. Cerebral blood flow studies by Heiss et al. in conscious cats demonstrated an immediate reduction in regional cerebral blood flow following MCA occlusion with substantial improvement in many cats during the subsequent 3 to 4 hours. Consequently, it was postulated that if mannitol protected the ischemic cerebral tissue during this critical early phase of cerebral blood flow reduction the resulting infarct would be reduced in size. The findings of this study, however, indicate that this is not the case.

Capillary narrowing at 12 hours was not modified by treatment. Mean capillary luminal diameter in the ischemic left Sylvian cortex was 4.5 ± 1.0μ in the 4 groups studied. Previous studies in cats and monkeys have demonstrated progressive capillary narrowing beginning as early as 30 minutes following MCA occlusion. The capillary lumens invariably had a normal, round configuration when cut transversely and capillary collapse was unusual. Reduction in capillary luminal diameter was detected only when systematic measurement was carried out.

The failure of continuous CSF drainage to alter mean capillary luminal diameter suggests that elevated intracranial pressure per se is not a major factor in the production of capillary narrowing. Suppression of edema and prevention of capillary narrowing during the initial 6 hours of MCA occlusion by treatment with mannitol in previous studies, however, indicates that elevated tissue pressure may play an important role. Subsequent reduction in capillary luminal diameter seen 12 hours following mannitol administration is likely the result of edema which develops once plasma osmolality has returned to the pretreatment level.

Carbon perfusion studies have shown that early capillary narrowing does not necessarily signify a state of "no-reflow" (i.e. capillary obstruction). Impaired carbon filling has not been demonstrated consistently in cats or monkeys with MCA occlusion less than 3 hours. The narrowing which occurs prior to obstruction of the passage of erythrocytes, however, may impair capillary flow at an early stage and subsequently contribute to ischemic neuronal injury.

Wolman et al. have shown that most sodium fluorescein exists in a free state or is loosely bound to plasma protein when given in an amount similar to that used in this study. Evans blue was found to bind firmly to plasma proteins. This binding was not altered by the concomitant administration of sodium fluorescein. Consequently, the simultaneous injection of these 2 dyes provides information regarding vascular permeability to a relatively small molecule (i.e., fluorescein) with a molecular weight of 332 and a large molecular complex (i.e., Evans blue-plasma protein).

Increased cerebral vascular permeability to fluorescein has been demonstrated as early as 90 minutes following MCA occlusion in the cat. Fluorescein staining initially appears to be confined to the ischemic cortex and caudate nucleus. Leakage of fluorescein into white matter occurs with MCA occlusion of 6 hours and longer. In this study, fluorescein was present in the gray matter only in 12 cats and in the gray and white matter in 10 cats.

Evans blue was not observed in the ischemic cerebral tissue stained with fluorescein when both dyes were injected simultaneously. This investigator, however, has observed concomitant Evans blue and fluorescein staining after shorter periods of MCA occlusion (i.e., 3 and 4 hours). These findings suggest a prolonged partial breakdown of the blood-brain barrier with increased permeability restricted to relatively small molecules (i.e., fluorescein) and perhaps an early, transient leakage of larger molecules (i.e., Evans blue-plasma protein). Transient breakdown of the blood-brain barrier to plasma protein (i.e., "maturation phenomenon") has been observed following temporary carotid artery occlusion in the gerbil.

Fluorescein staining was confined to areas of pallor. The delivery of fluorescein to the so-called "no-reflow" zone and subsequent leakage into ischemic cerebral tissue during the 15 minute period following fluorescein injection suggest that plasma flow in such zones is less severely impaired than circulation of colloidal particles (i.e., carbon). These findings substantiate the earlier hypothesis that a state of plasmapheresis may exist in ischemic cerebral tissue.

References
4. Little JR: Modification of acute focal ischemia by treatment
External Carotid Artery in Internal Carotid Artery Occlusion. Angiographic, Therapeutic, and Prognostic Considerations

ROGER W. COUNTEE, M.D. AND THURAIRASAH VIJAYANATHAN, M.D.

SUMMARY: Twenty-three instances of internal carotid artery occlusion occurring with minimal neurological deficit in 22 patients are described. Although each of these patients was referred to the neurosurgical service for evaluation for an extracranial-intracranial microvascular bypass procedure, complete arteriographic evaluations of their cerebrovasculature suggested that alternative methods should be the treatment of choice. For each patient reported the ipsilateral external carotid artery was demonstrated by angiography to be an important source of collateral blood supply to the cerebral hemispheres or retinae distal to the occluded internal carotid arteries. Ten patients with no significant atherosclerotic narrowing or ulceration of the external carotid artery have remained free of symptoms of cerebral ischemia for 6 to 40 months. In twelve patients who developed delayed recurrent cerebral or retinal ischemia ipsilateral to their internal carotid artery occlusion, there were found obstructive and/or ulcerative plaques involving the common and/or external carotid arteries. Thromboendarterectomy in 11 of these patients gave complete relief of ischemic symptoms during the 4 to 36 months of postoperative follow up. One of these 12 patients refused operation and went on to develop a major cerebral infarction. Angiographic identification of a functionally important external carotid artery ipsilateral to an internal carotid artery occlusion carries considerable prognostic and therapeutic significance.

EMBRYOLOGICAL STUDIES, postmortem dissections, and angiographic investigations have amply demonstrated the collateral connections between the external carotid artery and the intracranial and orbital circulations. In occlusion of an internal carotid artery in the neck, this contribution from the external carotid artery may be vital in preventing cerebral and/or ocular ischemia. This report describes our experiences with 23 such instances of internal carotid artery occlusion which occurred with minimal or no neurological residual. In each patient the homolateral external carotid artery was the major, if not the sole, source of alternative blood supply to the hemisphere or eye distant to the occluded vessel. In these patients the angiographic identification of a functionally significant external carotid artery proved to be of considerable value in determining prognosis and appropriate surgical management.

Patients and Methods

Twenty-two patients with 23 internal carotid artery occlusions were referred to the neurosurgical service for an extracranial-intracranial microvascular bypass procedure.
Treatment of acute focal ischemia with continuous CSF drainage and mannitol.
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