Temporary Experimental Intracranial Vascular Occlusion

Effect of Massive Doses of Heparin on Brain Survival

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It is widely held that the maximum permissible period for total cerebral ischemia is in the range of 5 minutes. Total absence of perfusion for a longer duration is felt invariably to result in an infarction. This propensity of cerebral tissue to ischemic damage remains an overwhelming problem in neurosurgery directed toward or concerned with intracranial vascular structures. Not infrequently in the operative attack of cerebral vascular problems such as vascular malformations, occlusive disease (endarterectomy), and especially intracranial aneurysms, it becomes necessary to occlude the vascular inflow temporarily. The danger of irreversible damage has led to the commonly accepted practice of performing multiple brief occlusions with intermittent periods of flow restoration. This is surgically undesirable as it greatly shortens the effective periods of operative manipulation and leads to technical error.

Various means have been tried in an effort to prolong the allowable ischemic period so that more precise and time consuming procedures might be performed. These have included efforts to lower the rate of cellular activity by hypothermia or barbiturate administration. Other investigators have tried to add excesses of physiological compounds to delay the onset of cellular damage. However, more impressive evidence gradually began to accumulate that the cerebral tissue could survive longer periods of ischemia if vascular patency was maintained. This concept gathered further support with the demonstration of microthrombus formation in capillaries during circulatory arrest; these thrombi can prevent perfusion of tissue even when the gross circulation is restored within a tolerable period.

Several agents have been administered in an effort to maintain capillary patency during temporary arrest of the circulation. These included the anticoagulants heparin and coumarin derivatives as well as osmotic agents such as Mannitol, low molecular weight dextran, and hypertonic glucose. Fibrinolytic substances have been administered to obtain dissolution of the microthrombi in situ.

After review of the accumulated evidence from experimental studies, the fact emerges that heparin has been the only substance that has consistently provided prolonged brain survival. Even this protection has not been guaranteed by the standard amounts of heparin but remains highly dependent on massive doses.

With this fact in mind, we undertook the present experimental study to establish the efficacy of temporary and reversible massive anticoagulation therapy in the prevention of cerebral infarction from transient middle cerebral arterial occlusion during intracranial operations.

Materials and Methods

Twenty-five Rhesus monkeys (Macaca mulata), which weighed 2.5 to 4 kg each, were selected for this study.* All animals were subjected to identical operative procedures. All were anesthetized with intravenous pentobarbital (30 mg/kg) and endotracheal tubes were passed to assure a patent airway. The Harvard pump respirator was

* The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed.
present should the need for respiratory assistance arise; however, it was required only on rare occasions.

As the initial step, the anterior neck was prepared and the carotid sheath contralateral to the intended craniectomy exposed through a short, oblique skin incision 1.5 cm superior to the clavicle. The common carotid artery and jugular vein were identified and isolated. The artery was doubly ligated. A polyethylene catheter was inserted into the jugular vein and positioned so that the tip lay in the superior vena cava. Patency of this central venous catheter was maintained by very slow infusion of Ringer's lactate. This catheter served both as the route for administration of all drugs and for withdrawal of blood specimens.

After closure of the cervical incision, the animals were positioned with the head rotated 45° toward the side of carotid ligation and slightly flexed. Cranietomy was carried out essentially as described by Sundt and Waltz with certain modifications. It was not found necessary to incise the temporalis muscle nor to remove the coronoid process of the mandible. A small trephine opening in the anterior margin of the temporal bone was widened by rongeurs. The orbit was entered at its lateral margin by rongeuring away the lateral sphenoid wing. The orbit roof was removed medially to the margin of the anterior clinoid and posteriorly to include the greater wing of the sphenoid. After adequate bony removal had been accomplished, the operating microscope was positioned (Zeiss Model 25124) and set to a magnification of 10. A spatula was inserted into the orbit and by retracting its contents downward only minimal retraction was necessary on the inferior surface of the frontal lobe. A No. 11 knife blade was used to make a small opening in the dura just lateral to the optic nerve. Small angle microscissors could then be used to enlarge this opening. The middle cerebral artery is quite apparent under the 10 magnification as it runs in the cleft between the frontal lobe and temporal tip. This was easily followed medially several millimeters until the internal carotid and anterior cerebral arteries were visualized. A sharp hook was used to strip the overlying arachnoid from the middle cerebral artery just distal to its origin. A small Mayfield clip was then applied to the vessel at this point and allowed to remain in place for the specified period. No attempt was made to suture the dura but the opening was covered with a small gelfoam patch. The temporalis muscle was tacked to the pericranium to achieve stability and the scalp was closed in layers.

Blood was drawn on all animals for Lee-White clotting time determinations at the following stages of the operation: 1) at commencement of the craniectomy, 2) while the clip was in position, and 3) after completion of the surgical procedure. All animals were then allowed to recover from surgery. They were evaluated for alertness, appetite, and evidence of neurological dysfunction.

At 7 to 10 days postoperative the animals were sacrificed with large doses of pentobarbital. The brains were immediately removed, suspended in 10% buffered formalin, and allowed to fix. Following this the brains were coronally sectioned and evaluated for the presence and degree of infarction. Grading of infarction was performed according to the following scale:

Grade 0 = no infarction  
Grade 1 = 1 cu cm or less brain tissue infarcted  
Grade 2 = approximately 2 cu cm infarcted brain tissue  
Grade 3 = approximately 3 cu cm (Fig. 1 A) infarcted brain tissue  
Grade 4 = greater than 3 cu cm infarction or death as a result of infarction (Fig. 1 B).

After grading, representative sections were embedded sectioned at 6 μ and stained with hematoxylin and eosin. The stained slides were then examined microscopically to confirm the gross diagnosis of infarction.

Prior to surgery the animals were divided randomly into groups as follows:

Group 1 (Occlusion for 15 minutes, controls). Nine monkeys comprised this group. These animals had the standard operative cranietomy with temporary occlusion of the middle cerebral artery for 15 minutes. No anticoagulation was given.

Group 2 (Occlusion for 15 minutes, treated). Eight monkeys were included. In these animals heparin was administered through the central venous catheter, in a dosage of 5 mg/kg, 1 to 2 minutes prior to mid-