Medical approaches to the treatment of acute focal cerebral ischemia[1]

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Acute focal cerebral ischemia is a common entity which has been intensively studied both experimentally and clinically. With the accumulation of knowledge, a framework for reducing tissue injury and improving neurological outcome has evolved. It has been clearly established that treatment must be initiated before irreversible damage occurs. The two basic, interdependent approaches are (*1*) to improve blood flow to the ischemic zone and (*2*) to increase the resistance of cerebral tissue to metabolic injury. Optimization of blood viscosity and maintenance of systemic arterial blood pressure are important factors in enhancing circulation. Agents such as mannitol and low-molecular-weight dextran have proved beneficial, whereas prostacyclin and calcium-entry blockers have not. Elevation of blood glucose levels before the ischemic event has been shown to have a deleterious effect upon circulation and metabolism in the ischemic zone. Barbiturate coma, although difficult to use in the usual clinical setting, has been shown to reduce ischemic injury. The rationale and application of the various therapeutic approaches are discussed.

Index term: Cerebral ischemia, therapy

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Acute focal cerebral ischemia is a frequently encountered problem. In the past, patients with impending or evolving cerebral infarction were oftentimes believed to be beyond help and were treated passively. With the accumulation of knowledge, a framework for positive action has evolved. Although it may be difficult to evaluate the effects of treatment upon individual patients, there is a gathering body of information which indicates that we are able to favorably modify the situation.

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Cerebral ischemia is defined as a reduction of blood flow to levels that are insufficient to sustain normal cerebral function, metabolism, and/or structure. Ischemia can further be classified as *incomplete* or *complete*, to specify whether blood flow is simply inadequate or has ceased altogether, and as *global* (i.e., generalized) or *focal* (i.e., regional), to distinguish between an overall hemodynamic failure or local disturbance. In this report, emphasis will be placed primarily on the approach to incomplete focal ischemia, that is, the kind of brain ischemia most often encountered clinically.

Knowledge of the early pathophysiological changes in acute focal cerebral ischemia has been derived largely from animal studies.[1,2] These experimental studies have shown that cerebral infarction invariably results from sustained reduction of regional cerebral blood flow (CBF) below 15–18 mL/100 g/min. The rapidity with which irreversible injury occurs correlates with the degree of CBF reduction below the ischemic threshold. These studies have also shown that even profound ischemia is reversible for a brief period. Reduction of CBF to or slightly below the ischemic threshold probably results in a three- to six-hour period during which changes are predominantly reversible.[3,4]

Unlike structural damage, neuronal electrical activity and neurological function cease immediately upon reduction of CBF below the ischemic threshold. If CBF rises above the threshold before infarction occurs, neuronal electrical activity and neurological function return. Consequently, a neurological deficit does not necessarily imply irreversible injury.

The overall objectives in treating acute focal cerebral ischemia include (*1*) improving blood flow to the ischemic zone and (*2*) increasing resistance of cerebral tissue to metabolic injury. Both approaches must be incorporated if treatment is to be effective. Accordingly, it is unlikely that a single agent will be identified which can effectively prevent all ischemic damage. In this report, our guidelines for the medical treatment of this condition will be presented.

Optimize cerebral circulation

Knowledge of the CBF changes in and around an ischemic focus has expanded substantially during the past 25 years. From these studies, a number of physiological factors and pharmacological agents have been identified which have either a beneficial or a detrimental effect. This information has allowed the definition of an approach for maintaining and improving cerebral perfusion during ischemia.

Blood viscosity

There has been considerable ongoing interest in the relationship of blood viscosity to the pathogenesis and treatment of cerebral ischemia.[5,6] Studies have shown that individuals with high blood viscosity are at greater risk of stroke than those with normal blood viscosity.[7,8] Other studies have shown that optimizing blood viscosity can potentially limit tissue injury during an ischemic event.[9–11]

Blood viscosity refers to the physical property of blood which is dependent upon the friction of the component elements as they move relative to one another. The main determinants of blood viscosity include the concentration of erythrocytes (i.e., hematocrit), rigidity of erythrocytes, plasma fibrinogen concentration, and shear stress.

Blood viscosity is not constant.[12] Blood is a non-Newtonian fluid in which viscosity varies with the rate of flow. Slow moving blood has a much higher viscosity than the same blood flowing rapidly. Viscosity increases logarithmically with increasing hematocrit. Hematocrit also varies from one region of the body to another. For example, the hematocrit in the cerebral microcirculation is 70% to 80% of that in the large vessels.[13]

CBF has been shown to be reduced with hematocrit levels exceeding 50%, whereas CBF increases with reduction of hematocrit levels below 30%.[14] Oxygen delivery is not impaired in normals when hematocrit is reduced below 30% or even 20% as the compensatory increase in CBF allows adequate oxygen delivery. However, in a setting of cerebral artery occlusion and limited collateral circulation, a similar compensatory increase in CBF would not be possible and could result in a more severe impairment of oxygen delivery and greater tissue damage.

Manipulation of hematocrit can be carried out safely and is an effective means of modifying blood viscosity. Hematocrit can be lowered by venipuncture together with the administration of agents to maintain or expand plasma volume. Conversely, hematocrit can be increased by transfusing packed erythrocytes. The optimal hematocrit has not been established although there is a body of information suggesting that it is between 35% and 40%.

Systemic arterial blood pressure

Reduction of systemic arterial blood pressure below the normal preexisting level has been shown to result in further reduction of CBF in the ischemic focus. In contrast, elevation of systemic arterial blood pressure might increase collateral blood flow and reduce ischemic injury.[15-18]

Therapeutic elevation of systemic arterial blood pressure should be initiated as soon after the onset of ischemia as possible. This can be done using a pressor agent, such as dopamine, together with correction of any total body blood volume deficiency. A mean systemic arterial blood pressure 10 to 15 mm Hg above normal for the individual patient is our usual starting point.

The use of such treatment may be limited by preexisting heart disease or the presence of an untreated cerebral aneurysm which has recently bled. Starting hypertensive treatment after a delay of hours to days should be avoided. Elevation of cerebral perfusion pressure at a time when irreversible tissue injury has already occurred or during recirculation (e.g., after dissolution of an embolism) could worsen the ischemic edema and increase the risk of hemorrhage.[19-21]

Total body blood volume

Total body blood volume varies with many factors, including age, sex, body weight, fat content, activity, position, medications, and disease. Many individuals at risk for stroke already have a reduced blood volume. This pre-existing reduction increases the likelihood of relative or absolute systemic hypotension which could reduce further the circulation in the ischemic zone.

The role, if any, of blood volume expansion above normal levels in treating cerebral ischemia has yet to be determined. Local blood volume expansion in the cerebral microcirculation is an early and consistent response to ischemia. When cerebral perfusion pressure and blood flow drop below the normal range, the cerebral arterial system dilates, producing relative blood volume expansion in the ischemic zone.[22] As blood flow approaches the ischemic threshold, maximal vasodilation and volume expansion of the microcirculation occur and there is loss of local autoregulation.[23] Consequently, it is unclear what benefit total body blood volume expansion per se would have upon the circulation in and around the ischemic zone.

There is no strong evidence that total body blood volume expansion reduces cerebral infarct size. Increased perfusion pressure which can occur with blood volume expansion probably has a beneficial effect, but many patients suffering an acute cerebral ischemic event have associated cardiac problems and may not tolerate rapid and excessive expansion of their blood volume. Under most circumstances, maintenance of blood volume at or slightly above normal is the safest approach. The use of a Swan-Ganz catheter, with measurement of central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output, is oftentimes invaluable in optimizing the patient's cardiovascular state.

Cerebral vascular reactivity

The cerebral arterioles in an ischemic zone lose their autoregulatory capacity and CO_2 reactivity and become maximally dilated. Consequently, therapeutic manipulations producing vasodilation have no effect upon those vessels in the ischemic area. Dilatation of collateral arterial channels outside the ischemic zone has been postulated as a means of enhancing flow to the ischemic area. This hypothesis has not been supported by the experience with $PaCO_2$ manipulation. In fact, elevation of $PaCO_2$ above normal levels with vasodilatation in nonischemic areas has been shown in some studies to further reduce blood flow in the ischemic zone (i.e., the "intracerebral steal phenomenon").[24] On the other hand, reducing $PaCO_2$ below normal levels or the administration of vasoconstricting agents does not appear to have any direct beneficial effect upon flow in the ischemic areas. In view of these findings, we attempt to maintain $PaCO_2$ in the 35 to 40 mm Hg range.

Administration of vasodilating agents, such as prostacyclin (PGI_2)[25] and calcium-entry blocking agents (e.g., nimodipine)[26,27] has not been shown to consistently improve CBF in experimental focal cerebral ischemia. Their use appears to produce a response similar to that induced by $PaCO_2$ elevation. Intravenously administered PGI_2 infusion has not proved helpful in controlled clinical trials of acute focal ischemia.[28-30] Although calcium-entry blockers have not been consistently shown to be beneficial in acute focal cerebral ischemia, the dihydropyridine derivative—nimodipine—might be useful in preventing cerebral vasospasm and ischemia following subarachnoid hemorrhage from ruptured aneurysm.[31-33]

Anticoagulation and thrombolytic therapy

For many years, immediate anticoagulation with heparin was thought to be the only available "treatment" for evolving brain infarction. Based on clinical data, heparin is still employed in carefully selected patients with progressing nonhemorrhagic infarction where large vessel thrombosis is the likely etiology. By retarding progressive thrombosis with its associated compromise of the collateral circulation, heparin may help to maintain perfusion of the ischemic zone.

Unfortunately, the mechanism of acute stroke progression is often multifactorial and may have little to do with active thrombus formation. Heparinization also carries a risk of hemorrhage into areas of infarcted brain, particularly during recirculation. Heparinoids, a newly identified group of antithrombotic agents with less hemorrhagic risk, are currently being evaluated for use in evolving infarction.

Thrombolytic therapy with streptokinase or urokinase is associated with a high risk of brain hemorrhage and has been abandoned. Tissue plasminogen activator (tPA) holds some promise because the potential for hemorrhage is thought to be less.[34] However, brain hemorrhage has occasionally occurred during the treatment of peripheral vascular or coronary thrombosis with tPA. Clinical trials of tPA for acute cerebral ischemia await further experimental evaluation.

Therapeutic agents

Results of the experimental studies and clinical use of low-molecular-weight dextran (LMWD) in treating acute focal cerebral ischemia have been encouraging.[6,9,11] LMWD consists of a mixture of glucose polymers with an average molecular weight of 40,000. The intravenous half-life of LMWD is five hours. It is slightly hyperoncotic, producing mild plasma volume expansion when given intravenously (i.e., 500 mL LMWD expands plasma volume approximately by 700 mL). Beneficial actions upon the microcirculation include retardation of rouleau formation and inhibition of platelet aggregation. LMWD administration is particularly useful in maintaining blood volume when venipuncture is used to reduce hematocrit levels.[9] Because many patients with cerebral ischemia have associated cardiac disease, LMWD should be used cautiously to avoid the development of acute congestive heart failure.

Intravenous administration of mannitol has also been shown experimentally to have beneficial effects when administered before or at the onset of ischemia.[35] It has been postulated that increased plasma osmolality produced by mannitol prevents impairment of microcirculatory perfusion by retarding the formation of ischemic edema. Mannitol has also been shown to increase erythrocyte plasticity and to quench potentially damaging hydroxyl free radicals which are produced during ischemia.[36,37] The actions of mannitol can be prolonged by giving a continuous low-dose infusion.[38] Optimally, plasma osmolality should be increased 15 to 20 mosm above preexisting normal levels. Patients with increased plasma osmolality and/or those suspected to be dehydrated should not be given this agent. Fluid losses from the associated diuresis must be adequately replaced so that intravascular volume is maintained. Because mannitol acts by producing an osmotic gradient across the blood-brain barrier, it is not effective and is potentially harmful if it is given after blood-brain barrier breakdown has occurred.

Experimental studies suggest a potential role for intravenously administered perfluorocarbons in treating acute focal cerebral ischemia.[39,40] Its unique oxygen-carrying property appears to enhance oxygen delivery to the ischemic tissue. As well, it can be used effectively as a plasma volume expanding agent. Serious side effects, including pulmonary failure, however, have prevented its use in humans.

Enhance resistance to metabolic injury

Our ability to favorably modify the cerebral metabolic response to ischemia is limited and progress in this area has been particularly slow. Regulation of blood glucose levels and the use of barbiturates have been shown to have beneficial effects. Other approaches are being evaluated, but information is currently insufficient to warrant an endorsement.

Blood glucose

Blood glucose levels existing before cerebral ischemia affect the extent and severity of subsequent tissue damage. Recognition of the importance of preexisting blood glucose levels originated from experimental studies which showed that fasted animals had a better recovery following cerebral ischemia than fed animals.[40] Other studies have clearly demonstrated that marked elevation of blood glucose levels before ischemia results in more severe reduction of CBF during ischemia, impairment of recirculation, increased infarct size, and a worse neurological outcome.[42,43]

The mechanisms for this response are incompletely understood. The high blood glucose levels existing prior to an ischemic event increase the tissue glucose content. During ischemia, the increased substrate content leads to increased anaerobic glucose metabolism resulting in excessive lactacidosis and increased tissue osmolality.[44] Elevation of blood glucose levels after the onset of ischemia does not have a similar deleterious effect. This is related partly to the impaired delivery of glucose secondary to decreased perfusion in the ischemic area. Consequently, the level of tissue glucose is far less than would occur when a state of hyperglycemia exists prior to the ischemic event.

The level of blood glucose that will exacerbate tissue injury has not been defined. However, the available information indicates that care should be taken to avoid elevation of blood glucose levels (i.e., >150 mg%) in patients at risk of suffering a cerebral ischemic event.[43] This includes those individuals who have suffered an infarct but are at risk of extending the zone of damage. Diabetic patients, in particular, must be carefully managed with insulin. Care should be taken that patients undergoing cerebrovascular surgery are not hyperglycemic prior to the procedure. Intravenously administered solutions containing glucose should be avoided.

Dexamethasone

The administration of dexamethasone or other glucocorticoids has been standard practice for many years for patients suffering acute cerebral ischemia. These agents continue to be given despite the lack of clinical and experimental evidence of their benefit. In fact, dexamethasone might worsen the situation by elevating blood glucose levels in patients suffering recurrent ischemic events. Additionally, a recent report demonstrated a direct deleterious effect of dexamethasone in an experimental model of cerebral ischemia.[45] Consequently, the use of dexamethasone and related drugs is not recommended.

Barbiturates

Barbiturates have been shown to have a protective effect in incomplete ischemia, that is, a situation which usually is present during a focal cerebral ischemic event.[46–49] In contrast, no protective effect has been demonstrated consistently with complete global ischemia.[50] This differential response can be explained partly by the fact that in incomplete ischemia, neuronal function is usually not completely abolished (i.e., at least initially), whereas in complete ischemia it is lost within seconds. Barbiturates have their primary effect upon neuronal electrical activity as opposed to those metabolic activities related to the maintenance of neuronal structural integrity. Accordingly, barbiturates would be expected to have a beneficial effect in incomplete ischemia and not in complete ischemia.

Neuronal function must be abolished by barbiturates for treatment to be effective. Consequently, a state of "barbiturate coma" or deep barbiturate anesthesia is necessary. The level of anesthesia is best monitored by electroencephalography (EEG). The usual goal in the clinical setting is to achieve a state of EEG burst suppression using a short-acting agent such as thiopental. Treatment is effective only when it is started before or at the onset of ischemia. Consequently, it can be initiated readily in the operating room when an ischemic event is deemed likely. A delay in starting treatment as in most clinical settings eliminates its effectiveness and may have a deleterious effect.[51]

Maintenance of deep barbiturate anesthesia is a major undertaking, particularly in the ward setting. Cardiac depression and hypotension are common side effects. Any reduction in systemic arterial blood pressure should be treated with pressor agents. The duration of treatment has to be tailored to the individual patient.

Other agents

There has been considerable recent interest in the use of the volatile anesthetic agent, isoflurane, in treating incomplete ischemia.[50] Isoflurane can produce an isoelectric EEG at concentrations that are hemodynamically tolerated. As well, this agent has minimal effects on intracranial pressure. Despite these favorable features, further studies will be needed to establish its efficacy and safety in this setting.

Preliminary studies with naloxone were encouraging and suggested that endorphins might contribute to ischemic brain damage.[52] Subsequent studies failed to substantiate the early findings and have reduced the enthusiasm for this approach.[53,54]

Conclusions

Treatment of acute focal cerebral ischemia must be started early if damage is to be prevented or limited. In the usual clinical setting, treatment is often ineffective because it is started too late. In patients undergoing cerebrovascular or car-

diovascular surgery with their potential risk of ischemia, however, the physiological state of the patient can be optimized and drug therapy can be initiated in anticipation of the onset of an ischemic challenge. Although it is difficult to prove a beneficial effect in any given patient, the findings of experimental and clinical studies strongly suggest that the situation can be favorably modified with resultant reduction of morbidity and mortality.

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