Effect of intrathecal fibrinolysis on cerebrospinal fluid absorption after experimental subarachnoid hemorrhage

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The effect of intrathecal fibrinolysis on cerebrospinal fluid (CSF) absorption was investigated after experimental subarachnoid hemorrhage (SAH). In 11 cats, SAH was induced by intracisternal application of 1 to 4 ml of fresh autologous blood. Thirty minutes after the experimental SAH, the CSF outflow resistance was found to be elevated from a median of 77 mm Hg/ml/min (range 41.3 to 109 mm Hg/ml/min) to a median of 580 mm Hg/ml/min (range 104 to 7000 mm Hg/ml/min). A logarithmic relationship could be demonstrated between the volume of subarachnoid blood and the elevation of the CSF outflow resistance. The intrathecal application of 2 mg of recombinant tissue plasminogen activator (rt-PA), which is a fibrinolytic substance suitable for lysis of subarachnoid blood clots in man, resulted in almost total restoration of CSF absorption after experimental SAH. The CSF outflow resistance after SAH was lowered by application of rt-PA from a median of 1028.05 mm Hg/ml/min (range 394 to 7000 mm Hg/ml/min) to 79 mm Hg/ml/min (range 56.7 to 223 mm Hg/ml/min). It is concluded that the impairment of CSF absorption after SAH may play an important role in the pathogenesis of post-hemorrhagic vasospasm.

KEY WORDS: subarachnoid hemorrhage · cerebrospinal fluid absorption · hydrocephalus · fibrinolysis · vasospasm

Acute hydrocephalus, defined as significant ventricular dilatation, has been observed in about 20% of all patients suffering from subarachnoid hemorrhage (SAH) and is considered to be the result of acute impairment of cerebrospinal fluid (CSF) absorption. However, even without demonstrable ventricular dilatation, it has been shown by CSF outflow resistance studies that CSF absorption may be impaired to a certain degree. These clinical observations are substantiated by several investigations which have demonstrated the acute and irreversible elevation of CSF outflow resistance after experimental SAH. Thus, impairment of CSF absorption seems to be a common pattern after SAH.

Mechanical obstruction of the CSF outflow pathways by clotted blood within the basal cisterns is considered to be the mechanism responsible for the acute impairment of CSF absorption after SAH. Fibrin has been demonstrated to play an important role in the impairment of CSF absorption, as it clogs the CSF outflow within the arachnoid villus. Apart from the induction of acute post-hemorrhagic hydrocephalus, the impairment of CSF absorption after SAH prevents the removal of substances such as lipids, proteins, erythrocytes, and other particles from the CSF, as this activity depends on CSF outflow. This mechanism may be an important causative factor in the pathogenesis of cerebral vasospasm. These suggestions are substantiated by the well-documented coincidence of cerebral vasospasm and hydrocephalus, as demonstrated by several clinical investigations.

Recently, it has been shown by Findlay and coworkers and by Seifert, et al., that by intrathecal application of the second-generation fibrinolytic substance, recombinant tissue plasminogen activator (rt-PA), experimentally placed cisternal blood clots can be reliably removed with consequent prevention of angiographic vasospasm. As obstruction of the CSF outflow pathways is mainly the result of clotted blood within the subarachnoid space, intrathecal injection of a potent fibrinolytic substance may lead to restoration of CSF absorption. The present study was undertaken to investigate the effect of rt-PA on CSF absorption by evaluating CSF outflow resistance after SAH in cats.
Materials and Methods

Animal Preparation

Cats of both sexes, each weighing between 2.6 and 4 kg, were used for the experiments. Anesthesia was induced by intramuscular injection of ketamine, 30 mg/kg, and maintained with continuous infusion of ketamine at a rate of approximately 30 mg/hr combined with pancuronium at a rate of 0.8 mg/hr. Thereafter, animals were intubated endotracheally and mechanically ventilated using a small animal respirator. Arterial blood gas parameters were checked routinely and kept within normal limits. The femoral blood vessels were catheterized for continuous arterial pressure recording and for continuous administration of drugs. Physiologically, the body temperature was maintained by a heating blanket. The animal was placed in the supine position with the head in a stereotactic frame and the external auditory canals approximately 5 cm above the heart. The scalp was reflected and, through a drill hole in the skull, a No. 18 needle was introduced stereotactically into the right ventricle 3 mm lateral to the midline and 7 mm posterior to the bregma. This catheter was used to measure ventricular fluid pressure. Fluid leaks at the puncture site were sealed by closing the drill hole with heated wax. The cisterna magna was cannulated percutaneously with a No. 20 catheter used for injection of test solutions.

Experimental Protocol

Starting from a stable baseline intracranial pressure (ICP) level, CSF outflow resistance was estimated by means of the bolus technique as described by Marfoum, et al. After intracisternal injection of 0.3 ml of saline, outflow resistance was calculated using the baseline ICP measured prior to the test, the peak value of ICP obtained immediately after the injection, and the ICP measured 2 minutes after the injection. The following formula was used:

\[ PVI = V(\log(P_m/P_o) \times t + \log(P_o/P_m) \times (P_m - P_o)/(P_t - P_o))] \]

where PVI is pressure-volume index (in ml), \( P_o \) is baseline ICP (in mm Hg), \( P_m \) = maximum pressure (in mm Hg) after bolus injection, \( P_t \) = ICP (mm Hg) at time \( t \) after injection, \( V \) = injected bolus volume (in ml), and \( R_o \) = CSF outflow resistance (in mm Hg/ml/min).

When a stable ICP baseline was reached, approximately 30 minutes after the above-described measurements were obtained, SAH was induced by continuous infusion of nonheparinized fresh autologous arterial blood into the cisterna magna at an infusion rate of 0.6 ml/min. Thirty minutes after SAH, resistance to CSF absorption was measured as described above. In six animals, 2 mg of rt-PA in 2 ml of saline was injected intracisternally. In two animals, rt-PA was infused at a constant rate of 0.1 ml/min. In order to prevent an increase of ICP, rt-PA was injected slowly into the cisterna magna in the other four. In three control animals, only saline was infused at the same infusion rate. After a further 30-minute interval, the CSF outflow resistance was estimated using the bolus technique. Arterial blood pressure and ICP were recorded continuously on a polygraph.

Results

CSF Outflow Resistance After SAH

The intracisternal application of fresh arterial autologous blood resulted in an increase of the CSF outflow resistance in all animals. The median value rose from 77 mm Hg/ml/min (range 41.3 to 109 mm Hg/ml/min) to 580 mm Hg/ml/min (range 104 to 7000 mm Hg/ml/min). This increase was significant (p < 0.01, Wilcoxon test). A dose-dependent exponential relationship between the volume of subarachnoid blood and the elevation of CSF outflow resistance could be observed (Fig. 1).

After intracisternal application of 3 or 4 ml of blood, a constant severe obstruction of the CSF absorption was found. In these animals, ICP remained elevated for a prolonged period after intracisternal bolus injection of saline, which was performed in order to estimate CSF outflow resistance. In one animal a paradoxical rise of ICP was found following the initial ICP peak after the bolus test (Fig. 2). This behavior of ICP is also found clinically after SAH in man and results from severely elevated CSF outflow resistance.

Effect of rt-PA Injection

The effect of rt-PA injection on the CSF outflow resistance was investigated in six animals. This procedure severely impaired CSF absorption after intracisternal application of 3 or 4 ml of blood. To avoid a marked ICP increase during the infusion of 2 mg of rt-PA at a rate of 0.01 ml/min, the infusion was interrupted repeatedly in four of these animals whenever the ICP rose above 50 mm Hg. In the other two animals,

![Fig. 1. Logarithmic presentation of the resistance to cerebrospinal fluid (CSF) absorption in relation to blood volume (ml) injected into the cisterna magna in 11 cats.](image-url)
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The infusion was continued despite the severe ICP increase. In all animals, the drug was administered within 30 minutes. After another 30-minute interval, CSF outflow resistance was estimated again. In all of these animals, CSF absorption was restored almost completely after rt-PA injection. The outflow resistance fell from a median of 1028.05 mm Hg/ml/min (range 394 to 7000 mm Hg/ml/min) to a median of 79 mm Hg/ml/min (range 56.7 to 223 mm Hg/ml/min). This decrease was significant (p < 0.01, Wilcoxon test). In this group, the median outflow resistance after rt-PA infusion was only slightly elevated as compared with the control value prior to SAH (Fig. 3).

The improvement of CSF absorption after infusion of rt-PA is reflected by the time course of ICP after a bolus injection of saline (Fig. 4). To exclude the possibility that this effect of rt-PA is mainly the result of washing out the subarachnoid space with infused fluid, a continuous infusion with saline 30 minutes after SAH at the same rate of 0.1 ml/min was performed in three further cats. In all three animals, CSF outflow resistance remained elevated despite the infusion of saline. Only a slight, nonsignificant fall in the CSF outflow resistance from a median of 1845 mm Hg/ml/min (range 400 to 1887 mm Hg/ml/min) to a median of 1600 mm Hg/ml/min (range 350 to 1700 mm Hg/ml/min) could be observed.

In the two animals in which rt-PA was given by continuous and not interrupted intracisternal infusion at a rate of 0.1 ml/min, ICP rose to 80 and 120 mm Hg, respectively, then displayed a plateau phase at this level. Five or 10 minutes later, ICP began to decrease slowly, reaching baseline levels after 25 or 30 minutes despite continued infusion. This effect was not observed during saline infusion after SAH and can therefore only be explained by a fall of CSF outflow resistance induced by the infusion of rt-PA (Fig. 5).

Discussion

Our results concerning the elevation of CSF outflow resistance after SAH are in good agreement with the experimental investigations of others. Furthermore, they are substantiated by clinical observations demonstrating the acute impairment of CSF absorption after SAH.

FIG. 2. Typical time course of intracranial pressure (ICP) after intracisternal bolus injection of 0.3 ml saline in three animals. Left: Recording in a cat without subarachnoid hemorrhage (SAH) (calculated outflow resistance 43 mm Hg/ml/min). Center: Recordings in a cat with SAH using a volume of 4 ml intracisternal blood (calculated outflow resistance 1885 mm Hg/ml/min). Right: Recording in a third animal showing a paradoxical rise of ICP after the bolus test caused by fluctuations of the arterial blood pressure.

FIG. 3. Logarithmic presentation of cerebrospinal fluid (CSF) outflow resistance in six animals prior to and after subarachnoid hemorrhage (SAH) as well as after application of recombinant tissue plasminogen activator (rtPA). Each line represents one animal.

FIG. 4. Typical time course of intracranial pressure (ICP) after intracisternal bolus injection of 0.3 ml saline in one animal prior to subarachnoid hemorrhage (SAH) (left), after induction of SAH with injection of 4 ml of blood (center), and after application of 2 mg of recombinant tissue plasminogen activator (rtPA) (right). CSF = cerebrospinal fluid.

FIG. 5. Typical time course of intracranial pressure (ICP) during recombinant tissue plasminogen activator (rtPA) infusion at a rate of 0.1 ml/min after experimental subarachnoid hemorrhage. The ICP began to fall 10 minutes after the start of the infusion and reached baseline levels within 25 minutes despite continued infusion.
Tissue Plasminogen Activity and CSF Absorption

The present study indicates that impaired CSF absorption after SAH may be restored by the intrathecal application of rt-PA. This important effect of a fibrinolytic agent on CSF absorption after SAH substantiates the results of Blasberg and coworkers, who examined the effect of heparin on the impairment of CSF absorption after SAH. It is furthermore demonstrated that this effect of rt-PA is not produced simply by irrigation of the CSF space, as the cisternal infusion of saline alone did not improve CSF absorption after SAH. The decrease of ICP during infusion of rt-PA despite continued volume loading of the CSF space demonstrated that the effect of rt-PA started some minutes after its intrathecal application.

Fibrin and Impaired CSF Absorption

Our work supports the results of other investigations concerning the role of fibrin for impairment of CSF absorption after SAH. Davson, et al., demonstrated that CSF outflow resistance is irreversibly elevated by whole blood as well as by plasma. In addition, Butler, et al., found that CSF outflow resistance is markedly elevated by plasma but not by serum. They demonstrated fibrin layers within the arachnoid villi, which they assumed to be the anatomical correlate responsible for the raised CSF outflow resistance.

The important pathogenic role of fibrin for elevation of the CSF outflow resistance is well documented during experimental meningitis. Impairment of CSF absorption is also known to be the result of blockage of the arachnoid villi after intracisternal applications of washed erythrocytes. However, according to our data as well as the results of others, fibrin should be a major pathogenic factor responsible for the irreversible post-hemorrhagic impairment of CSF absorption. This is substantiated by the observation that the use of antifibrinolytic agents seems to increase the rate of hydrocephalus after SAH.

Prevention of Vasospasm

Based on the results of the present investigation as well as the well-documented ability of rt-PA to prevent cerebral vasospasm after experimental SAH, an intact CSF absorption mechanism may be an additional important factor for the prevention of cerebral vasospasm after SAH, as it enables the removal of spasmodenic substances from the CSF. As rt-PA improves the CSF absorption after SAH, it may be concluded that this agent prevents vasospasm by 1) premature lysis of the subarachnoid blood clots and 2) facilitation of a rapid clearance of the breakdown products of subarachnoid blood from the CSF through the arachnoid villi. This hypothesis is substantiated by the fact that clinical administration of antifibrinolytic agents, given in order to prevent rebleeding from a ruptured aneurysm, results in a strong increase of vasospasm.

Further investigations are needed to establish the relationship between CSF absorption and the incidence of cerebral vasospasm after SAH. It is suggested that this mechanism could form the pathophysiological basis for new therapeutic possibilities in the prevention of cerebral vasospasm after SAH.

References

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