Hemorrhagic Complications of Thrombolytic Therapy in Experimental Stroke

Andrew Slivka, MD, and William Pulsinelli, MD, PhD

Recent success with thrombolytic therapy for acute myocardial infarction has stimulated interest in its use for stroke. To determine the hemorrhagic potential of thrombolytic therapy in experimental cerebral infarction, we compared a group of tissue plasminogen activator-treated rabbits (n = 4) with 2 groups of streptokinase-treated rabbits (n = 6 in each), as well as with 3 groups of heparin-treated rabbits (n = 5 in each) and untreated controls (n = 12). Focal cerebral infarction was produced in rabbits by occlusion of the right common carotid and middle cerebral arteries coupled with 2 hours of halothane-induced hypotension. Treatment with heparin or thrombolytic agents began 24 hours after occlusion. One additional group was treated with streptokinase 1 hour after occlusion (n = 6) to determine the hemorrhagic potential of thrombolytic agents in evolving infarction. Rabbits were killed 29–33 hours after occlusion, and brain sections were examined using light microscopy. The results demonstrate that microscopic hemorrhage is frequently present in infarcted tissue irrespective of treatment. Gross cerebral hemorrhage did not occur in untreated rabbits or in rabbits treated with streptokinase 1 hour after occlusion. Only rabbits treated with streptokinase, tissue plasminogen activator, or excessive doses of heparin 24 hours after occlusion, at a time when cerebral infarction was well established, exhibited gross hemorrhage in the area of infarction. These data suggest that treatment of ischemic stroke with thrombolytic agents carries an increased risk of cerebral hemorrhage unless the agents are given early after the onset of symptoms.

Materials and Methods

Focal Ischemia

Rabbits were chosen as the experimental animal because in vitro there is a greater similarity between human and rabbit clot lysis caused by human tPA than there is between human and dog or rat clot lysis. Furthermore, the thrombolytic efficacy of human tPA in rabbits has been demonstrated in vivo. New Zealand white rabbits (2.0–3.0 kg) of either sex were anesthetized initially with 5% halothane; the halothane concentration was reduced to 2.5–4.0% during the surgical procedure. The right common carotid artery (CCA) was exposed through a midline neck incision and occluded with 4-0 surgical silk. A PE-50 polyethylene cannula was inserted into the proximal CCA and kept patent with a minimal amount of dilute (10 U/ml) heparinized saline.

The right middle cerebral artery (MCA) was exposed transorbitally, in a manner different from that previously described in other species. After collapsing...
the eyeball, the posterior contents of the orbit were separated from the bony orbit. The lacrimal gland was removed, and the orbital contents were retracted from the exposed bone. The temporalis muscle was dissected from its insertion over a bony prominence, and a small craniotomy 3–4 mm in diameter was drilled just medial to this bony landmark. Using a microligature carrier, 9-0 surgical silk was passed around the proximal MCA and tied to occlude the artery. The craniotomy was covered with gelfoam, and the orbit was packed with a 2 x 2 in. gauze sponge; the eyelids were sutured together. Bleeding was minimal and was controlled by the application of gelfoam. Body temperature was maintained at 37° C throughout the procedure with a heat lamp connected to a rectal thermistor. 

Pilot studies indicated that occlusion of the right CCA and MCA did not consistently produce cerebral infarction. However, reliable infarction could be produced by the addition of halothane-induced hypotension to a mean arterial blood pressure of 30 ± 4 mm Hg for 1.5–2 hours. Anesthesia was then discontinued, and the rabbits were allowed to recover for 24 hours. Rabbits were anesthetized with halothane and decapitated 29–33 hours after MCA occlusion.

Physiologic Variables

Carotid artery pressure was monitored throughout the surgical procedure, during the period of hypotension, and for up to 20 minutes after the anesthesia was discontinued. \( P_{O_2}, \ P_{C_0_2}, \) and arterial blood \( \text{pH} \) were measured just after CCA cannulation, before MCA occlusion, twice during the hypotensive period, and 5–15 minutes after the halothane was stopped. Hematocrit was measured before occlusion and again just before decapitation.

Experimental Design

The experimental design is outlined in Table 1. All groups except 1 were treated with heparin or fibrinolytic agents 24 hours after MCA occlusion. One group (Group IV) was treated with SK 1 hour after occlusion of the MCA to determine the hemorrhagic potential of thrombolytic agents in evolving infarction.

All drugs were administered through the carotid cannula directed toward the heart. A Razel pump (Razel Scientific Instruments, Stanford, Conn.) was used to administer drugs by continuous infusion. Heparin (porcine intestine, Elkins-Sinn, Cherry Hill, N.J.) doses were chosen to increase the partial thromboplastin time (PTT) to approximately twice control values in Group I rabbits and to >150 seconds in Group II rabbits. The dose used in Group III was about double that used in Group II (Table 1). The 2 SK (Sigma Chemical Co., St. Louis, Mo.) doses were chosen because they were shown to be effective in producing thrombolysis in rabbit venous thrombosis models.\(^7,10\) Natural tPA (50,000 U/mg) obtained from melanoma cell culture (Eli Lilly and Co., Indianapolis, Ind.) was used at a dose (17,000–25,000 U/kg/hr; 0.34–0.5 mg/kg/hr) that produced fibrinolysis when given in a rabbit pulmonary embolus model (N. Bang, personal communication).

Brain Histology

After decapitation, the rabbit brains were rapidly removed from the cranium and placed in neutral buffered formalin for a minimum of 1 week. They were then cut into 6 0.5-cm coronal sections, dehydrated, and embedded in paraffin. Sections 12 \( \mu \text{m} \) thick were cut from each of the 6 blocks and stained with hematoxylin and eosin. Microscopic hemorrhage appeared as clusters of red blood cells outside the lumen of blood vessels. Gross hemorrhage was defined as blood that was evident to the unaided eye on freshly cut brain sections and on the stained slides. Gross hemorrhage was used synonymously with hemorrhagic infarction for purposes of discussion. Infarct size was estimated from the number of 0.5-mm coronal slices in which the infarct appeared.

Partial Thromboplastin Time

Blood drawn from either an ear artery or vein into a syringe containing 3.8% sodium citrate (9:1 vol:vol)
was centrifuged at 10,000g for 10 minutes. The supernatant was then centrifuged at 11,700g for 1 minute to obtain platelet-poor plasma (PPP), which was stored on crushed ice and tested within 4 hours. PTTs were obtained platelet-poor plasma (PPP), which was stored on ice. Samples were added to wells of the fibrin plate at time 0, and 10-μl aliquots were taken at 10-minute, 1-, 2-, and 3-hour intervals to quantify the release of $^{125}$I fibrin degradation products. $^{125}$I in these aliquots was measured with a gamma counter.

### Statistical Analysis

The results were analyzed statistically using Fisher’s exact test with the Bonferroni correction. The incidence of gross hemorrhage in each treatment group was compared with that in the control group.

### Results

#### Physiologic Variables

Mean arterial blood pressure ranged from approximately 50 to 60 mm Hg, and arterial blood gases were within physiologic limits during the surgical procedure (Table 2). During the period of hypotension pH commonly fell below 7.30 and $\text{Paco}_2$ increased to >60 mm Hg, though this occurred in both treated and control rabbits. $\text{Paco}_2$ and pH returned to physiologic ranges and blood pressure rose to prehypotensive levels 10–15 minutes after halothane was discontinued. The hematocrit was unchanged over 24 hours in all groups.

### Partial Thromboplastin Times

Mean PTT for Groups I, II, and III are listed in Table 3. The range of preheparin values for all but 3 rabbits was from 32.6 to 106.7 seconds. For unknown reasons, 1 rabbit in Group II and 2 in Group III had pretreatment PTTs of >120 seconds, which explains the large mean and standard deviation in these 2

### Table 2. Physiologic Variables

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During 2 hr occlusion and hypotension

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After anesthesia

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24 hours after occlusion of middle cerebral artery

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groups. Rabbits in Groups II and III had PTTs of >150 seconds for the entire infusion period. Rabbits in Group I had PTTs of >150 seconds within 1.5 hours of starting the infusion, but by the end of the infusion period PTTs were approximately twice control. The variability in results for a single sample of human normal coagulation control, which was measured in conjunction with every rabbit assay, was 0.2-0.3 seconds. This is in contrast to the variability in control and treated rabbits, which was commonly 3-5 seconds and as high as 16 seconds. Although we have no explanation for the variability of PTTs in these rabbits, it did not seriously interfere with our efforts to establish grades of anticoagulation. We wish to emphasize that because of possible species differences in the PTT response to a given heparin dose, the results obtained in Table 3 cannot be translated to PTTs obtained in humans treated with heparin.

**Fibrin Plate Assay**

The fibrin plate assay was used as an index of the total plasma thrombolytic activity achieved in rabbits treated with SK or tPA. As such, the assay measured the capacity of plasma from rabbits treated with SK or tPA to lyse radiolabelled clot (fibrin) in vitro. The release of radioactivity from $^{125}$I-fibrin-coated plates by plasma obtained from rabbits treated with SK or tPA is shown in Figure 1. The maximum cpm obtained when the curves plateau are only qualitative estimates of thrombolytic activity. The results obtained with this assay suggest that the doses of SK and tPA used in our study were sufficient to cause thrombolysis in vivo and that the thrombolytic activity for the dose of tPA was similar to that attained with the lower dose of SK.

**Pathology**

The relation between infarct size and severity of brain hemorrhage for all rabbits is presented in Table 4. Infarct size is expressed as the number of 0.5-mm thick sections (out of a total of 6) in which the infarct appeared. For example, in the control group there was 1 rabbit in which the infarct appeared in only 1 section. This particular rabbit is designated N to signify that no hemorrhage was present in the infarct. Rabbits with microscopic or gross hemorrhage are designated M and G, respectively.

Infarction was present in all rabbits and was localized to the neocortex in all except 3, in which it involved only subcortical structures. Infarction occurred in a single coronal section in 12% (6 of 49), in 2 or 3 sections in 31% (15 of 49), and in 4 or 5 sections in 57% (28 of 49) of the rabbits. Microscopic and gross brain hemorrhage occurred with equal frequency in small (1-3 sections) and large (4—5 sections) infarcts. Gross hemorrhage was present in 19% (4 of 21) of small infarcts and in 25% (7 of 28)
of large infarcts. Two of the 49 rabbits showed infarction with no microscopic hemorrhage. One was treated with SK (Group V) and the other was a control rabbit. In both rabbits the infarcts were small and localized to subcortical structures.

Microscopic hemorrhage occurred in infarcts of control (Figure 2) and treated rabbits. Clusters of red blood cells outside the blood vessels were focally distributed within the infarct. Microscopic hemorrhage was present in multiple sections of the infarction, though it was more uniformly distributed in treated than in control rabbits. Of 43 sections with infarction in the 12 control rabbits, microscopic hemorrhage was found in 34 (79%); in the 37 treated rabbits microscopic hemorrhage was present in 95% (112 of 118) of the sections with infarction.

Of the 12 rabbits treated with SK 24 hours after MCA occlusion (Groups V and VI), 2 had gross hemorrhage within the infarct. Only tPA-treated rabbits (Group VII) showed a significantly greater (p<0.05) incidence of gross hemorrhage than controls. Significance was not demonstrated for either SK group when compared with controls, but because of small sample size a Type II error cannot be excluded. None of the 12 control rabbits or the 6 rabbits receiving SK 1 hour after MCA occlusion (Group IV) exhibited gross hemorrhage. The extent of gross hemorrhage was variable. All rabbits with gross hemorrhage had 1 or more areas of punctate hemorrhage within the margins of the infarct visible to the naked eye (Figure 3, Top). Two rabbits, 1 tPA-treated (Group VII) and 1 SK-treated (Group VI), showed confluent hemorrhage extending over several sections (Figure 3, Bottom). While the incidence of gross hemorrhage in the tPA-treated rabbits (3 of 4) was greater than in those treated with SK (2 of 12), this difference was not significant (Fisher's exact test).

Of the rabbits treated with heparin (Groups I, II, and III) only those with a PTT of >150 seconds for the entire 4-hour infusion period (Groups II and III) exhibited gross hemorrhage. In fact, rabbits from both Groups II and III had a significantly greater (p<0.05) incidence of gross hemorrhage than controls. However, since rabbits were treated for only 4 hours, it is possible that some Group I rabbits would have developed hemorrhage if infusions were continued for longer intervals. Despite the variability of PTT values found in these rabbits, we demonstrated a dose response for the 3 treatment groups in terms of mean PTTs and gross cerebral hemorrhage. The results support the hypothesis that excessive heparinization carries a risk for the development of hemorrhagic infarction.

Discussion

The present study demonstrates that cerebral infarction is frequently associated with microscopic brain hemorrhage in rabbits, regardless of treatment. Whether microscopic hemorrhage is common among other experimental animal models or in humans experiencing focal brain ischemia is unclear since it has been infrequently reported. Careful examination of serial sections through the infarct using light microscopy is necessary to detect such hemorrhage, and its presence may have been overlooked in many studies of brain infarction. Yet, several reports suggest that microscopic hemorrhage within cerebral infarcts is not unique to rabbits and that it may occur with greater frequency in animals and humans than is commonly thought.

In contrast to microscopic hemorrhage, gross hemorrhage is well documented in human and experimental brain infarction. Autopsy studies of patients with ischemic stroke indicate that 18-42% of infarcts are grossly hemorrhagic. Examination of computed axial tomograms (CT) indicate a 5-10% incidence of hemorrhagic infarction. Prospective studies of stroke patients whose initial CTs were nonhemorrhagic show that 11-42% develop hemorrhagic infarction over the next 3 weeks.

While gross hemorrhage occurs most often in the context of temporary brain ischemia, for example reversible MCA occlusion in animals or embolic stroke in humans, permanent brain ischemia may also result in gross hemorrhage. Weinstein et al reported hemorrhagic infarction in 2 of 10 cats and in 10 of 20 dogs subjected to permanent MCA occlusion. In 1 autopsy series, gross hemorrhage was found in approximately 20% of infarcts associated with permanent occlusion of thrombotic origin.

The pathogenesis of hemorrhagic infarction, whether microscopic or gross, is poorly defined. Causative factors can be segregated into those necessary for the initiation of bleeding and others that modify the extent and severity of the hemorrhage. Vascular damage, reflected by dysfunction of endothelial cell transport mechanisms or frank endothelial cell necrosis, seems to be a necessary prerequisite for hemorrhagic infarction. The tendency of infarcts to bleed and the degree of bleeding are undoubtedly influenced by factors such as infarct size, cerebral perfusion pressure, and altered clotting mechanisms. The interaction of these factors in cerebral infarction creates a hemorrhagic spectrum from microscopic to gross.

While vascular damage may be a prerequisite for hemorrhage, experimental data supporting vessel wall necrosis as a necessary factor for hemorrhagic infarction are conflicting. Meyer noted a frequent association between hemorrhage and necrotic vessels in monkeys subjected to permanent MCA occlusion. In contrast, Hain et al demonstrated that leakage of red blood cells from cerebral venules, arterioles, and capillaries was nearly complete before necrosis of endothelial cells occurred. Jorgensen and Torvik found histologic signs of vessel wall necrosis in both pale and hemorrhagic areas of cerebral infarcts but also reported normal vessel walls in many areas with hemorrhage. They postulated that extravasation and diapedesis of red blood cells from damaged, though not necessarily necrotic, vessels was responsible for bleeding.

Vascular injury initiates platelet aggregation and formation of a platelet plug, which is further stabilized
FIGURE 2. Top: Microscopic hemorrhage in control rabbit. Coronal section showing neocortical infarction (pale area outlined by arrows). Section stained with hematoxylin and eosin, 1.5 x. Rectangular area is magnified in left. Left: Rectangular area from top; 26 x. Dark areas represent red blood cells within and outside blood vessels. Rectangular area is magnified in right. Right: Rectangular area from left; 98 x. Note capillary filled with dark-staining red blood cells (large open arrow) and individual red blood cells outside vessels (small arrows).
FIGURE 3. Top: Coronal section from tissue plasminogen activator-treated rabbit showing gross hemorrhage (small arrow) in area of infarction. Infarction of right neocortex is seen as pale area outlined by large arrows. Section stained with hematoxylin and eosin, 1.5× magnification. Bottom: Coronal section of streptokinase-treated rabbit showing neocortical infarction (pale area outlined by large arrows). Note extensive confluent hemorrhage (small arrow) in lateral ventricle and inferior hippocampus outside cortical infarction. Section stained with hematoxylin and eosin, 1.5× magnification.
Thrombolytic Therapy in Stroke

by thrombin and fibrin. Under normal conditions this process may prevent or limit hemorrhage into brain infarcts, but the use of anticoagulants or thrombolytic agents can interfere with this normal clotting mechanism. These drugs may initiate or exacerbate bleeding into an infarct by their direct action on fibrin and thrombin and possibly by their interaction with platelets and plug formation.27-28 In the present study, only rabbits with established brain infarcts (24 hours after MCA occlusion) treated with thrombolytic agents or high doses of heparin showed gross brain hemorrhage. In this regard, tPA showed no apparent advantage over SK and, in fact, rabbits treated with tPA showed a greater incidence of gross brain hemorrhage. This occurred with a dose of tPA that falls within the range used by other investigators in rabbits7,9,30 and is less than the doses used in patients treated for acute myocardial infarction.2,3 Moreover, clinical trials comparing SK and tPA in acute myocardial infarction have not demonstrated a significant difference in the incidence of systemic bleeding complications.2,3 Such results cast doubt on the advantage of tPA versus SK with regard to either cerebral or systemic hemorrhage.

Reestablishing blood flow through a previously occluded artery may initiate or exacerbate hemorrhagic infarction. This so-called reperfusion hemorrhage has been well described experimentally in several animal species subjected to temporary MCA occlusion9,12,23-25 and clinically after emergency carotid endarterectomy for evolving stroke.31-33 Reperfusion is also frequently used to explain the greater tendency toward hemorrhagic infarction with cerebral emboli that cause local vascular injury and then fragment. A common misconception is that blood flow ceases to the vascular territory supplied by an occluded artery and thus reperfusion provides a renewed source of blood cells to the vascular tree. In experimental animals subjected to MCA occlusion, blood flow is preserved, though at severely reduced levels.34-36 Similarly, studies of cerebral blood flow in acute stroke patients have shown reduced but not absent perfusion in the ischemic zone.37,38 Accordingly, a more likely explanation for reperfusion hemorrhage is not a renewed source of blood cells, but rather exposure of damaged vessel walls to the full force of cerebral perfusion pressure through resistance vessels rendered vaso-incompetent by ischemia. By analogy, systemic arterial hypertension can cause hemorrhage in animals subjected to permanent MCA occlusion presumably by increasing the perfusion pressure in collateral channels supplying the ischemic vascular bed.14,27,39

By employing a nonthrombotic permanent occlusion model in the present study, we avoided reperfusion through extracranial or large pial vessels as a mechanism of hemorrhage. Moreover, although the rabbits were temporarily hypotensive, hypertension was not demonstrated and therefore did not contribute to the hemorrhages observed. We conclude that thrombolytic therapy can lead to gross hemorrhagic infarction independent of reperfusion or hypertensive mechanisms. One might speculate that under conditions in which cerebral reperfusion occurs, such as cerebral embolism, the incidence of hemorrhagic infarction with thrombolytic therapy might be further increased provided sufficient time had elapsed for vascular damage to develop.

Since larger infarcts place more cerebral vessels at risk, they might be expected to be hemorrhagic more frequently than smaller infarcts. Some, though not all, clinical20,21 and experimental40 studies report more hemorrhage in larger infarcts. In the present study we found no correlation between infarct size and microscopic hemorrhage in control rabbits. Treated rabbits also showed no apparent relation between the presence of either microscopic or gross hemorrhage and infarct size.

This study demonstrates that SK and particularly tPA administered to animals with established brain infarcts are associated with gross hemorrhage into the infarct. In contrast, our study and the work of others show that when thrombolytic therapy is used within several hours of the onset of ischemic hemorrhagic infarction is less likely.30,41,42 Furthermore, cerebral reperfusion, if accomplished sufficiently early after vascular occlusion, does not cause hemorrhage and significantly decreases the extent of pathologic infarction in experimental animals.13,23,24,43 Therefore, tPA or SK should be given early after the onset of ischemic symptoms to effectively prevent or limit pathologic infarction and simultaneously avoid hemorrhage into an evolving infarct. In experimental animals this therapeutic window can be approximated at <4-6 hours after the onset of focal brain ischemia.13,23,24,43 The precise time when the risk of hemorrhagic complication outweighs the potential benefit of thrombus lysis in humans with acute stroke can be determined only from carefully controlled clinical trials.

Acknowledgments

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References


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