Rapid Reversal of Anticoagulation Prevents Excessive Secondary Hemorrhage After Thrombolysis in a Thromboembolic Model in Rats

Li Sun, MD; Wei Zhou, MD; Robert Ploen, MSc; Sabine Heiland, PhD; Markus Zorn, MD; Roland Veltkamp, MD

Background and Purpose—Thrombolysis is the only approved therapy for ischemic stroke, but secondary hemorrhage is a severe complication. Because oral anticoagulants are believed to increase the risk of hemorrhage, thrombolysis is usually contraindicated in patients on vitamin K antagonists. We studied whether thrombolysis in a thromboembolic middle cerebral artery occlusion model in rats pretreated with warfarin increases secondary hemorrhage, and whether substitution of coagulation factors before thrombolysis prevents hemorrhagic complications.

Methods—Wistar rats were anticoagulated using warfarin in drinking water (0.4 mg/kg per 24 hours). Strength of anticoagulation was monitored using benchside international normalized ratio (INR) coagulometry. Two hours after middle cerebral artery occlusion, recombinant tissue-type plasminogen activator (9 mg/kg) was administered. Two of 5 groups of animals received prothrombin complex concentrate (PCC, 50 U/kg) 15 minutes before thrombolysis. Serial magnetic resonance imaging was performed 20 minutes, 2.5 hours, and 24 hours after middle cerebral artery occlusion. Secondary hemorrhage was quantified on T2* magnetic resonance images as previously established.

Results—Severity of hypoperfusion on initial perfusion-weighted imaging—magnetic resonance did not differ among groups. Thrombolysis resulted in successful reperfusion in all groups. Anticoagulated animals had significantly more secondary hemorrhage and a higher mortality rate compared with nonanticoagulated animals. PCC rapidly reversed the increased international normalized ratio. Although PCC failed to prevent hemorrhage in the strongly anticoagulated, it reduced the incidence of severe hemorrhage in moderately anticoagulated rats (INR, 2–3) to the level of nonanticoagulated controls.

Conclusions—Preceding anticoagulation increases risk and extent of secondary hemorrhage after thrombolysis. Reversal of moderate anticoagulation using PCC may allow thrombolytic therapy without increasing the risk of secondary hemorrhage. (Stroke. 2011;42:00-00.)

Key Words: cerebral ischemia ■ oral anticoagulation ■ thrombolysis ■ hemorrhage

Intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA) is currently the only approved therapy for acute ischemic stroke.1–3 Nevertheless, secondary hemorrhage is a severe complication of thrombolytic therapy. In large clinical trials and registries, symptomatic hemorrhage occurred in 5.2% to 7.3% of ischemic patients receiving rt-PA.4,5 and was associated with worse outcome.6

The already high number of patients receiving oral anticoagulants (OAC) is expected to increase in parallel to the prevalence of atrial fibrillation, the most frequent indication for long-term therapy with vitamin K antagonists (VKA).7 Despite anticoagulation, these patients remain at an elevated risk of suffering ischemic stroke. The optimal management of ischemic stroke in patients on VKA is currently unclear. Because of concerns of excessive bleeding risk, current guidelines recommend to exclude patients with an international normalized ratio (INR) >1.5 (European Stroke Organization) or >1.7 (American Stroke Association), respectively, from systemic thrombolysis.1,3 Whereas chronic treatment with VKA increases long-term risk of intracerebral hemorrhage 2- to 5-fold,8 data on secondary hemorrhage following thrombolysis under effective OAC (INR, 2–3) in ischemic stroke are limited. In small case series, patients received thrombolysis after reversal of anticoagulation,9,10 but the effectiveness and safety of this regimen is unclear.

The purpose of the present study was to determine whether anticoagulation with warfarin increases secondary hemorrhage.
stroke in a thromboembolic ischemia model in rats. We also examined whether treatment with PCC before injection of rtPA prevents excessive bleeding after thrombolysis.

Materials and Methods
All experiments (n=68) were performed on male Wistar rats weighing 300 to 350 g (Charles River Laboratories). The study was approved by the governmental animal care authorities (Regierungspaaesidium Karlsruhe, Germany).

Warfarin Administration and INR Measurement
Pretreatment with warfarin was performed as described with some modifications. Briefly, 2.5 mg of warfarin (coumadin, Bristol-Myers-Squibb) was dissolved in 800 mL of drinking water. Accordingly, rats received approximately 0.12 mg of warfarin per day (0.4 mg/kg per 24 hours). The actual effect of warfarin on coagulation was measured by a point-of-care coagumeter (PoC; Coaguchek XS) as described.

To calibrate INR measurements of the PoC coagumeter, samples from 4 separate rats treated with warfarin were measured daily for 4 days both by the PoC coagumeter and by the standard coagulometric technique used by the central laboratory of the University Hospital Heidelberg (Innovin clotting assay, CA-7000, Siemens Healthcare Diagnostics).

Surgical Procedure
Ischemia was induced using a thromboembolic MCAO model that we previously established based on a previous protocol from Toomey et al. The model has a low rate of spontaneous recanalization after MCAO, but good reperfusion after intravenous thrombolysis (Supplemental Methods).

Experimental Protocol
All animals underwent treatment with rtPA 2 hours after MCAO. Animals were randomly assigned to 1 of 5 groups (Supplemental Figure 1S). Rats in the control group (n=14) received no warfarin. In groups 2 (n=14) and 3 (n=11), rats were pretreated with warfarin for 72 or 96 hours, resulting in moderate (INR, 2–3) or strong (INR, 3.5–5) anticoagulation, respectively. Groups 4 (n=13) and 5 (n=13) were treated as groups 2 and 3, but received IV PCC (Beriplax CSL Behring; 50 U/kg) 15 minutes before thrombolysis. INR was measured after injection of PCC just before thrombolysis.

MRI Measurements
Diffusion-weighted images (DWI), T2*, and postcontrast T1-weighted images were performed 2.5 hours and 24 hours after emboli injection in a MRI scanner (Bruker Biospec, 2.35T). Perfusion-weighted imaging was performed 20 minutes, 2.5 hours, and in surviving rats 24 hours after MCAO to document perfusion status before and immediately after thrombolysis, and at the end of the experiment (Supplemental Methods).

Macroscopic Examination of Secondary Hemorrhage
Twenty-four hours after MCAO, brains were removed. Unstained coronal cryosections were photographed without magnification. Macroscopic evidence of intracerebral hemorrhage was compared with T2* images on corresponding sections.

Assessment of Macroscopic Hemorrhage
Hemorrhage on T2* MRI was classified into 5 categories as previously described: no hemorrhage (score 0); evidence of slightly hypointense T2* signal (score 1); single punctate hemorrhage with high-contrast, hypointense T2* signal of <4 mm² diameter (score 2); multiple punctate hemorrhages with high-contrast, hypointense T2* signal <4 mm² diameter (score 3); and large hemorrhage defined by high-contrast, hypointense T2* signal >4 mm² diameter (score 4). In our previous studies, hemoglobin volume as well as macroscopic bleeding on unstained coronal cryosections corresponded well with the hypointense area on T2* MRI. In animals that died prematurely (ie, before the 24-hour MRI), scoring of hemorrhage was performed on unstained coronal cryosections according to MRI criteria. Hemorrhage scoring of T2* images was performed by 2 independent observers with good interrater reliability (k=0.81; P<0.001; interrater reliability analysis, SPSS).

Statistical Analysis
All values are expressed as mean±SD. For comparison of physiological values and MRI data (except T2* images), ANOVA was used followed by posthoc Fisher Protected Least Significant Difference test. MRI hemorrhage scores were assessed by the Kruskal-Wallis test and then by the Mann-Whitney U test. Correlation of ordinal variables was performed by χ². Mortality was assessed by the Fisher exact test. All analyses were performed using SPSS software. Probability value <0.05 was considered statistically significant.

Results
Calibration of PoC Coagulometer and Coagulation Status Before Thrombolysis
INR measurements by the central laboratory of the same samples correlated well with PoC (Figure 1; r=0.973; P<0.001). Mean baseline INR was 1.0±0.1 in the nonanticoagulated control group, 2.2±0.3 and 2.4±0.4 in the moderately anticoagulated groups 2 and 4, and 4.3±0.5 and 4.1±0.7 in the strongly anticoagulated groups 3 and 5. Fifteen minutes after injection of PCC, INR decreased to 1.1±0.2 in the moderately anticoagulated and 1.1±0.1 in the strongly anticoagulated groups.
Physiological Parameters and Effect of Thrombolysis on Reperfusion

Physiological parameters before MCAO and 5 minutes after the end of thrombolysis (ie, 2.5 hours after MCAO) did not significantly differ among groups (Supplemental Table).

After injection of emboli, lower cerebral blood volume (CBV) resulted in a relatively hyperintense perfusion-weighted imaging signal in the ischemic hemisphere compared with the hypointense signal in the nonischemic hemisphere that is induced by the passage of the paramagnetic contrast agent. Three animals without initial perfusion-weighted imaging changes were excluded. Relative CBV (ischemic/nonischemic) did not differ among groups 20 minutes after MCAO (Figure 2; \(P>0.05\), ANOVA). Thus, ischemia was equally severe in all groups initially. After infusion of rtPA, perfusion-weighted imaging–MRI revealed good reperfusion of the previously ischemic territory 2.5 hours after MCAO in all groups (Figure 2; \(P<0.05\), ANOVA). Relative CBV changes 2.5 hours after embolism did not significantly differ among groups. Thus, effective anticoagulation with warfarin did not enhance reperfusion after thrombolysis. Moreover, perfusion did not differ between moderately anticoagulated animals receiving PCC (group 4) and control animals 24 hours after MCAO (Figure 2; \(P>0.5\)). Hence, administration of coagulation factors before thrombolysis did not attenuate reperfusion.

24-Hour Mortality and Secondary Post-Thrombolytic Hemorrhage

The 24-hour mortality rate was 64% \((n=14)\) in moderately anticoagulated and 100% \((n=11)\) in strongly anticoagulated animals compared with 29% \((n=14)\) in nonanticoagulated control \((P<0.05\); Fisher exact test). With PCC treatment, mortality rate in moderately anticoagulated animals \((31%; n=13)\) was identical with that of the control group. In contrast, 24-hour mortality was significantly increased in animals with high INR and PCC treatment \((n=13)\) compared with control group \((69% \text{ versus } 29%; P<0.05)\). Interestingly, all animals that prematurely died had extensive secondary cerebral hemorrhage on cryosections of brains harvested postmortem \((hemorrhage \text{ score}, 3–4)\).

T2*-weighted MR imaging, which correlated well with macroscopic bleeding on unstained cryosections, was used to detect intracerebral hemorrhage (Figure 3). We first analyzed hemorrhage on T2* images 2.5 hours after MCAO in all groups. In the control group, hemorrhage was observed in 9/14 animals, and only 3 animals had a hemorrhage score \(\geq 2\). In contrast, hemorrhage was observed in all animals in groups 2 and 3 receiving warfarin and hemorrhage scores \(\geq 2\) were more frequent, especially in INR \(>3.5\) \((P<0.05\); Mann-Whitney \(U\) test; Figure 4). After receiving PCC before thrombolysis, 9/13 animals with INR 2 to 3 \((group 4)\) showed any hemorrhage at 2.5 hours, but only 3/13 animals had hemorrhage scores 2 to 3. Compared with the control group, no significant differences of hemorrhage incidence and severity were detected in this group. In animals with high INR and PCC treatment, \((group 5)\) thrombolysis resulted in a lower incidence of hemorrhage scores 2 to 4 compared with corresponding animals without PCC therapy \((group 3)\) 2.5 hours after MCAO. However, secondary hemorrhage was still significantly increased compared with the nonanticoagulated control group \((Figure 4)\).

A high 24-hour mortality in anticoagulated animals limited the prespecified assessment of hemorrhage on 24-hour MRI in prematurely dying animals. We addressed this problem by...
scoring hemorrhage 24 hours after MCAO using both T2*-MRI and unstained coronal cryosections. Secondary hemorrhage increased 24 hours after MCAO in all groups. Eight animals in the control group had a hemorrhage score ≥2 at this time point. All anticoagulated animals in groups 2 and 3 had extensive hemorrhage (scores, 3–4). In contrast, rate and severity of secondary hemorrhage did not differ between moderately anticoagulated animals with PCC and control (Figure 4). In animals with high INR and PCC treatment (group 5), hemorrhage was significantly increased compared with the control group (*P<0.05; Mann-Whitney U test; Figure 4).

**Early Blood–Brain Barrier Damage**

Our previous findings showed that early appearance of blood–brain barrier damage (BBBD) on T1-weighted images 2.5 hours after MCAO reveals tissue at risk for subsequent secondary hemorrhage 24 hours after MCAO.12,13 Thus, we performed early postcontrast T1-weighted MR images as a surrogate parameter of subsequent hemorrhage in the present study. Volumes of enhancement on T1-weighted images at this time point were substantially increased in groups 2 and 3 under anticoagulation compared with controls. In contrast, no differences of postischemic BBBD were detected in animals in group 4 compared with in controls. Animals in group 5 had decreased BBBD compared with animals without PCC. However, BBB damage was significantly larger compared with in controls (Figure 5).

**PCC Did Not Increase Ischemic Lesion**

No significant differences on DWI lesion volume were seen 2.5 hours after MCAO (P>0.5; ANOVA; Figure 6). To examine whether the administration of PCC before thrombolysis affects the ischemic lesion volume, DWI MR was measured also 24 hours after MCAO in surviving animals in the control group and in group 4. DWI lesions were 363±65 mm³ in controls and 387±73 mm³ in the PCC group (P>0.5; Figure 6), respectively. Hence, PCC did not increase infarct size after thrombolysis.

**Discussion**

The present translational study provides 3 major new findings: pretreatment with warfarin dose-dependently increases the risk and severity of secondary hemorrhage after thrombolysis, reversal of moderate anticoagulation by PCC before thrombolysis results in a similar bleeding risk and equal mortality compared with rats without warfarin pretreatment, and administration of PCC does not attenuate the effect of rtPA on reperfusion in this model.

To date, therapeutic or elevated INR >1.7 values are considered contraindications for systemic thrombolysis after...
ischemic stroke. However, these management guidelines are based on plausibility rather than on experimental or clinical data. Whereas the majority of studies regarding thrombolysis in anticoagulated patients with subtherapeutic or lower INR (<1.7) showed no increased risk of secondary hemorrhage after thrombolysis in patients with INR <1.7, a recent study reported a nearly 10-fold higher risk of secondary hemorrhage in anticoagulated patients with INR <1.7 compared with those without OAC. However, that study was small and baseline age was significantly higher in the anticoagulated group, which increases the likelihood of secondary hemorrhage. More importantly, it is largely unknown whether therapeutic anticoagulation levels (INR, 2–3) increase the risk of secondary hemorrhage after thrombolysis. The present study shows for the first time that pretreatment with VKA indeed increases the frequency and severity of secondary hemorrhage after thrombolysis, and that a stronger level of anticoagulation is associated with a higher risk of this serious adverse event. Interestingly, these findings are consistent with a recent Murine study modeling ischemia–reperfusion by means of filament removal instead of by thrombolysis.

Previous clinical studies reported that stroke patients under therapeutic anticoagulation with warfarin had substantially smaller infarct sizes. It has been hypothesized that therapeutic anticoagulation accelerated spontaneous lysis of thrombus. However, in our experimental study, no significant differences of reperfusion were observed between control and anticoagulated animals with different levels of anticoagulation. Our data suggest, rather, that the beneficial effect of anticoagulation results rather from prevention of development of large thrombi.

From a translational perspective, the most relevant finding of our study is that normalizing INR values by PCC administration in moderately anticoagulated rats (INR, 2–3) reduced secondary hemorrhage after thrombolysis to the levels of nonanticoagulated animals. Indeed, the vast majority of ischemic strokes in patients on OAC occur when the INR is below or within the therapeutic range (ie, INR, 2–3). Nevertheless, it is unclear why normalization of the INR was not equally effective in strongly anticoagulated rats. An alternative explanation for the lack of effect of PCC on hemorrhage and mortality in the strongly anticoagulated group is that normalization of INR values may not fully reflect the coagulation status. For example, the monitoring of INR fails to assess levels of factor IX and factor VII appropriately. Theoretically, the INR may rise to higher levels again after PCC administration in the following hours because of the limited half life of certain coagulation factors and the long half life of warfarin in humans. However, this is unlikely in our experimental model as the half life of warfarin is considerably shorter in rodents than in humans, and a secondary increase of the INR does not occur in rats.

Would rapid administration of coagulation factors (eg, PCC) as performed in the present experimental study be feasible in acute human ischemic stroke before thrombolysis? Emergency replacement of coagulation factors, such as PCC, has been used to prevent hematoma growth in warfarin-associated intracerebral hemorrhage for many years. Recently, we showed that the use of a PoC INR coagumeter can hasten the initiation of thrombolysis. Moreover, the PoC coagumeter can be used for bedside monitoring of rapid INR reversal in anticoagulated patients. An important caveat is that the present experimental study cannot rule out thromboembolic complications resulting from rapid PCC application. Administration of PCC, which is usually performed in the context of bleeding during therapy with VKA, may occasionally induce a hypercoagulable state that predisposes patients to thromboembolic side effects. Nevertheless, it is unknown whether PCC attenuates the thrombolytic effect of rtPA in clinical stroke. In the present study, we did not find any evidence of a counteractive effect of PCC on thrombolysis in this experimental context. However, we did not assess neurological function. Additional studies are needed to assure the safety of PCC administration especially in the clinical setting.

In conclusion, our experimental results confirm that effective anticoagulation with warfarin should be a contraindication for systemic thrombolysis in acute ischemic stroke. Rapid reversal of anticoagulation using PCC before thrombolysis may be a promising approach for the increasing number of patients suffering an acute ischemic stroke while under OAC with VKA.

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Disclosures
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References


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Supplemental Material

Supplemental Methods

Preparation of clots from blood drawn from separate donor rats
500 µL of fresh arterial blood from a donor rat were drawn into an Eppendorf tube and mixed with 1.0 National Institutes of Health (NIH) unit of human thrombin (Sigma Aldrich) and 5 µL of 1mol/L CaCl₂ for a final CaCl₂ concentration of 10mmol/L. Within 5 seconds, a small portion of the mixture was drawn into a 15-cm-long PE-50 tube and allowed to coagulate for 2 h at 37 °C. Then, the clot was transferred from the tube into a petri dish which was then filled with saline and stored at 4 °C for 12 h. Before MCAO, the clot was incubated in deionized water at room temperature for 5 min. Subsequently, the clot was placed into isotonic saline and inspected under a microscope at fivefold magnification. Twelve thrombi - each 0.35 mm in diameter and 1.5 mm in length - were cut under the microscope and then drawn into PE-50 tubing.

Surgical Procedure
Anaesthesia was induced with 4% halothane in O₂ and continued with 0.8–1.2% halothane in a 70/30 mixture of nitrous oxide/oxygen under spontaneous respiration. During surgery, rectal temperature was maintained at 37°C. The femoral artery and vein were cannulated for continuous monitoring of arterial blood pressure and heart rate, to provide samples for blood gas measurements, and to inject the MR contrast agent and rt-PA.

The right external carotid artery (ECA) and the internal carotid artery (ICA) were dissected. The ECA stump was permanently ligated and mobilized. The pterygo-palatine artery, an extracranial branch of the ICA, was ligated. A PE-50 catheter with 12 clots was inserted into the right ECA stump proximal to the ligation and advanced from the ECA into the ICA. The tip of the catheter was placed just beyond the origin of the pterygo-palatine artery. The catheter was inserted into the right ECA proximal to the ligation and advanced through the bifurcation into the proximal internal carotid artery (ICA). Ischemia was induced by injecting the 12 clots into the ICA over a 30-s period with 50 µL of saline. Twenty minutes after MCAO, perfusion–weighted MR imaging (PWI) was performed in a MRI scanner (Bruker Biospec, 2.35T) to ensure hypoperfusion in the territory of the occluded MCA. After removing the catheter, ligating the proximal ECA and closing the neck, rats were allowed to wake up.

MRI sequences
For diffusion-weighted MRI, we acquired a spin-echo--echo-planar imaging (SE-EPI) sequence (TR = 8000 ms, TE = 71.2 ms, matrix = 128x 64, field of view = 4 cm x 4 cm, 16 slices, slice thickness = 0.75 mm, NA=8, b values = 200 and 700 s/mm² in 6 directions). T2*-weighted imaging was performed 2.5 and 24 h after emboli injection with a multiecho fast low angle shot (FLASH) sequence (TR= 1500 ms, TE= 5.5, 11, 16.5 … 44ms, flip angle=25°, matrix 256x256, FOV= 4cm x 4cm, number of slices=6, slice thickness = 1.5 mm and NA=1). For perfusion-weighted imaging (PWI), we used a gradient-echo--echo-planar imaging (GE-EPI) sequence (repetition time = 800ms, echo-time = 25 ms, field of view = 4 cm x 4 cm, matrix: 64x64, 8 slices, slice thickness = 1.5 mm, 40 repetitions with a time resolution of 0.8 s/image data set) to monitor the bolus passage of 1 mmol/kg of a paramagnetic contrast agent (Omniscan, Nycomed Amersham, Oslo, Norway). The MR protocol also comprised a T1 spin-echo sequence (TR = 800 ms, TE = 25 ms, matrix =256x 192, field of view 4 cm x 4 cm, 8 slices with slice thickness = 1.5 mm).
**MRI data analysis**

For analysis of PWI, the relative cerebral blood volume (rCBV) and the relative mean transit time (rMTT) were calculated in two predefined corresponding regions of interest of both hemispheres from the signal-time curve determined from the PWI data set as previously described\(^1\). DWI and T1w data were analyzed by encircling areas of abnormal signal intensity for each MR section using a side-to-side comparison on the screen. Volume of abnormally hyperintense signals on DWI was calculated by multiplying the total area by a 0.75-mm section thickness. Abnormally hypointense signal on T2* reflecting macroscopic hemorrhage was analyzed on sections by TE= 33ms. All of assessments were performed blindly.

Supplementary figure 1. Schematic overview of experimental groups and design.

Supplementary figure 2. Brain water content (A) and brain swelling (B) were determined in surviving animals with INR 2 to 3 (group 4, n=9) with PCC therapy and control animal (group 1, n=10) 24h after MCAO. No significant difference was observed between these two groups.
Supplementary figure 3. Multimodal MRI images showing the topography of the perfusion status (PWI before and 24h after rt-PA), parenchymal infarct (DWI at 24 h), BBB permeability (postcontrast T1w at 2.5 h), and hemorrhage (T2* at 24h) in two rats receiving PCC treatment. A: rat with INR 2-3, B: rat with INR 4-5.

Supplemental table Physiological parameters

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<th>Parameter</th>
<th>Group1 (n=14)</th>
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