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ORIGINAL RESEARCH

Ischemic and Hemorrhagic Complications after Intra-Arterial Fibrinolysis in Vertebrobasilar Occlusion

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BACKGROUND AND PURPOSE: To evaluate the incidence and location of hemorrhagic and ischemic lesions after local intra-arterial (IA) fibrinolysis in patients with acute vertebrobasilar occlusion (VBO).

METHODS: One hundred forty-three patients with VBO treated with local IA fibrinolysis were retrospectively evaluated. Two different thrombolytic substances, namely urokinase (UK, $n = 57$ patients) and recombinant tissue plasminogen activator (rtPA, $n = 86$ patients), were used. Incidence and location of intracranial hemorrhage and ischemic infarction were assessed by means of 403 peri-interventional CT and MR imaging scans. Recanalization success and bleeding rate were correlated with the type and dosage of fibrinolytic agent. Multiple logistic regression was used for statistical analysis.

RESULTS: Intracranial hemorrhage was detected in 46 (32%) patients. Bleeding rate was significantly higher for high-dose rtPA than for UK (36% versus 21%, $P < .01$). Neurologic outcome was worse in patients with postinterventional bleeding ($P < .001$). Ischemic infarctions were present in 136 (95%) patients. Ischemic lesions of the occipital lobe and thalamus were more frequently seen in the case of successful recanalization than after absent recanalization ($P < .005$). Occlusion of the postcommunicating segment of the posterior cerebral artery after successful recanalization was seen in 39% of patients.

CONCLUSIONS: In acute VBO, bleeding rate after IA rtPA seems to be higher than that using IA UK, especially after high-dose rtPA. Ischemic lesion patterns after successful local IA fibrinolysis are common and correspond to the frequent distal migration of the thrombus. Novel recanalization techniques allowing for endovascular thrombectomy are needed to reduce ischemic and hemorrhagic complications in the treatment of acute VBO.

Acute vertebrobasilar artery occlusion (VBO) is a catastrophic disease. Mortality rate is reported to be 80%–90% in patients treated with nonthrombolytic drugs.[1-2] Local intra-arterial (IA) fibrinolysis has increased the recanalization rate up to 70% and decreased mortality rate to 40%–60%.[3-5] Despite this, the neurologic outcome is frequently poor even after successful endovascular recanalization. A crucial complication of the treatment with local IA fibrinolysis is the risk of potentially lethal intracerebral hemorrhage.[5,6] Furthermore, ischemic lesions involving brain stem, cerebellum, thalamus, and occipital lobe due to delay of treatment or distal migration of thrombotic material might deteriorate neurologic outcome.

Our purpose was to evaluate the incidence and location of hemorrhagic and ischemic lesions after local IA fibrinolysis as well as the influence of different thrombolytic substances, namely urokinase (UK) and recombinant tissue plasminogen activator (rtPA), on recanalization and development of intracranial hemorrhage.

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Methods

Patients

One hundred forty-three adult patients (95 men, 48 women; mean age, 58.1 ± 13.8 years; range, 22–83 years) with angiographically confirmed VBO treated with local IA fibrinolysis at 5 neurointerventional stroke centers were retrospectively evaluated. Patients were included in this multicentric analysis if 1) at least 1 postinterventional MR imaging or CT examination was available, 2) acute VBO was shown by IA digital subtraction angiography, 3) no clinical or laboratory contraindications for local IA fibrinolysis were present, and 4) no intracranial hemorrhage was visible on pretreatment CT scan. Informed consent for the angiographic and thrombolytic procedures from each patient and/or nearest relative was obtained if possible. Before angiography, each patient underwent detailed neurologic examination revealing symptoms consistent with an acute thrombosis of the vertebrobasilar system. The type of occlusion was subdivided into 3 categories according to the angiographic results, as described previously[4]: 1) atherothrombotic, 2) artery-to-artery embolism from the proximal vertebral artery (VA; V0–V2 segments), and 3) embolism from the heart or aortic arch. The neurologic status was rated by an experienced vascular neurologist by means of the modified Rankin scale (mRS) before treatment and at the time of discharge or transfer of the patient (mRS 0–6, where 0 = no symptoms and 6 = dead).

CT and MR Imaging Scans

All together, 346 native CT scans and 57 MR imaging examinations were carried out peri-interventionally. Autopsy findings were available in only 1 case. Ischemic infarction size was subdivided into 3 groups: small, medium, and large. Because the absolute size of the lesion in centimeters did not take into account the striking differences

in normal size of the parenchymal structures and their functional importance (eg, occipital lobe versus mesencephalon) involved in the ischemic territory, semiquantative estimation was made on MR and CT scans as follows: *small ischemic lesion* if only small mottled areas were visible; *medium-sized ischemic lesion* if less than a half of a transverse section of the thalamus or brain stem (pons, mesencephalon, and/or medulla oblongata) or less than 50% of the territory of the posterior cerebral arteries (PCAs) or superior cerebellar arteries (SCAs), or combined anterior and posterior inferior cerebellar arteries (AICAs and PICAs) were involved; and *large ischemic lesion* if more than half of the transverse section of the thalamus or brain stem or more than 50% of the territory of the PCAs or SCAs or combined AICAs and PICAs were involved.

Intraparenchymal hemorrhage was classified as hemorrhagic transformation or intraparenchymal hematoma on CT scan: *hemorrhagic transformation* was defined as petechial, irregular, and patchy hyperattenuated areas within the hypoattenuated ischemic territory but without space-occupying effect; *intraparenchymal hematoma* was defined as an attenuated and homogenous area of hyperintensity within the infarcted area with associated slight or substantial space-occupying effect. Intraparenchymal hematoma was labeled as a *secondary intraparenchymal hematoma* if it occurred at least 3 days after local IA fibrinolysis. Furthermore, the presence of subarachnoid and intraventricular bleeding was documented. Postprocedural contrast enhancement was differentiated from hemorrhage by means of serial CT examination or MR imaging.

Angiography and Endovascular Procedure

Occlusion of the basilar artery was documented by selective diagnostic 4-vessel IA digital subtraction angiography. An approximation of the thrombus volume was calculated using the intraluminal visible radiopaque tip of the microcatheter as a reference, as reported previously.[4] Recanalization was assessed on the control angiogram after local IA fibrinolysis and classified according to Thrombolysis in Myocardial Infarction (TIMI) grades.[7] For statistical analysis, TIMI grades 0 and 1 were combined, leading to 3 categories: no recanalization (TIMI 0 and 1), partial recanalization (TIMI 2), and complete recanalization (TIMI 3). The TIMI classification was applied for the perfusion of the distal vertebral arteries and basilar artery, whereas potential additional occlusions of the PICA, AICA, SCA, and the distal PCA were not taken into account.

Local IA fibrinolysis was performed under general anesthesia. After placing a guiding catheter in the dominant vertebral artery, a microcatheter was advanced to the proximal portion of the occluding thrombus. Recombinant tissue plasminogen activator ($n = 86$ patients) or UK ($n = 57$ patients) was administered. Because the length and the volume of the thrombus differed markedly and the multicentric data were retrospectively evaluated, dosage of the thrombolytic drug as well as the duration of local IA fibrinolysis varied substantially. Dose ranges of thrombolytic agents were: 25–160 mg for rtPA (mean dose, 73.5 mg) and 150,000–1,700,000 IU (mean dose, 694,000 IU) for UK. For statistical analysis, we subdivided the patients treated with rtPA into 2 dose subgroups: rtPA <80 mg and rtPA >80 mg. The duration of fibrinolytic infusion was usually confined to 2 hours; it was prolonged if a beginning recanalization was visible on the control angiogram. Local IA fibrinolysis was stopped when the distal segments of the vertebral arteries, the entire basilar artery, and the precommunicating segments of the PCAs were recanalized. Fibrinolytic treatment was carried out under systemic heparin administration that was maintained after the procedure, except for patients with intracranial hemorrhage. Before the angiography, a bolus of 5000 IU heparin was applied. Acetylsalicylic acid was not regularly given before IA fibrinolysis, but some patients were on aspirin at admission to the hospital. All neuroradiologic examinations (CT, MR imaging, diagnostic angiography, and endovascular procedure) were evaluated by an experienced neuroradiologist who was unaware of the clinical findings.

Table 1: Recanalization rates for different fibrinolytic agents

Fibrinolytic Agent	Recanalization			*n*
	None	Partial	Complete	
rtPA	18 (21%)	13 (15%)	55 (64%)	86
Urokinase	10 (18%)	19 (33%)	28 (49%)	57

Note:—rtPA indicates recombinant tissue plasminogen activator.

Table 2: Bleeding rates for different fibrinolytic agents

Fibrinolytic Agent	*n* (%)
Urokinase ($n = 57$)	12 (21%)
rtPA ($n = 86$)	31 (36%)
Dosage <80 mg ($n = 43$)	11 (26%)
Dosage ≥ 80 mg ($n = 43$)	20 (46%)

Note:—rtPA indicates recombinant tissue plasminogen activator.

Multiple logistic regression analysis was used to identify independent variables for intracranial bleeding after local IA fibrinolysis. The odds ratio within the 95% confidence interval was determined. The Fisher exact test and χ^2 test were used for univariate analysis and cross-tabulation, respectively. Significance was declared at the $P < .05$ level. This analysis is part of a more extended research project investigating factors influencing the outcome in acute VBO treated with local IA fibrinolysis.

Results

Fifty-seven (40%) of 143 patients died. The cause of the occlusion was atherothrombotic in 48 patients, embolic from the heart or aortic arch in 81 patients, and embolic from the proximal vertebral artery in 14 patients, respectively. The post-treatment mRS was 0–2 in 38 patients, 3–4 in 42 patients, and 5–6 in 63 patients. The mean thrombus volume was 155 μL for rtPA-treated patients and 196 μL for UK-treated patients, respectively. Complete recanalization was achieved in 83 (58%) patients, partial recanalization in 32 (22%) patients, and no recanalization in 28 (20%) patients, respectively. Table 1 lists recanalization rates for the 2 fibrinolytic agents. After univariate analysis, complete recanalization occurred significantly more frequent in rtPA-treated patients than in UK-treated patients ($P < .05$).

Intracranial Hemorrhage

After local IA fibrinolysis, intracranial hemorrhage was found in 46 (32%) of 143 patients. Twenty of these 46 patients had an intracerebral hematoma, 21 patients had hemorrhagic transformation, 3 patients had secondary intracerebral hematoma, and 2 patients had subarachnoid and intraventricular bleeding. Nine of the 20 patients with an intracerebral hematoma had also a subarachnoid and intraventricular bleeding. After multiple regression analysis, the type and dosage of the fibrinolytic agent remained independent variables predicting intracranial hemorrhage (Table 2). The administration of rtPA in a dose of more than 80 mg caused a significantly higher

Table 3: Relationship between intracranial bleeding (hemorrhagic transformation and primary intracerebral hematoma) and neurologic outcome

	Modified Rankin Scale Score *n* (%)			
	0–2	3–4	5–6	*n*
Bleeding	1 (2%)	9 (21%)	33 (77%)	43
No bleeding	37 (37%)	33 (33%)	30 (30%)	100

Table 4: Incidence and location of ischemic lesions in 143 patients

	Incidence of All Ischemic Lesions *n* (%)	Incidence of Large Ischemic Lesions *n* (%)
Occipital lobe	59 (41%)	11 (8%)
Thalamus	54 (38%)	8 (6%)
Mesencephalon	55 (39%)	33 (23%)
Pons and medulla oblongata	95 (66%)	51 (36%)
Territory of the SCA	63 (44%)	23 (16%)
Territory of the AICA & PICA	62 (43%)	22 (15%)

Note:—SCA indicates superior cerebellar artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery.

bleeding rate than UK. There was a bleeding rate of 44% after a rtPA dosage of more than 80 mg, whereas hemorrhage after administration of UK was observed in only 20% of the patients. The neurologic outcome was significantly worse in patients with intracranial hemorrhage than in patients without bleeding ($P < .001$) (Table 3).

Ischemic Lesions

Ischemic lesions were present in 136 (95%) of 143 patients. In Table 4, the location of ischemic territories is given. Pons and medulla oblongata were most often involved. Particularly large ischemic lesions affected the brain stem more frequently than other regions (Table 4). After successful recanalization, medium-sized to large ischemic lesions were significantly more often found in the occipital lobes ($P < .005$), thalami ($P < .02$), and the territory of the SCAs ($P < .005$) than in the case of absent recanalization. Conversely, ischemic infarctions of the pons ($P < .020$) and mesencephalon ($P < .005$) were more frequent seen in the case of absent recanalization than after successful recanalization.

On angiograms, occlusion of the postcommunicating segment of one or both PCAs was present in 39% of patients with successful recanalization. In the case of absent recanalization, no occlusion of the postcommunicating segment of PCA was seen ($P < .001$).

Discussion

In this retrospective multicentric analysis, we found a trend toward more complete recanalization with the use of rtPA compared with UK in patients with acute VBO (64% versus 49%; Table 1). However, according to our semiquantitative analysis, the mean thrombus volume was greater in patients treated with UK than in patients treated with rtPA. Eckert et al[5] found a lower recanalization rate for UK (39%) than for low-dose rtPA (71%), high dose rtPA (67%), and rtPA + Lys-plasminogen (89%) in 83 patients treated with local IA fibrinolysis due to acute VBO, which is similar to our results. However, Zeumer et al[8] reported recanalization rates of 88% (7/8 patients) for UK and 70% for rtPA (14/20 patients). Cross et al[6] found complete basilar artery recanalization in 50% (10/20) of patients treated with IA UK and in 75% (3/4) treated with IA rtPA, respectively. Except for the study by Zeumer et al,[8] recent studies and our results underline the results of in vitro models and animal experiments of clot resolution, which have shown the superiority of the highly fibrin selective rtPA compared with UK.[9]

In previous studies, bleeding rate after IA administration of UK, pro-UK, or rtPA in middle cerebral artery infarction ranged between 14% and 35%.[10-13] Symptomatic hemorrhage occurred in 5%–11%.[11,13] Intracranial bleeding has been reported to occur in 5%-75% of the patients with acute VBO when using IA rtPA or UK.[5,6,8,14,15]

We found a significantly higher bleeding rate for rtPA than for UK ($P < .01$, Table 2). In particular, the administration of high dose-rtPA (≥80 mg) caused a significant increase of intracranial hemorrhage compared with UK (46% versus 21%). Only 3 other studies have compared the bleeding rates of UK and rtPA after local IA fibrinolysis in acute vertebrobasilar occlusion.[5,6,8] Eckert et al[5] found hemorrhagic transformation without clinical deterioration in 17 (22%) of 76 patients and fatal parenchymatous hematomas in 7 (8%) patients. Four of these 7 patients experienced intracranial hemorrhage after treatment with high-dose rtPA (30–80 mg), whereas only 1 of the 7 patients was treated with UK (750,000 IU).

Zeumer et al[8] compared rtPA (dose up to 20 mg) with UK (dose up to 750,000 IU) for local IA fibrinolysis in the setting of acute thromboembolic carotid stroke ($n = 31$ patients) and vertebrobasilar stroke ($n = 28$ patients). No symptomatic intracerebral hemorrhages were reported. Secondary hemorrhagic infarction without clinical deterioration was seen in 2 of 28 patients with vertebrobasilar stroke.[8] The low bleeding rate was probably due to the low dosages of fibrinolytic agents.

However, Cross et al[6] observed a higher rate of spontaneous cerebral hemorrhage, including subarachnoid bleeding, after rtPA (3 of 4 patients) was infused than after UK (5 of 20 patients) was infused. The authors attributed the significantly higher bleeding rate after rtPA therapy mainly to the dosage applied; the rtPA doses ranged from 20 to 50 mg, lower than the dosages used by Eckert et al[5] and by us. Similar to our study and that by Eckert et al,[5] the UK doses ranged from 250,000 to 1,750,000 U in the study by Cross et al.[6] In our opinion, it is difficult to draw conclusions from these data because the numbers of patients in the 2 groups were too low and unequal in the study by Cross et al.[6]

We believe that the higher bleeding rate in our study compared with the studies of Eckert et al[5] and Zeumer et al[8] is caused by the higher dosage of both fibrinolytic agents. In particular, the administration of high-dose rtPA (≥80 mg) may induce bleeding. We used a cutoff point of 80 mg for the dosage of rtPA, because this was the maximal dose used in the National Institute of Neurological Disorders and Stroke study[16] establishing the efficacy of IV rtPA in middle cerebral artery infarction. Another factor to consider is the large mean thrombus volumes of 155 and 196 μL for the rtPA and UK groups, respectively, in our study, which required high doses of fibrinolytic agents for achieving at least partial recanalization.

Nearly all patients (95%) had ischemic lesions on follow-up CT scan or MR imaging in our study. By comparing

the location of the ischemic lesions with the success of recanalization, we could demonstrate that brain stem structures were significantly more frequently involved in the infarcted area than supratentorial brain parenchyma (ie, occipital lobe and thalamus) in the case of absent recanalization. However, the occipital lobe, the thalamus, and the superior part of the cerebellum were significantly more often affected by ischemic lesions in the case of successful recanalization. This result corresponds to the angiographic finding that occlusion of the postcommunicating segment of one or both PCAs was frequently found in the case of successful recanalization but not in the case of absent recanalization (39% versus 0%). Therefore, our findings prove that the successful recanalization by means of fibrinolytic agents comes with the price of distal migration of thrombotic material into the PCA, SCA, and perforators branching from the precommunicating segment of the PCA.

Our findings underline the idea that ischemic and hemorrhagic complications after local IA fibrinolysis in acute VBO are common and intrinsic. By means of new recanalization techniques, such as endovascular thrombectomy by means of a snare or local vortex suction,[17-19] it seems to be feasible to remove the occluding thrombus with less fragmentation and less distal migration of thrombotic material. Excellent recanalization rates for extended occlusions of the anterior and posterior circulation have been reported for sole mechanical maneuvers as well as for combined treatment with IV glycoprotein IIb/IIIa receptor inhibitors, IA rtPA, IA UK, and mechanical thrombolysis.[17,18,20-23] Thus, there would be no need for hazardous high-dose fibrinolytic agents even in cases of extended vertebrobasilar artery thrombosis, resulting in a significant lower risk of intracranial hemorrhage.

Conclusion

The bleeding rate after administration of rtPA seems to be higher compared with that of UK, especially after high-dose rtPA. The ischemic patterns after local IA fibrinolysis depend on the recanalization success and on the unavoidable distal migration of the thrombus after successful local IA fibrinolysis. Ischemic brain stem lesions are usually found in the case of absent recanalization, whereas the superior part of the cerebellum, the thalamus, and the occipital lobe are more often involved in cases of successful recanalization. Novel mechanical recanalization techniques alone or combined with low dose IA rtPA or IV glycoprotein IIb/IIIa receptor inhibitors might reduce ischemic and hemorrhagic complications after treatment of acute VBO in the future.

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