Intraarterial thrombolysis in vertebrobasilar occlusion.

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Intraarterial Thrombolysis in Vertebrobasilar Occlusion

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PURPOSE: To report our experience using intraarterial thrombolysis in the treatment of vertebrobasilar occlusion. METHODS: Twelve patients with 13 angiographically proved thromboses of the vertebrobasilar system underwent local intraarterial thrombolysis with urokinase. Angiographic and clinical outcomes were analyzed with respect to clinical examination at presentation, arterial occlusion patterns, and time to recanalization. RESULTS: The overall mortality was 75%. Recanalization could not be achieved in 3 of 13 treatments; all patients in whom recanalization failed died. The mortality rate was 60% in those patients in whom recanalization was successful. Coma or quadriparesis at the time of therapy uniformly predicted death. There were two cases each of bilateral proximal vertebral occlusions and midbasilar occlusions and nine cases of bilateral distal vertebral occlusions. There were three cases of fatal rethrombosis after initial successful thrombolysis. The mortality rate in the recanalized group before rethrombosis was 30%. There were two fatal hemorrhages of the central nervous system. CONCLUSION: Recanalization of the vertebrobasilar system is necessary but not sufficient for effective treatment of vertebrobasilar occlusive disease. The site of occlusion may help predict angiographic and clinical outcome. Time to initiation of thrombolysis is not an invariable correlate of survival, although clinical condition at presentation may be. Rethrombosis and hemorrhage are significant problems affecting mortality after successful thrombolysis.

Index terms: Arteries, basilar; Arteries, stenosis and occlusion; Thrombolysis; Efficacy studies

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Vertebrobasilar thrombosis is a life-threatening event with mortality rates of 75% to 86% (1–3). The gravity of this disease has been recognized for decades, yet no effective therapy has been developed. Despite the lack of data demonstrating clinical benefit, many physicians advocate anticoagulation as standard therapy in progressive ischemia of the posterior circulation. The reported mortality rates reflect the use of heparin (2, 3). Patients who do survive rarely regain functional independence (3, 4) and are at risk for recurrent strokes (4–6). A number of authors have recently reported success in treating vertebral and basilar artery thromboses with local intraarterial thrombolysis (3, 7–12). These are largely retrospective reports of a limited number of patients. Only three groups have published results of treatment on a cohort of more than 10 patients (3, 9, 13).

We reviewed our experience with intraarterial thrombolysis on a North American patient population using urokinase in the treatment of progressive vertebrobasilar occlusion. We attempt to address the relationship between clinical presentation, site of occlusion, and time to recanalization with clinical and angiographic outcome. We compare our methods and results with those previously reported. We also present pathologic data on one patient in whom recanalization was successful but who died after continued neurologic progression.

Materials and Methods

Twelve patients with vertebrobasilar occlusive disease presented between February 1991 and May 1994 and were treated with intraarterial thrombolysis. All patients were referred to the Neurosciences Critical Care Unit with

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signs and symptoms consistent with acute progressive thrombosis of the vertebrobasilar system.

The neurologic examination done immediately before the start of angiography was considered to be the reference neurologic examination. Time to angiography/therapy is expressed in relation to the last neurologic progression, defined as the occurrence of new neurologic signs indicative of ischemia in another arterial branch of the vertebrobasilar system. Patterns of angiographic occlusion were classified as bilateral proximal vertebral (extracranial), bilateral distal vertebral (distal to the origin of the posteroinferior cerebellar arteries to the level of the vertebrobasilar junction), proximal basilar, midbasilar, and distal or top-of-the-basilar. Clinical outcome was stratified as either good (alive with minimal deficits) or bad (death, major disability, or locked-in).

All patients were screened with computed tomography (CT) or magnetic resonance (MR) imaging before thrombolysis to exclude the presence of consolidated hemorrhage. Patients were not excluded from therapy by the presence of ischemic changes or petechial hemorrhages in the vertebrobasilar territory. We elected to treat these patients aggressively because of continued neurologic decline and the overall poor prognosis associated with vertebrobasilar occlusion. Patients were included only if the signs and symptoms predicating therapy did not correlate with the area of radiologic infarction. The aim of therapy was to promote recanalization of the occluded vessel in order to reverse these neurologic findings and prevent further deterioration. All patients or their families gave informed consent before thrombolysis. Urokinase was infused through a microcatheter embedded into the face of the arterial clot at an initial rate of 250 000 to 500 000 units per hour for 1 to 2 hours then at 250 000 units for 4 hours. The total dose of urokinase varied among patients but most received approximately 1 000 000 units with a maximal dose of 2 000 000 units given to patient 8. All patients received concomitant heparin at a rate of 1000 units per hour during thrombolysis and then adjusted to maintain the activated partial thromboplastin time at 1.5 times normal. All 12 patients were intubated for airway management. Seven of the 12 patients required vasopressors to maintain a mean arterial blood pressure greater than 100 mm Hg.

Results

Thirteen vertebrobasilar sites were occluded in 12 patients (1 woman and 11 men) whose ages ranged from 46 to 77 years (mean, 60 years). Only one occlusion was clinically consistent with an embolic origin. Only 4 of the 13 patients presented for treatment less than 24 hours after ictus; the remaining 9 patients had progressive symptoms of approximately 24 to 48 hours' duration. All 9 of these patients continued to worsen neurologically, despite heparinization. Nine of the 12 patients had evidence of infarct in the vertebrobasilar territory at CT or MR imaging before the start of thrombolysis (Table 1). Four of these patients had evidence of acute ischemic changes and the other five had evidence of subacute or remote infarcts on CT scans or MR images. Intraarterial thrombolysis was started within 1 to 48 hours from the patient's last clinical neurologic progression. Mean time from the presenting neurologic event to thrombolysis was 24 hours.

The patients' clinical and angiographic characteristics are displayed in Table 1. Nine of the 13 occlusions occurred in the distal vertebral arteries. Six patients appeared to have a hypoplastic vertebral artery; all six had vertebral artery occlusions that were either proximal or distal.

Patients' outcomes with respect to clinical and angiographic characteristics are given in Table 2. The occluded vessel was recanalized in 10 of 13 patients. Both patients with midbasilar occlusions had successful recanalizations, as did seven of nine patients with distal vertebral artery occlusions. There was no correlation between the ability to achieve recanalization and the time to therapy from the last neurologic deterioration (Table 3). The overall mortality rate was 75%; among those who had recanalization, the mortality rate was 60%. Average time from presentation to initial angiography and treatment was longer among patients who had recanalization and among survivors. For the three patients in whom recanalization could not be achieved, mortality was 100%. One of these, patient 10, initially survived in a locked-in state but ventilatory support was later removed and he died. All patients who presented with coma or quadriparesis of any duration died. Factors associated with mortality are given in Table 4.

All three patients in whom rethrombosis occurred died. In patient 2, heparin was stopped briefly for tracheostomy 1 week after initial successful thrombolysis of a midbasilar occlusion, at which time the vertebrobasilar system reoccluded at the confluence of the distal vertebral arteries proximal to the site of the prior occlusion. Patients 8 and 9 both had rethrombosis at the same site (distal vertebral arteries) as their initial occlusion when their activated partial thromboplastin time inadvertently fell to 1.2 times normal. Both patients underwent repeat attempts at thrombolysis. Initial mortality rate in

TABLE 1: Clinical and angiographic characteristics of patients undergoing intraarterial thrombolysis for vertebrobasilar occlusion

Patient	Age, y/ Sex	Transient Ischemic Attack	Stroke Mechanism	Level of Consciousness at Time of Therapy	Findings at Motor Examination	Site of Occlusion	CT/MR Findings
1	51/M	Yes	Thrombosis	Alert	Hemiparesis	Midbasilar	Normal
2	47/M	No	Thrombosis	Sleepy	Hemiparesis	Midbasilar	Bilateral occipital and pontine infarcts, left cerebellar infarct†
			Thrombosis	Coma	Quadriparesis	Bilateral distal vertebrals*	Bilateral occipital and cerebellar infarcts, right pontine infarct
3	65/M	Yes	Thrombosis	Coma	Quadriparesis	Bilateral distal vertebrals	Bilateral subacute cerebellar infarcts
4	49/F	No	Embolism	Coma	Quadriparesis	Bilateral distal vertebrals	Normal
5	77/M	No	Thrombosis	Alert	Normal	Bilateral proximal vertebrals*	Normal
6	66/M	No	Thrombosis	Alert	Hemiparesis	Bilateral distal vertebrals	Bilateral cerebellar and pontine infarcts†
7	56/M	Yes	Thrombosis	Alert	Normal	Bilateral distal vertebrals*	Bilateral cerebellar, right occipital, left medullary infarcts†
8	65/M	Yes	Thrombosis	Alert	Hemiparesis	Bilateral distal vertebrals	Right occipital and left pontine infarcts
9	67/M	Yes	Thrombosis	Alert	Hemiparesis	Bilateral distal vertebrals	Left pontine, cerebellar, and midbrain infarcts†
10	64/M	No	Thrombosis	Alert	Hemiparesis	Bilateral distal vertebrals*	Right parietal, pontine, and peduncular infarcts
11	66/M	Yes	Thrombosis	Alert	Normal	Bilateral distal vertebrals	Right occipital infarcts†
12	46/M	Yes	Thrombosis	Alert	Normal	Bilateral proximal vertebrals*	Left parietotemporal and cerebellar infarct

* Presence of hypoplastic vertebral artery.
† On MR image.

TABLE 2: Angiographic and clinical outcome of patients undergoing intraarterial thrombolysis for vertebrobasilar occlusion

Patient	Time to Therapy, h	Angiographic Outcome	Clinical Outcome	Rethrombosis	Hemorrhagic Complications
1	16	Recanalized	Alive/well	No	None
2	48	Recanalized	Alive	Yes	None
	6	Not recanalized	Dead	. . .	None
3	<1	Recanalized	Dead	No	None
4	5	Recanalized	Dead	No	None
5	12	Not recanalized	Dead	. . .	None
6	48	Recanalized	Dead	No	Fatal subdural
7	24	Recanalized	Alive/well	No	None
8	24	Recanalized	Dead*	Yes	None
9	48	Recanalized	Dead	Yes	Fatal intracerebral/ intraventricular hemorrhage
10	24	Not recanalized	Dead*	. . .	None
11	48	Recanalized	Alive/well	No	None
12	8	Recanalized	Dead	No	None

* Patients initially survived in a “locked-in” state but life support was later withdrawn at patient/family request.

TABLE 3: Factors affecting recanalization in vertebrobasilar occlusion and frequency of rethrombosis after successful thrombolysis

Recanalization Rate*	10/13 (77%)
Site of occlusion	
Proximal vertebral arteries	1/2 (50%)
Distal vertebral arteries	7/9 (78%)
Midbasilar artery	2/2 (100%)
Mean time to angiography	
Recanalized	27 hours (1–48)†
Not recanalized	14 hours (6–24)†
Stroke origin	
Thrombotic	9/12 (75%)
Embolic	1/1 (100%)
Frequency of rethrombosis‡	
Immediate	2/10 (20%)
Delayed	1/10 (10%)

* Number of patients recanalized per number of recanalizations attempted.

† Range of time from presentation to angiography/therapy.

‡ Number of rethromboses per number of patients recanalized.

the recanalized group before rethrombosis was 3 (30%) of 10.

Two hemorrhagic complications occurred; both were fatal. In patient 6, findings on a CT scan obtained at admission showed evidence of subacute cerebellar and pontine infarcts, but no evidence of subdural blood. After thrombolysis and anticoagulation, however, an acute subdural hematoma developed and was associated with an area of intraparenchymal and subarachnoid blood. Subsequent questioning revealed a history of head trauma associated with ataxia and falls in the weeks before admission. In patient 9, hemorrhage occurred upon rethrombosis of the distal vertebral arteries and progression to a locked-in state. This patient received a bolus of heparin, was given aspirin, and underwent a second course of thrombolysis in which 500 000 units of urokinase were used with recanalization of the left vertebral artery. Four hours later the patient became acutely unresponsive with marked hypertension and systemic bleeding. A CT scan of the head revealed a right temporal lobe intraparenchymal hematoma with extension of blood into the subarachnoid and intraventricular space. No hemorrhage occurred at the site of a previously defined infarct. Patient 7, on the other hand, had evidence of a petechial hemorrhage in a subacute right occipital lobe infarct at presentation; he received a total of 1 000 000 units of urokinase and was anticoagulated without evidence of hemorrhage on follow-up scans.

Clinicopathologic correlation was obtained in patient 12, who presented with symptoms consistent with vertebrobasilar occlusion and signs of left pontine ischemia. An angiogram revealed bilateral vertebral artery occlusion proximal to the level of the posteroinferior cerebellar arteries. Urokinase infusion was performed 8 hours after presentation, with rapid recanalization of the artery after the start of the infusion. Marked stenosis of the vessel at the site of occlusion was noted after thrombolysis, and angioplasty was performed with a 3F microcatheter (Target, Fremont, Calif) to decrease the risk of rethrombosis. Angioplasty was done 8 hours after the initiation of thrombolysis. Nevertheless, brain death occurred within 18 hours. Autopsy findings revealed extensive calcific atherosclerotic vascular disease and marked ischemic cellular damage and neuronal death. Edema was noted throughout the brain stem, particularly in the pons. All of the microvasculature and pial vessels were patent and there was no evidence of microemboli related to clot fragmentation or an-

TABLE 4: Factors associated with mortality in patients undergoing intraarterialthrombolysis for vertebrobasilar occlusion

Overall Mortality = 9/12* (75%)			
Site of occlusion		Mean time to angiography	
Proximal vertebral arteries	2/2 (100%)	Alive	34 hours (16–48)†
Distal vertebral arteries	7/9 (78%)	Dead	19.5 hours (1–48)†
Midbasilar artery	0/2 (0%)	Motor examination	
Mental status		Normal	2/4 (50%)
Alert	6/9 (67%)	Hemiparesis	4/6 (67%)
Comatose	3/3 (100%)	Quadriparesis	3/3 (100%)
Recanalization		Stroke origin	
Established	6/10 (60%)	Thrombotic	8/11 (72%)
Not established	3/3 (100%)	Embolic	1/1 (100%)

* Number of deaths divided by total number of patients per category.

† Range of time from presentation to angiography.

TABLE 5: Comparison of the four major reported series of intraarterial thrombolysis for vertebrobasilar occlusion

	Series			
	Hacke (3) (n = 43)	Zeumer (9) (n = 28)	Bockenheimer (13) (n = 13)	Present Study (n = 13)
Urokinase dosage, U	100 000/h up to 4 h*	750 000 over 2 h	400 000–1.8 million over 1.5–5.5 h	250 000–500 000 over 1–2 h followed by 250 000 over 4 h†
Average time to therapy, h	≤24	8	≥12	≤24
Overall mortality	67%	46%	54%	75%
Recanalization rate	44%	75%	54%‡	75%
Recanalized mortality rate	26%	. . .	71%‡	60%
Hemorrhagic complications	9%	7%	0%	15%
Rethrombosis	. . .	10%	. . .	30%

* Some patients received 100 000 units per hour for 12 to 48 hours.

† Infusions were continued until recanalization was complete or no further progress was made; total dosage varied from 1 million to 2 million units.

‡ Bockenheimer reported four patients with partial recanalization, seven patients with complete recanalization, and two who were not recanalized. Mortality in the partially recanalized group was 50% but survivors were severely impaired. Mortality with complete recanalization was 57% with one of the survivors being locked in. The numbers reported here reflect a combination of the data from the recanalized and partially recanalized groups.

gioplasty. Prophylactic angioplasty was not performed in the other patients.

Discussion

Occlusion of the vertebrobasilar system is strongly associated with atherosclerotic cerebral vascular disease and has a predilection for the distal vertebral arteries. Recanalization of the occluded vessel can be achieved with local intraarterial thrombolysis, but this does not ensure survival. Thrombolysis can be performed safely relative to the natural history of the disease. A prolonged time to presentation should not exclude the potential for therapy if neurologic deterioration is continuing while eloquent neurologic function remains. Rethrombosis was a significant problem in our patient population and limited the effectiveness of therapy. Mechanisms by which to prevent rethrombosis will need to be explored in detail. Fatal hemorrhage is also a serious therapeutic complication. Any new clinical regimen must address both these factors if substantial improvement is to be made in patient outcome.

Stroke, with its attendant major morbidity and mortality rates, remains a significant health care problem worldwide. This is particularly true in patients who have thrombosis of the vertebrobasilar system, because the mortality from this type of stroke is greater than 75% (1–3). It seems intuitive that effective stroke therapy must involve recanalization of the occluded artery, but no adequate therapy for stroke has yet been identified. A number of controlled thrombolytic trials are currently in progress (14–17); unfortunately, most of these are limited to infarctions of the carotid or middle cerebral artery and focus on treatment during the initial 1.5 to 6 hours after symptomatic presentation. These territories are subject to more frequent embolic infarctions and to fewer incidents of severe intracranial atherosclerosis than are seen in the posterior circulation. No placebo-controlled thrombolytic trials have been done in studies of vertebrobasilar occlusion, although cohort mortality is decreased compared with historic control subjects when successful thrombolysis has been achieved. This benefit occurs as late as 24 hours after presentation (3, 9, 13).

Our patient population differs from those previously reported in that we treated patients who had radiologic findings consistent with infarctions in the vertebrobasilar territory upon admission. Because prior reports (3, 9, 13) were based on CT assessment, the increase in infarct detection in our series may in part be related to the use of more sensitive MR screening techniques. The presence of preexisting infarction by itself did not adversely affect outcome, as two of the three survivors had radiologic evidence of stroke before thrombolysis. Of the three patients in whom recanalization could not be achieved, two had infarctions at presentation. Clearly, infarction of a critical amount of brain stem tissue is associated with poor outcome, but the precise volume and location of

this critical tissue within the brain stem are not currently known.

Our urokinase dosage is similar to that published by other groups (Table 5). There is little difference in the initial thrombolytic doses used among the groups: 400 000 units over 4 hours in the series reported by Hacke et al (3); 750 000 units over 2 hours in the series of Zeumer and coworkers (9); and 500 000 units over 2 hours in the currently reported series. The dosing strategy used in the series of Bockenheimer et al (13) was more variable. The major difference in dosing is our practice of using a prolonged low-dose infusion of urokinase after the initial infusion. This practice was adopted to optimize the prevention of early rethrombosis in our patients, all of whom had severe atherosclerotic disease.

Pathologic studies have shown that the most common site of atherosclerotic disease within the intradural portion of the vertebrobasilar system is just after the confluence of the vertebral arteries (18) and that disease of the distal basilar artery is distinctly rare (18–20). Nine of the 13 occlusions in our series occurred in the vertebral arteries just before their confluence. Of interest, 46% of the occlusions occurred in conjunction with a hypoplastic vertebral artery, a phenomenon that has previously been described in 23% (21) to 75% (22) of patients with vertebrobasilar occlusions. Sixty percent of the atherosclerotic vertebral artery occlusions in our group had the appearance of a hypoplastic vertebral artery with a very constricted lumen by angiography. The discrepancy in arterial size was out of proportion to that seen with normal vertebral artery dominance. The contribution of vertebral hypoplasia to vertebrobasilar occlusion remains unclear. And, as found in our single autopsy, the angiographic finding of a hypoplastic vessel may merely reflect severe atherosclerotic disease with luminal narrowing in an otherwise normal-sized vessel.

Like others (3, 9, 13), we found that coma or quadriparesis at presentation portends a poor outcome, regardless of the recanalization status. In our series, time to therapy from last neurologic deterioration did not seem to correlate with the ability to achieve recanalization or with the overall outcome, although this has not been the experience of others (9). Also like others (3, 13), we identified recanalization as a necessary but not sufficient criterion for good outcome after thrombolysis. That patients may not improve after angiographically successful thrombolysis implies that the ischemia has been too prolonged to effect a reversal of neuronal dysfunction simply by restoration of blood flow. Additionally or alternatively is the notion that recanalization may lead to reperfusion injury, which is characterized by leukocyte plugging within the microcirculation (23–28) and cell death due to oxidative stress and free radical damage (29–31).

Rethrombosis occurred in 3 of 10 cases of successful thrombolysis and represented an important adverse event, as it effectively increased our mortality rate from 30% to 60% in those patients in whom recanalization was initially successful, thus increasing the overall mortality rate from 50% to 75%. All of these patients had severe atherosclerotic lesions underlying the site of thrombosis. Zeumer et al (9) reported a reocclusion rate of 13% in patients with initially successful thrombolysis (9). The cardiac literature suggests that rethrombosis rates are higher when the residual stenosis after thrombolysis is greater than 75% (32). Aggressive anticoagulation tends to decrease the rate of early rethrombosis (33–35) but may not have a long-term effect (36). This issue seems to have particular relevance in our patient population, as the primary mechanism of occlusion in our series was thrombosis, which occurred in 92% of cases. By comparison, the frequency of presumed thrombosis was 50% and 77% in the series of Zeumer et al (9) and Hacke et al (3), respectively. The results of all reported series of 10 or more patients are compared in Table 5. To date, the results obtained by Hacke and colleagues (3) are most impressive, with a mortality rate of 26% in the recanalized group. Excluding cases of rethrombosis, our mortality rate in those recanalized would be nearly the same, or 30%. The problem with rethrombosis and consequent higher mortality rates in recanalized patients may be related to the greater frequency of intrinsic atherosclerotic vascular disease in our group as compared with the series of Hacke et al.

The rate of central nervous system hemorrhage in our series, 15%, is higher than the 9%, 7%, and 0% rates reported by Hacke et al (3), Zeumer et al (9), and Bockenheimer et al (13), respectively. Both patients with hemorrhage in our series had successful recanalization and both had evidence of acute ischemic changes before onset of thrombolysis. It is important to

note that these hemorrhages occurred at sites distant from the radiologically defined infarcts and recanalized vessels. Eight of the nine patients with evidence of infarction before thrombolysis had no adverse hemorrhagic events, including one patient with evidence of hemorrhagic transformation at presentation. Thus, the presence of infarction does not uniformly lead to hemorrhage after thrombolysis.

Our experience, in conjunction with the experience of Hacke et al (3), Zeumer et al (9), and Bockenheimer et al (13), suggests that there are subpopulations of patients with vertebrobasilar occlusion whose presentation may allow the prediction of clinical and radiologic response to therapy. There are patients who seem to benefit from intraarterial thrombolysis and those who do not. The latter group of patients includes those in whom recanalization cannot be achieved, those who die despite recanalization, and those who would have done well without thrombolytic infusion. The ability to distinguish between these subpopulations before initiation of thrombolytic therapy has important clinical, ethical, and financial ramifications. Taken together, all four series suggest that coma and quadriparesis are poor prognostic signs, whereas embolic occlusion may be associated with a higher likelihood of beneficial outcome from therapy. In order to define and identify these subpopulations prospectively, it will be necessary to perform a randomized, controlled trial of intraarterial thrombolytic therapy versus standard therapy in the treatment of vertebrobasilar thrombosis.

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