AJNR

Stent-Assisted Angioplasty of Intracranial Vertebrobasilar Atherosclerosis: Midterm Analysis of Clinical and Radiologic Predictors of Neurological Morbidity and Mortality

Michael M. Chow, Thomas J. Masaryk, Henry H. Woo, Marc R. Mayberg and Peter A. Rasmussen

Stent-Assisted Angioplasty of Intracranial Vertebrobasilar Atherosclerosis: Midterm Analysis of Clinical and Radiologic Predictors of Neurological Morbidity and Mortality

Michael M. Chow, Thomas J. Masaryk, Henry H. Woo,
Marc R. Mayberg, and Peter A. Rasmussen

BACKGROUND AND PURPOSE: Initial reports of stent-assisted angioplasty for intracranial vertebrobasilar atherosclerosis suggest this is a feasible treatment, but there have been little data regarding predictors of success or failure. We analyzed a series of patients for independent predictors of neurologic morbidity and mortality.

METHODS: Patient charts and angiograms from 39 patients who underwent intracranial angioplasty and stent placement of vertebrobasilar stenoses were retrospectively reviewed to obtain clinical and detailed angiographic data on potential predictors of neurologic morbidity and mortality. Univariate analyses of these predictors were performed with either Fisher's exact test or simple logistic regression. Multivariate analysis was subsequently performed on the statistically significant predictors.

RESULTS: Complete clinical data were obtained for 39 patients, and angiographic review was possible for 35 of them. Angiography revealed severe intracranial vertebral ($n = 18$), basilar ($n = 15$), or basilar and vertebral ($n = 2$) stenoses. Two patients (5.1%) died in the periprocedural period, nine patients (23.1%) had neurologic complications, and one patient (2.6%) had transient neurologic symptoms. Univariate analysis revealed female sex, diabetes, and failure of coumadin or heparin therapy were associated with neurologic morbidity, whereas female sex, Mori B lesion, and length-to-stenosis ratio were associated with mortality. The presence of diabetes was the only independent predictor of neurologic morbidity and mortality.

CONCLUSION: Because of the limited number of patients available for analysis, the only independent predictor of neurologic morbidity and mortality was diabetes, but several other predictors showed trends that deserve further review in future series.

There are few good therapeutic options in the treatment of symptomatic intracranial vertebrobasilar atherosclerotic occlusive disease. Medical treatment with antiplatelet agents and coumadin has been disappointing, with stroke rates as high as 10 per 100 patient years for those patients experiencing recurrent posterior circulation transient ischemic attacks (TIAs; 1, 2). Initial reports of treatment with stent-assisted angioplasty suggest this is a feasible treatment (3–10), but there have been little data regarding potential predictors of success or failure.

One such attempt has been the Mori classification, in which lesions are categorized by their length, plaque eccentricity, and degree of occlusiveness (9). Mori A lesions are short, concentric or moderately eccentric, and less than totally occlusive. These lesions tend to have better outcomes than do Mori B and Mori C lesions, which are progressively longer, more eccentric, and more occlusive. This classification, however, has not been validated in a large series of posterior circulation atherosclerotic lesions. Furthermore, the Mori classification system does not take into account potential clinical and procedural factors that may predict outcome.

This report attempts to analyze potential clinical and radiographic predictors of neurologic morbidity and mortality in our initial series of 39 consecutive

patients treated with stent-assisted angioplasty for medically refractory intracranial posterior circulation TIAs secondary to atherosclerotic disease.

Methods

Prospective gathering of data into a database was performed from March 1999 to December 2002 for all patients undergoing intracranial angioplasty and stent placement for vertebrobasilar atherosclerotic disease at the Cleveland Clinic. All patients had failed a trial of conservative medical treatment, including antiplatelet agents or coumadin or heparin.

All patients were treated under general anesthesia to minimize their motion and maximize their safety. Aspirin and clopidogrel were administered for at least 3 days before the procedure. Patients receiving coumadin continued on this regimen. Previously, this treatment was converted to heparin before the procedure, but now patients are treated under full coumadinization. For patients not receiving coumadin before the procedure, heparin was administered during the procedure and the activated clotting time (ACT) was adjusted to between 250 and 350 seconds. An abciximab infusion was not routinely given. Stents used during the last half of this series were either the Tetra (Guidant, Indianapolis, IN) or Velocity (Cordis, Miami, FL). Only one patient required predilation with an angioplasty balloon; all others were primarily stented without predilation or postdilation. The sheath was removed immediately after the procedure, and the arteriotomy was closed with the Perclose device (Abbott Labs, Chicago, IL) or Angioseal (St. Jude Medical, St. Paul, MN). The heparin was not reversed, and clopidogrel and aspirin were continued on hospital discharge. Clopidogrel was maintained for 6 weeks, and aspirin was continued indefinitely. Patients taking coumadin discontinued it.

Clinical follow-up was performed by the neurointerventionalists (T.J.M., H.H.W., P.A.R.) involved in each procedure at 1, 3, 6, and 12 months and yearly thereafter. Analysis of clinical data and angiographic review was retrospective in nature. The following clinical and demographic data were obtained: age, sex, race, presence of comorbidities, failure of antiplatelet therapy, date of procedure (first half of series versus latter half), operator, and preoperative transcranial Doppler velocity. On review of pretreatment and post-treatment angiograms, angiographic data were obtained for degree and length of stenosis (pre- and postprocedural), concentric versus eccentric lesion, presence of ulceration, Mori classification, existence of tandem lesions, presence of contralateral vertebral occlusion, and presence of collateral circulation (posterior communicating arteries, hypoplastic or aplastic P1 segments, pial collaterals). All measurements were taken with the aid of a magnifying loupe with 0.1-mm gradations. Finally, treatment factors such as type of stent deployed, use of platelet receptor IIb–IIIa inhibitors (e.g., abciximab), and any complications encountered, neurologic or otherwise, were recorded.

The three outcome measures selected were 1) mortality—secondary to neurologic causes; 2) combined permanent neurologic morbidity and mortality; and 3) all neurologic morbidity and mortality. To distinguish between the latter two outcome measures, permanent neurologic morbidity was defined to include a permanent neurologic complication (including death) directly related to the intervention, whereas "all neurologic morbidity" included not only the permanent neurologic complications, but also transient neurologic complications, asymptomatic vessel dissections, and mortality from neurologic causes. Permanent complications were defined as complications lasting >30 days from the day of the procedure.

Statistical Analysis

Statistical analyses consisted of a univariate screen of all potential demographic, clinical, angiographic, and treatment-procedural variables. Because of the binary nature of the outcome variables and the small numbers available for analysis, Fisher's exact test was used for the binary predictor variables and logistic regression was used for the predictors of a continuous nature. Any significant predictors uncovered in the univariate screen were subjected to a multivariate logistic regression analysis in an attempt to control for confounding. A potential predictor was deemed statistically significant in the univariate screen if $P < .10$. In the multivariate analysis, however, statistical significance was set at a more stringent $P < .05$. Statistical analysis was performed by the lead author (M.M.C).

Results

Complete clinical data were obtained for all 39 patients, whereas detailed angiographic review was possible for 35 (89.7%) of the 39 patients. Mean clinical follow-up was 13 months (median, 9 months). Angiography revealed severe intracranial vertebral ($n = 15$), basilar ($n = 18$), or combined basilar and vertebral ($n = 2$) stenoses. The detailed reviews for the other four patients, for whom angiograms were not available, included two basilar and two vertebral lesions. From the available angiograms, the mean preprocedural stenosis of the treated lesion(s) was 75% (range, 42–98%). The mean postprocedural residual stenosis was 18% (range, 0–86%).

Thirty-eight of the 39 patients were successfully revascularized, the lone failure being a patient with a lengthy 85% (Mori C) stenosis of the basilar artery who sustained a distal vertebral dissection extending into the basilar artery leading to brain stem infarction and death. One other patient died in the periprocedural period after developing a catastrophic subarachnoid hemorrhage subsequent to treatment with abciximab for a procedure complicated by proximal vertebral occlusion before successful deployment and revascularization with a stent. The mortality rate in this series was 2/39 (5.1%).

Permanent neurologic morbidity was experienced by 9/39 (23.1%) of our patient population, with three patients sustaining pontine infarcts, two with thalamic infarcts, one posterior inferior cerebellar artery infarct, one high cervical incomplete cord infarct, one medullary infarct, and one hemorrhagic conversion of an old hemispheric infarct. One patient developed transient encephalopathy (2.6%). In addition, two patients experienced an asymptomatic vertebral artery dissection, and one patient was asymptomatic from occlusion of an anterior inferior cerebellar artery.

Clinical Predictors

Results of the statistical analysis are shown in Tables 1–3. The only statistically significant predictor of neurologic mortality on univariate analysis was female sex ($P = .0283$). Two of the five female patients in the series died, accounting for both fatalities in the entire series. Statistical significance for female sex was also seen with the other two outcome measures. Increased permanent neurologic complications or death occurred in female patients, with 57% experiencing this outcome compared with only 22% of the male patients ($P = .0825$). Similarly, when consider-

TABLE 1: Clinical predictors (*P* values) of neurologic morbidity and mortality

Clinical Predictor	All Neurocomplications	Permanent Neurocomplications	Neuromortality
Age	0.4014	0.7392	0.2549
Sex	**0.0846**	**0.0825**	**0.0283**
Race:			
White	1.0000	1.0000	1.0000
Black	1.0000	0.6548	1.0000
Failed antiplatelet	0.4499	1.0000	1.0000
Failed coumadin ± heparin	0.1312	**0.0685**	0.1417
Comorbidity history:			
Cardiac	0.3172	1.0000	0.5142
Hypertension	0.7110	0.6927	0.4130
Diabetes	**0.0378**	**0.0604**	0.5277
Smoking	0.5470	0.1866	1.0000
Lipids	0.8759	0.4770	0.5142
CRF	1.0000	1.0000	1.0000
PVD	0.7110	0.6927	1.0000
Other	1.0000	1.0000	0.1498
>3 factors	**0.0931**	0.4770	0.5142
Preprocedural U/S velocity	0.9746	0.6557	0.3544
Postprocedural U/S velocity	0.7409	0.8019	0.8061

Note: Boldface indicates statistical significance. (*P* <.10).

TABLE 2: Procedural predictors (*P* values) of neurologic morbidity and mortality

Procedural Predictors	All Neurocomplications	Permanent Neurocomplications	Neurologic Mortality
Initial vs. later experience	0.6485	0.6481	1.0000
Primary Interventionalist:			
TM	0.2677	0.4355	0.5277
JP	0.4401	1.0000	1.0000
JB	0.3846	0.2821	**0.0513**
PR	0.6857	0.6486	1.0000
Type of stent (velocity vs. other)	0.8394	0.7983	0.4872
Use of abciximab	0.2591	0.6985	1.0000

Note: Boldface indicates statistical significance. (*P* <.10).

TABLE 3: Angiographic predictors (*P* values) of neurologic morbidity and mortality

Angiographic Predictors	All Neurocomplications	Permanent Neurocomplications	Neurologic Mortality
Basilar lesion	0.2651	0.1552	1.0000
Maximum stenosis:			
Percentage	0.3186	0.4652	0.7075
L/S ratio	0.5460	0.2441	**0.0518**
Residual	0.1386	0.2459	0.1144
Concentric	0.4551	1.0000	1.0000
Mori A	0.7267	0.4110	0.1477
Mori B	1.0000	1.0000	**0.0530**
Mori C	0.6285	0.1167	1.0000
Tandem or bilateral vertebral artery lesions:			
Presence	0.9658	0.7139	0.5294
Both treated	1.0000	1.0000	1.0000
>50%	0.8002	1.0000	0.5134
PICA distal to lesion	0.3201	1.0000	1.0000
AICA distal to lesion	0.6372	0.6305	0.4444
Presence of collaterals	0.9808	0.4328	1.0000
Ulceration	1.0000	0.6493	0.3176

Note: Boldface indicates statistical significance. (*P* <.10).

ing all neurologic complications, 71.4% of female patients experienced a neurologic complication compared with 31.2% of male patients ($P = .0846$).

Statistical significance on univariate analysis was achieved by diabetes, which was negatively associated with two outcome measures, all neurologic complications ($P = .0378$) and permanent neurologic morbidity and mortality ($P = .0604$). It was surprising that the presence of diabetes appeared protective, because only 2/15 (13.3%) diabetic patients developed permanent or transient neurologic complications compared with 13/25 (52%) nondiabetics. Similarly 1/15 (6.7%) patients with diabetes versus 10/25 (40%) without diabetes developed permanent neurologic complications or death.

Another clinical predictor that achieved statistical significance on univariate analysis was the presence of three or more comorbidities in association with all neurologic complications ($P = .0931$). Once again, a protective effect was seen in that those patients with three or more comorbidities developed fewer neurologic complications (3/15 or 20%) than did healthier patients (12/24 or 50%). This trend was not reflected in the relationship between this predictor and the two other outcome measures, neurologic mortality and permanent neurologic complications.

The failure of coumadin or heparin therapy before intervention was another clinical predictor that was statistically significant on univariate analysis. Oddly enough, patients who had failed coumadin or heparin before treatment were less likely to experience a permanent neurologic complication or death. Poor outcomes occurred in 4/24 (16.7%) patients who had failed coumadin or heparin compared with 7/15 (46.7%) patients who had not failed anticoagulation therapy.

It is noteworthy that neither age, race, failure of antiplatelet agents, smoking, nor pre- and postprocedural transcranial sonography velocity was associated with any of our three outcome measures.

Procedural Predictors

There did not appear to be any temporal association with neurologic morbidity or mortality. Patients in the latter half of the series were just as likely to experience complications as patients in the initial half of our experience. The type of stent and the use of abciximab did not influence outcome either.

Angiographic Predictors

Considering the angiographic predictors, the ratio of length to stenosis (L/S ratio) and the presence of a Mori B lesion (5–10 mm in length, extremely eccentric and moderately angulated, or chronic and totally occlusive for <3 months) were statistically significant predictors of neurologic mortality on univariate analysis. Increased mortality was associated with lesions that had high L/S ratio ($P = .0518$). In other words, lesions that were longer and narrower tended to have a higher mortality rate.

Not surprisingly, Mori B lesions were also signifi-

cantly associated with mortality ($P = .0530$). Two of the eight patients with Mori B lesions died, accounting for both deaths in this series. Similarly, Mori C lesions were associated with increased permanent neurologic complications or death, although this did not reach statistical significance ($P = .1167$). Three (60%) of the five patients with Mori C lesions suffered permanent neurologic complications or death compared with 7/28 (25%) of patients who did not have a Mori C lesion.

An interesting trend that did not reach statistical significance was the association between permanent neurologic complications and basilar lesions ($P = .1552$). It is not surprising that increased residual stenosis also appeared to be associated with an increased incidence of all neurologic complications and mortality. That tandem lesions, more severe stenoses, ulceration, and the absence of collaterals did not predict the development of a neurologic complication or death is noteworthy.

Multivariate Analysis

Three models were created on the basis of each outcome measure and their statistically significant clinical and angiographic predictors as determined by univariate analysis ($P < .10$). Considering the neurologic mortality model, female sex, L/S ratio, and presence of a Mori B lesion were entered into this model, and none of these potential predictors achieved statistical significance (at the $P < .05$ level). Similarly, female sex, failure of coumadin treatment with or without heparin, and diabetes were not independently significant predictors of permanent neurologic complications (including death).

When one considers all neurologic complications (including death), however, the presence of diabetes was found to be the only independent predictor of this outcome. Female sex and the presence of three or more comorbidities were not independent predictors of all neurologic complications, despite being significant on univariate analysis.

Discussion

Ischemic disease of the intracranial posterior circulation is a formidable problem with an abysmal natural history. In fact, some studies have estimated the stroke rate at about 7–10/100 patient years while on medical treatment (1, 2). Furthermore, patients who continue to experience symptoms despite maximal medical treatment have a 45% per year risk of recurrent stroke or death (11). In some cases, an extracranial-intracranial bypass is possible, but these procedures are associated with significant mortality (3–21%) and morbidity (13–55%) and have not been conclusively demonstrated to reduce stroke risk (12, 13).

There have been a number of relatively small series describing balloon angioplasty and stent placement for intracranial vertebrobasilar atherosclerosis (3–10). This newer procedure is still associated with

considerable morbidity (0–25%) and mortality (0–36.4%) but appears promising in properly selected patients. In comparison to prior reports, our mortality rate was 5.1% (2/39), and our permanent neurologic morbidity rate was 23.2% (9/39).

Part of the problem with determining an individual patient's risk is that no single institution has an extensive experience with performing the procedure for this indication. The largest series published to date numbers only 16 patients (5). Therefore, we analyzed our series of 39 patients in an effort to determine the clinical, procedural, and angiographic risk factors for neurologic complications or morbidity. Despite having the largest published series to date, many potential predictors did not achieve statistical significance on univariate and subsequent multivariate analysis.

On multivariate analysis, only diabetes was found to be a statistically significant and independent predictor of all neurologic complications. This relationship was actually somewhat surprising, because diabetic patients were *less* prone to developing neurologic complications when one might expect the converse to be true. We are not sure how to explain this phenomenon and believe that larger studies are required before any conclusions can be made about the relevance of this factor.

Nevertheless, univariate analysis demonstrated certain predictive factors related to procedural risk. Among the clinical predictors examined, female sex was the only statistically significant predictor of neurologic mortality. One might postulate that, theoretically, the typically smaller blood vessels in women might make it more technically challenging to perform this intervention without complications. Because only two patients died and both were female, however, it is more likely that the small sample size contributed to this finding rather than the existence of a true association. Regardless, it would be worth reassessing the importance of this factor in a larger series of patients.

Another clinical predictor of interest is the failure of coumadin or heparin before the intervention. Patients who did not respond to coumadin or heparin were less likely to develop any neurologic complication, permanent or otherwise. This cohort of patients receiving anticoagulation may differ from those who did not in terms of local hemodynamics, blood coagulability, or other indeterminate factors. Alternatively, the difference between these two cohorts may reflect the importance of anticoagulation periprocedurally. All patients were fully heparinized during the procedure via intravenous heparin boluses, and the level of anticoagulation was intermittently tested with their activated clotting time (ACT). Many patients who had failed coumadin or heparin, however, were in-patients and often arrived for their procedure already on intravenous heparin at therapeutic levels. At least theoretically, these patients would have a more stable level of anticoagulation before the procedure began, and presumably this would carry through to the actual procedure itself. The other group of patients could potentially have fluctuating heparin levels, because heparinization is administered as a bolus and intermittent ACT checks are inherently less accurate than preprocedural partial thromboplastin time levels determined in the laboratory.

Our analysis of angiographic risk factors was hampered because some angiograms were not available for retrospective review. Nevertheless, we found two relationships to be statistically significant on univariate analysis. The L/S ratio and Mori B lesions appeared to be correlated with neurologic mortality.

Some authors believe that a combination of factors is important in determining the risk of treatment for a particular lesion, and to that end, the Mori classification was developed (14). In this classification system, the Mori C lesions (> 10 mm in length, extremely angulated with an excessively tortuous proximal segment, or chronic and totally occlusive for 3 months or longer) are thought to be higher risk lesions, because the stenosis is lengthier and more occlusive. In the present study, a significant relationship was found between Mori B lesions and mortality, although a trend toward increased permanent neurologic morbidity and mortality was seen with Mori C lesions. Stronger correlations were not evident probably because the numbers in each category were small.

One of the problems with the Mori classification system is that each category is not mutually exclusive. For example, a lesion could be 5–10 mm in length and concentric, which would not fit perfectly into either the Mori A or B category. To simplify this classification system and make it more objective and reproducible, we derived a ratio of the length of the stenosis to the minimal diameter of the vessel at the site of the lesion. For example, a 10-mm-long lesion with a minimal lumen diameter of 0.5 mm would have an L/S ratio of 20. Therefore, a higher L/S ratio would represent a longer or more occlusive lesion.

By examining this number for each treated lesion, we found a statistically significant correlation between L/S ratio and mortality and a trend toward increased permanent neurologic complications with higher L/S ratios. This appears to be clinically logical, because a longer and more narrow lesion would be technically more challenging and thus at a higher risk for distal plaque embolization. Use of the L/S ratio is advantageous in another respect, in that measurement errors secondary to magnification are obviated if both length and minimal diameter are measured on the same film. We did not derive an L/S ratio "threshold" from our data, because it was not found to be statistically significant and any further analysis would be invalid. It might be worthwhile, however, to examine this variable in a larger series of patients.

Surprisingly enough, tandem lesions or bilateral vertebral lesions did not predict an increased complication rate. Once more, because only three patients had treatment of both lesions during the same procedure, the small number of patients could explain why no association was found. There was also no association between complication rate and absence of pial collaterals either. Furthermore, lesion morphology in terms of the degree of stenosis, eccentricity of

the plaque, and presence of ulceration were not associated with an increased risk of complications.

Conclusion

The presence of diabetes was found to be the only independent statistically significant clinical predictor of neurologic mortality. It is surprising that diabetic patients were less likely to die from this procedure. Although several other clinical and angiographic predictors were statistically significant on univariate analysis, none of these factors proved significant once confounders were addressed. Therefore, despite having the largest reported series of patients thus far, we were unable to find any statistically significant angiographic predictors of neurologic complications or mortality. There was, however, a trend toward a higher complication and mortality rate with an increased L/S ratio. Unfortunately, the small number of patients in our study limits our conclusions, and therefore further studies with larger cohorts and perhaps even a national registry is needed to address this clinically important question.

References

1. **Prognosis of patients with symptomatic vertebral or basilar artery stenosis: the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group.** *Stroke* 1998;29:1389–1392
2. Qureshi AI, Ziai WC, Yahia AM, et al. **Stroke-free survival and its determinants in patients with symptomatic vertebrobasilar stenosis: a multicenter study.** *Neurosurgery* 2003;52:1033–1039; discussion 1039–1040
3. Higashida RT, Tsai FY, Halbach VV, et al. **Transluminal angioplasty for atherosclerotic disease of the vertebral and basilar arteries.** *J Neurosurg* 1993;78:192–198
4. Barakate MS, Snook KL, Harrington TJ, et al. **Angioplasty and stenting in the posterior cerebral circulation.** *J Endovasc Ther* 2001;8:558–565
5. Lylyk P, Cohen JE, Ceratto R, et al. **Angioplasty and stent placement in intracranial atherosclerotic stenoses and dissections.** *AJNR Am J Neuroradiol* 2002;23:430–436
6. Levy EI, Horowitz MB, Koebbe CJ, et al. **Transluminal stent-assisted angiplasty of the intracranial vertebrobasilar system for medically refractory, posterior circulation ischemia: early results.** *Neurosurgery* 2001;48:1215–1221; discussion 1221–1213
7. Levy EI, Hanel RA, Bendok BR, et al. **Staged stent-assisted angioplasty for symptomatic intracranial vertebrobasilar artery stenosis.** *J Neurosurg* 2002;97:1294–1301
8. Terada T, Higashida RT, Halbach VV, et al. **Transluminal angioplasty for arteriosclerotic disease of the distal vertebral and basilar arteries.** *J Neurol Neurosurg Psychiatry* 1996;60:377–381
9. Mori T, Kazita K, Chokyu K, et al. **Short-term arteriographic and clinical outcome after cerebral angioplasty and stenting for intracranial vertebrobasilar and carotid atherosclerotic occlusive disease.** *AJNR Am J Neuroradiol* 2000;21:249–254
10. Gress DR, Smith WS, Dowd CF, et al. **Angioplasty for intracranial symptomatic vertebrobasilar ischemia.** *Neurosurgery* 2002;51:23–27; discussion 27–29
11. Thijs VN, Albers GW. **Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy.** *Neurology* 2000;55:490–497
12. Ausman JI, Diaz FG, Vacca DF, Sadasivan B. **Superficial temporal and occipital artery bypass pedicles to superior, anterior inferior, and posterior inferior cerebellar arteries for vertebrobasilar insufficiency.** *J Neurosurg* 1990;72:554–558
13. Hopkins LN, Budny JL. **Complications of intracranial bypass for vertebrobasilar insufficiency.** *J Neurosurg* 1989;70:207–211
14. Mori T, Fukuoka M, Kazita K, Mori K. **Follow-up study after intracranial percutaneous transluminal cerebral balloon angioplasty.** *AJNR Am J Neuroradiol* 1998;19:1525–1533