Subacute Stent Thrombosis in Intracranial Stenting

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Background and Purpose—We sought to determine the safety of intracranial stenting with respect to subacute stent thrombosis in patients being treated with standardized antiplatelet therapy.

Methods—We retrospectively evaluated the outcome of primary intracranial stenting of atherosclerotic stenoses and of stenting in coil embolization procedures in 67 patients. We focused on those cases that led to subacute stent thrombosis even though the patients had been treated with standardized antiplatelet therapy before, during, and after stent placement. Patient age ranged from 19 to 78 years. In 33 patients, stents were placed for treatment of atherosclerotic stenoses; in the remaining 34 patients, stents were placed to assist coiling of aneurysms. The patients in this study were treated between January 2003 and August 2007.

Results—Of the total 67 patients initially treated successfully by intracranial stenting, 7 patients developed subacute stent thrombosis. Of these 7 patients, 3 received stent placement into the basilar artery because of an underlying stenosis; in 1 patient, a stenosis of the M1 segment of the middle cerebral artery was treated. In 3 patients, aneurysms of the anterior cerebral artery, the posterior inferior cerebellar artery, and the basilar artery were treated by stent-assisted coil embolization. In 4 of the 7 patients with subacute thrombosis, recanalization of stents by local application of recombinant tissue-type plasminogen activator was successful.

Conclusions—Intracranial stenting can lead to subacute stent thrombosis, even in patients who are treated with standardized antiplatelet therapy. Such complications have been described for patients after coronary artery stenting, but to our knowledge, no one has reported on a comparable number of cases of intracranial stenting procedures. In certain clinical scenarios, local thrombolysis with recombinant tissue-type plasminogen activator is an important treatment option to deal with subacute stent thrombosis.

Key Words: antiplatelet drugs ■ antithrombotics ■ imaging ■ interventional neuroradiology ■ intracranial aneurysm ■ intracranial stenosis ■ neuroradiology ■ stenting ■ stents ■ thrombolysis ■ thrombosis

Subacute stent thrombosis after intracranial stenting procedures is a potentially fatal complication that has not been discussed in detail in the literature.1 In contrast, stent thrombosis after coronary artery angioplasty is an important issue that has been reported on a regular basis for >10 years.2–4 Furthermore, researchers in interventional cardiology have analyzed the underlying pathophysiology of stent thrombosis in depth5–9 and have presented treatment options to lower the overall risk for this complication.10–12 Apart from that, effective treatment procedures have been reported for cases of subacute stent thrombosis after coronary angioplasty.13–16

Several reports17–20 suggest intracranial angioplasty as a technically feasible and clinically effective way to treat symptomatic intracranial arterial stenoses, which results in a substantial reduction in long-term stroke and death rates. Nevertheless, the overall number of patients being included in these studies is relatively small compared with cases presented in the interventional cardiology literature. The high periprocedural stroke and death rates reported by some authors21–23 indicate how extremely fragile the arterial wall of the intracranial circulation is and how easily manipulation can lead to disastrous patient outcome. This is 1 reason why only very recently have general recommendations regarding stenting for intracranial stenoses been published.24

The situation is similar for stent-assisted coiling of intracranial aneurysms, where stents are placed across the neck of an aneurysm to allow for coil deployment into the aneurysm without compromising the parent vessel. Thus, it is now possible to coil aneurysms that would have been untreatable without stents.25 Unfortunately, it is not clear yet to what extent serious postprocedural complications such as in-stent stenosis or stent thrombosis26 will influence overall long-term patient outcome after stenting and coiling of aneurysms.

Taking into account how delicate and potentially dangerous intracranial stenting procedures can be and how small the number of different therapeutic options is in patients with symptomatic intracranial arterial stenoses, it seems even more...
important to gain deeper insight into subacute stent thrombosis to prevent this potentially fatal complication.

The purpose of this study was to find out how often subacute thrombosis occurs after intracranial stenting, under what circumstances this complication can be expected, and how it can be effectively treated.

**Patients and Methods**

**Patients**

Between January 2003 and August 2007, we treated 67 patients with endovascular interventions that involved stent placement into intracranial vessels. Stenting was done either for clinically significant stenoses or in cases of coiling of nonruptured aneurysms. We analyzed all patient data retrospectively to gain detailed information about the clinical history, indication for stent placement, the stenting procedures, associated interventional procedures, and patient outcome. Concerning outcome, we were especially interested in those cases that presented with subacute stent thrombosis, and we wanted to know how this complication could be dealt with.

The age of patients included in our analysis (31 men and 36 women) ranged from 19 to 78 years (median, 54 years). From 29 patients who were stented in the anterior cerebral circulation, 5 patients received stent angioplasty in the M1 segment of the middle cerebral artery (MCA). In another 6 patients, stenoses of the intracranial part of the internal carotid artery (ICA) were treated. In the remaining 18 patients of this anterior circulation subgroup, stents were used for coiling of aneurysms. In 7 of these patients, we treated aneurysms of the proximal anterior cerebral artery (ACA) and in 11 patients, aneurysms of the intracranial part of the ICA.

Of 38 patients being stented in the posterior circulation, 9 patients received coiling of a basilar artery aneurysm after vessel reconstruction. In 5 patients, aneurysms of the posterior cerebral artery (PCA) and in another 2 patients aneurysms of the posterior inferior cerebellar artery (PICA) were treated by stent placement before coiling. Significant stenoses in the basilar artery were stented in the remaining 22 of 38 patients.

The indication for stent-assisted angioplasty was given in clinical symptomatic stenoses refractory to medical treatment with a loss of luminal diameter of >50%. The grades of stenosis were calculated according to the North American Symptomatic Endarterectomy Trial criteria.27 Reconstruction of the aneurysm-bearing vessel by stenting was done when the aneurysm had a broad neck, when coils for other reasons prolapsed into the parent vessel, when fusiform or dissecting aneurysms had to be coiled, or in cases where giant aneurysms had to be treated.

**Interventional Procedure and Medication**

According to the treatment guidelines of recent international multicenter trials on stenting in intracranial arteries,28,29 all patients received a daily dose of 100 mg aspirin and 75 mg clopidogrel 3 days before each stenting procedure. Intracranial stenting for treating significant stenoses in the ICA and in the vertebral artery were performed under local anesthesia. All cases with stenoses in the MCA or basilar artery and all patients with stent-assisted coiling were treated under general anesthesia. In all patients, we administered an intravenous bolus of heparin after placing a 6F sheath into the ICA or the vertebral artery, a microguidewire (eg, Transend 14; Boston Scientific, Fremont, Calif). After successful stent placement, we coiled the aneurysm through the open stent struts.

The correct stent position was controlled by injection of contrast agent through the guiding catheter. After slow inflation of the balloon over 3 to 5 seconds for placing the stent, the balloon was immediately deflated to restore blood flow. In the next step, the balloon was withdrawn to document correct stent positioning by contrast agent injection with the guiding catheter. In those patients who were treated for vascular stenoses, the guidewire was withdrawn after a satisfying result of the angioplasty procedure had been documented.

In patients who were treated for aneurysms, the aforementioned procedure of stent placement with balloon assistance was replaced by deployment of a self-expanding stent (Neuroform; Boston Scientific, Fremont, Calif). After successful stent placement, we coiled the aneurysm through the open stent struts.

After the intervention, heparinization was continued only in those patients in whom the treatment result was less satisfying because of a slight residual stenosis or because of coil herniation into the stent lumen. In these patients, heparin was administered for 24 hours after the intervention to reach a partial thromboplastin time >50 seconds.

After leaving the angiographic suite, the patients received a detailed neurologic examination, and their status was monitored on a neurologic or neurosurgical intensive care ward for the following 24 hours. Blood pressure was maintained at normal rates or slightly below normal to prevent hyperperfusion syndrome in those patients who had been stented because of severe stenoses. Furthermore, all patients were examined by transcranial vascular ultrasound 4 and 24 hours after the intervention to monitor early flow changes in the stented artery. Subacute follow-up digital subtraction angiography was performed in those patients who showed new neurologic symptoms. Whenever those angiograms showed stent thrombosis, local intra-arterial thrombolysis was used to fully recanalize the vessel. This was done by infusion of an initial weight-adapted intravenous dose of abciximab (ReoPro) and local administration of rtPA into the thrombus, along with mechanical irritation.

**Results**

Seven of the 67 patients (10.4%) who were stented in the intracranial circulation developed subacute stent thrombosis. The complication occurred in 4 of 33 (12.1%) patients who were treated for atherosclerotic stenoses and in 3 of 34 (8.8%) patients receiving stent-assisted coiling. An overview of all 7 cases is presented in the Table. Overall, we observed a median delay of 3 days in the 7 patients who experienced stent thrombosis between the stenting procedure and the occurrence of the complication.

Three patients developed stent thrombosis after stenting of significant atherosclerotic stenosis in the basilar artery; in 1 patient, severe stenosis of the M1 segment of the left MCA had been treated 3 days before the complication. Patients who had been stented for stenoses in the posterior circulation developed stent thrombosis after 3, 4, and 5 days. One of the patients being stented for basilar artery stenosis started to develop facial nerve palsy, dysarthria, and mild weakness of the right arm 4 days after the stenting procedure. Symptoms in this patient developed so slowly that he was only referred to the neuroradiologic service on the next day when magnetic resonance imaging demonstrated an already definitive infarction in the pons due to stent thrombosis (Figure 1).

Thrombolysis in 1 patient with short-term stent thrombosis in a basilar artery stent (3 days after stenting) resulted in transient hemianopsia due to a small embolism into the left PCA and several microembolic infarcts in the cerebellar hemispheres. In the case of subacute MCA stent thrombosis, early thrombolysis also led to only minor transient deficits with mild aphasia and hemiplegia resolving within days after the intervention (Figure 2). Only the fourth patient with
subacute stent thrombosis after treatment of severe atherosclerotic stenosis in the vertebral and basilar artery had a fatal outcome, as he had already developed large embolic infarctions in the brain stem and thalamus before the basilar artery stent was reopened by local thrombolysis.

In the 3 remaining patients who developed subacute stent thrombosis, aneurysms of the ACA, of the tip of the basilar artery, and at the ostium of the PICA had been coiled 12, 1, and 2 days, respectively, before stent thrombosis occurred. In the patient with an aneurysm of the PICA, thrombosis remained untreated, because angiography revealed sufficient perfusion of the corresponding cerebellar territory by collaterals. The patient who had undergone reconstruction of an aneurysm in the proximal right ACA before coiling suddenly reported weakness in the left leg 12 days after the interventional treatment, which resulted in complete plegia. After thrombolysis of the subacute stent thrombosis in the right ACA, the patient was almost immediately able to move the left leg against gravity.

After thrombolysis of an in-stent thrombosis in the basilar tip, the third patient being stented in the posterior circulation for aneurysm coiling experienced a residual hemianopsia due to infarction in the perfusion territory of the right PCA. Nonetheless, the severe hemiplegia of the left side of the body accompanied by a horizontal gaze palsy vanished completely after successful thrombolysis. In all cases treated for subacute stent thrombosis, initially abciximab was given intravenously in a dose that was adapted to body weight before intra-arterial thrombolysis. Thrombolysis of subacute stent thrombosis was performed with superselective local infusion of rtPA (10 to 20 mg within 60 minutes). We did not observe any bleeding complications during or after thrombolysis in these cases.

**Discussion**

With 7 patients developing subacute instant thrombosis of a total of 67 (10.4%) patients who received stenting of intracranial vessels in our hospital, the rate of this serious complication was certainly higher than expected. Concerning the pathophysiology of instant thromboses, we actually analyzed 2 distinct groups of patients: those who were treated for atherosclerotic stenoses and those who received stent-assisted coiling. In patients being stented for atherosclerotic stenoses,
plaque rupture with release of intrinsic factor promoting thrombosis is very likely to occur. In stent-assisted coiling, a different stent strut design and potential prolapse of coil segments into the parent artery might determine the risk for thrombosis. Nonetheless, instant thrombosis occurs at a similar rate in both groups and in a similar time interval, ie, only a few days after the stenting procedure. Although we do not know the exact pathophysiologic of stent thromboses in our series, the overall outcome of the patients is encouraging.

Of the 7 patients with intracranial stent thrombosis, 5 had a long-term outcome of no or only minor neurologic deficits. In 1 patient, severe neurologic deficit resulted from delayed diagnosis of instant thrombosis. Only 1 patient treated with intra-arterial thrombolysis had a fatal outcome directly due to subacute stent thrombosis.

To our knowledge, there are no reports in the neurointerventional literature with which to compare our findings on the frequency of subacute in-stent thrombosis. In the interventional cardiology literature, a number of reports present numbers on the occurrence rates of subacute thrombosis in coronary artery stents. Subacute thromboses are defined by cardiologists to occur within the first 28 days after the procedure. For bare metal stents, the numbers are in the range of 0.5% to 1.5%. In drug-eluting stents for coronary artery intervention, subacute thrombosis was reported to be higher compared with bare metal stents (0.9% to 3.1%) but still did not reach the frequency that we observed in our study for intracranial stents. This should be considered in the current ongoing discussion on using drug-eluting stents in the intracranial circulation. As in our study, there is a high level of uncertainty about the reasons for instent thrombosis in the interventional cardiology literature. One reason being frequently debated by many authors is the low response or nonresponse of some individuals to platelet inhibitors (eg, acetylsalicylic acid or clopidogrel). It has therefore repeatedly been suggested that platelet function in patients who develop subacute thrombotic complications should be analyzed in depth.

Testing of patients receiving clopidogrel has demonstrated a nonresponse rate of up to 17.5%. This exceeds the rate of subacute thrombosis in our patients treated for atherosclerotic stenosis by 5.4% and in patients with stent-assisted coiling by 8.7%. Although we did not perform a systematic analysis of platelet function in our patients with thrombosis, we hypothesize that at least in those patients with atherosclerotic stenoses, inadequate responsiveness to clopidogrel is the major risk factor for developing stent thrombosis in the subacute period after stenting. It may be patients with incomplete response to regular platelet inhibition are partially protected during or early after stenting because of the additional administration of heparin. Obviously, with the reduction or elimination of heparin after the intervention, these nonresponders develop stent thrombosis in the subacute period.

According to our experiences, we postulate that sufficient platelet inhibition should be demonstrated before intracranial stenting is performed in all elective cases. In cases with no or a low response to platelet inhibition, increase of the dosage of clopidogrel or acetylsalicylic acid normally results in sufficient inhibition and should significantly reduce the risk for subacute thrombosis. As an alternative, additional application of glycoprotein IIa/IIIb inhibitors could be discussed; however, this may result in an increase of the secondary hemorrhage rate and therefore would not be favorable. For the same reason, we would not recommend an increase in the dosage of platelet inhibitors (clopidogrel or acetylsalicylic acid) routinely in stent patients but to limit this to those 15% who are low- or non-responders.

A striking finding of our study is the fact that the rate of in stent thromboses is ~7 times higher for the intracranial circulation than for coronary artery stenting with bare metal stents. This might be due to the fact that intracranial vessel luminae being stented are smaller or that the perfusion pressure in coronary artery stenting is higher. Another reason for this difference between intracranial and coronary subacute stent thrombosis might be that subacute coronary stent occlusion does not always show the dramatic clinical symptoms we observe after stent thrombosis in cerebral vessels. Therefore, some subacute coronary stent thrombosis may go unrecognized.

Finally, it might be very interesting to look at specific differences in the vessel wall regarding platelet adherence in a comparison between the coronary arteries and the intracranial vessels.

Conclusions

Intracranial stenting leads to subacute stent thrombosis in ~10% of patients, even if they are treated with standardized antiplatelet therapy. To our knowledge, no one has yet reported on a comparable number of cases of intracranial stenting procedures. In certain clinical scenarios, local thrombolysis with rtPA is an important treatment option to deal with subacute stent thrombosis.

The logical next step in research about subacute stent thrombosis in the intracranial circulation would be a thorough analysis of platelet function in search of nonresponders to antiplatelet therapy before stenting. This might help to find the patients who are at risk for stent thrombosis and to prevent this life-threatening complication.

Disclosures

As a consultant for Boston Scientific, O. Jansen has a relationship with modest relevance to the topic of the article. There are no other potential conflicts of interest for the other authors of this research article.

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