Intra-arterial Administration of Papaverine during Mechanical Thrombectomy for Acute Ischemic Stroke

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Background: The use of stent retrievers for mechanical thrombectomy in acute ischemic stroke may induce significant vasospasm, which at the early phases of reperfusion may be crucial for rethrombosis of the recanalized vessel. We aimed to study whether the use of intra-arterial papaverine in selected cases of vasospasm was associated with improved cerebral perfusion, arterial reocclusion, or increased hemorrhagic complications. *Methods:* We retrospectively studied 9 consecutive patients with large artery acute occlusion, treated with stent retriever and intra-arterial papaverine. Onset to administration of intravenous recombinant tissue-plasminogen activator time, baseline National Institute of Health Stroke Scale, time to reperfusion, number of passes of the stent retriever, modified Rankin Scale score at discharge, postprocedural hemorrhage, onset to reperfusion time, papaverine dose, and thrombolysis in cerebral infarction grade were recorded in all patients. *Results:* After papaverine administration, the caliber of the infused arteries and their flow was increased in all cases. In none of the treated cases a reocclusion occurred after papaverine infusion. In one of the studied patients (11%), a parenchymal bleeding occurred 36 hours postoperatively. *Conclusions:* This small study suggests that intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after mechanical thrombectomy in acute ischemic stroke is effective and safe. **Key Words:** Acute ischemic stroke—mechanical thrombectomy—stent retriever—vasospasm—papaverine.

Introduction

In case of a large artery occlusion, the recanalization efficacy of intravenous (IV) recombinant tissue-plasminogen activator (rt-PA) has been shown to be poor compared with intra-arterial rt-PA.[1-6]

The use of mechanical devices, such as stent retrievers for blood flow restoration, has gained importance during recent years and large vessel occlusions became a target of endovascular treatment.[7-11] However, the use of stent retrievers and especially multiple passes of the device may induce significant vasospasm, which in the early phases of reperfusion may be crucial for rethrombosis of the recanalized vessel. Use of vasodilator agents in this context may decisively improve the re-established perfusion by fast and effective elimination of vasospasm. The role of these vasodilator agents has been evaluated in cases of cerebral vasospasm secondary to subarachnoid hemorrhage,[12-16] but there have been only a few studies evaluating their role in ischemic stroke.[17-27] The reports about the use of vasodilators during intra-arterial treatment of stroke suggested that it might be associated with higher reperfusion rates, but clinical outcomes were not significantly different.[22] We aimed to study whether the combination of

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mechanical thrombectomy with intra-arterial papaverine in selected cases of vasospasm was associated with improved cerebral perfusion, arterial re-occlusion, or increased hemorrhagic complications.

Patients and Methods

We retrospectively studied consecutive patients admitted from January 2012 to January 2014 with large artery acute occlusion and treated by mechanical thrombectomy with stent retriever and received intra-arterial papaverine as an adjunct to endovascular treatment. The indication of treatment with intra-arterial thrombectomy was based on the established criteria regarding time after onset and on the presence of a mismatch in perfusion imaging. Demographic and clinical characteristics of the patients were collected from the electronic case records. Digital angiography was performed under general anesthesia in all cases. Patients were treated with mechanical thrombectomy, by using the same stent retriever (Solitaire 2 Revascularization Device, ev3/Covidien, Irvine, CA). The decision to use papaverine was taken after detection of vasospasm induced by mechanical thrombectomy in the previously occluded segment and/or proximal to it, with evidence or suspicion of progressive flow reduction or delay in consecutive angiographic controls. Depending on the localization and extension of vasospasm, papaverine was infused through the guiding catheter or the microcatheter used for stent deployment. Papaverine was prepared as a solution of 300 mg in 100 mL of normal saline and infused with a rate of approximately 30 mg/minute. The amount of infused papaverine was determined by the response of the spastic vessels, and no fixed protocol was followed. Thrombolysis in cerebral infarction (TICI) criteria were used for evaluation of the degree of recanalization before and after treatment with papaverine.[14] For this retrospective study, no institutional review board approval was necessary.

Results

We identified 9 consecutive patients, 4 women and 5 men aged from 38 to 76 years (mean age, 58.1 years). Patients included in this study underwent endovascular therapy within 190-380 minutes (mean, 344 minutes) from the onset of symptoms. All patients showed angiographic evidence of significant vasospasm appearing during the procedure. Seven patients had a middle cerebral artery (MCA) occlusion, 1 patient had MCA and cervical internal carotid occlusion with evidence of chronic stenosis at the carotid bifurcation (case 5), and 1 additional patient had basilar occlusion.

IV rt-PA was given to patients who presented within the 4.5 hours time window. Eight patients received IV rt-PA, whereas 1 patient (case 4) did not receive any IV rt-PA because he developed ischemia 6 hours after cardiac surgery while on anticoagulation. The period from the onset of symptoms till administration of IV rt-PA, baseline National Institute of Health Stroke Scale, time to reperfusion, number of passes of the stent retriever, modified Rankin Scale at the time of discharge, postprocedural hemorrhage, onset to reperfusion time, papaverine dose, and TICI flow grade are summarized in Table 1. In 1 patient, remarkable vasospasm appeared after 1 stent pass, whereas in the rest of the patients, vasospasm appeared after 2-5 passes of the stent. The administered dose of papaverine ranged from 45 to 120 mg. In all cases, a full reperfusion of occluded branches (TICI grade 3 or 2b) was achieved before infusion of papaverine. After papaverine administration, the caliber of the infused arteries and their flow was clearly increased in all cases. In none of the treated cases a reocclusion occurred after papaverine infusion. In 1 patient (patient 3), a parenchymal bleeding occurred 36 hours postoperatively (11%). Another patient (patient 4) presented a small subarachnoid bleeding within 24 hours, clearly attributed to mechanical manipulations during deployment of the stent retriever.

Illustrative cases: The angiographic images of 2 cases are presented shortly in Figures 1 and 2.

Discussion

Calcium channel blockers (nimodipine, Nicardipine) and some peripheral vasodilators such as papaverine have been used for treatment of vasospasm after subarachnoid hemorrhage,[28-36] but its use in ischemic stroke is poorly studied. Cilostazol was found to protect against ischemic brain injury and hemorrhagic transformation after transient ischemic stroke in animal studies, and sildenafil has been reported to improve cerebral perfusion in the early phase of recovery after stroke. Isosteviol has been demonstrated to have protective effects against ischemia–reperfusion injury in animal studies.[17-19]

Papaverine is a benzylisoquinoline alkaloid derived from opium. It has been used as a vasodilator agent for over 70 years to treat cerebral and coronary artery vasospasm.[28] This powerful vasodilator acts by inhibiting cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) phosphodiesterases in smooth muscle, leading to increased intracellular levels of cAMP and cGMP.[29] Also it blocks the calcium ion channels and inhibits release of calcium. The half-life of papaverine has been estimated to be .8 hours.

Rosenbaum et al[23] reported on a pilot study about the safety of nicardipine for acute ischemic stroke, administered within a mean of 6.9 hours from onset, and recommended a larger study for evaluating its efficacy. Another pilot study from Japan by Shiino et al[25] in animal models with calcium channel blockers (nilvadipine and nicardipine) showed that in the nilvadipine-treated