Incidence and Predictors of the In-stent Restenosis after Vertebral Artery Ostium Stenting

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Background: The incidence and predictors for in-stent restenosis (ISR) was not fully explored. We aim to investigate the incidence and predictors of ISR after stenting at the origin of vertebral artery. *Materials and Methods:* Two hundred and six patients with 229 stents implantation between July 1, 2005 and July 31, 2015 were included in the study. All patients underwent conventional clinical and angiographic (digital subtraction angiography) follow-up at around 6 months post procedure. ISR was defined as greater than 50% stenosis within or immediately (within 5 mm) adjacent to the stent. Multivariate Cox regression analyses were utilized to investigate the predictors for ISR. *Results:* The ISR was found in 30 patients (30/206, 14.6%) with 31 lesions (31/229, 13.5%) with the mean follow-up duration of 11.1-month (range: 3 - 92 months). Stent diameter (hazard ratio 0.504, 95% confidence interval 0.294 - 0.864) was an independent predictor for ISR. *Conclusion:* ISR rate after Vertebral artery ostium stent placement is acceptable, which was conversely associated with the stent diameter.

Key Words: In-stent restenosis—Vertebral artery ostium—Ischemic stroke—Atherosclerotic stenosis

Introduction

Vertebral artery ostium (VAO) is regarded as the most common stenotic position in posterior circulation ischemic stroke.[1] Patients with atherosclerotic stenosis of 50% or more in VAO might exert a higher risk on the occurrence and recurrence of stroke or death.[2-4] However, the treatment of posterior circulation stroke remains a great challenge.

In addition to intensive medical therapy, stenting in VAO was safe and effective for preventing stroke.[5,6] Although the primary endpoint (any stroke during follow-up) of Vertebral artery Ischemic Stenting Trial showed no statistical deference between stenting and medical treatment arms,[7] the study would lend a perspective to the benefit from extracranial vertebral artery stenting which might reduce recurrent stroke.[7-9]

One of the problems for stenting in VAO is in-stent restenosis (ISR), which is induced by the excessive neointimal hyperplasia in the lumen of stent and the thrombosis in the stent. Lin et al study[10] found that CYP2C19 mutations might be a risk factor of ISR in patients with

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Conflicts of Interest: None.

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vertebral artery stent placement. However, the incidence and predictors for ISR was not fully investigated. Therefore, our study aims to explore the incidence and predictors of ISR after VAO stent implantation in Chinese patients.

Materials and Methods

Patient Information

Between July 1, 2005 and July 31, 2015, all the patients were retrieved from the Nanjing stroke registry that was an ongoing single center prospective database on stroke in Jinling Hospital in Nanjing. In the study, patients were included if they met the following criteria: (1) symptomatic stenosis greater than or equal to 50% in VAO (defined as transient ischemic attack [TIA] or stroke in the territory of vertebral artery); (2) asymptomatic stenosis greater than or equal to 70% in the VAO; (3) successful stent implantation and residual stenosis Less than or equal to 30%; (4) the imaging and clinical data were available. Patients were excluded if (1) non-atherosclerosis; (2) poor quality of the imaging.

Stent Implantation Protocol

Dual antiplatelet drugs (aspirin 100 mg and clopidogrel 75 mg) were prepared for at least 3 days prior to the stent placement. The procedure was performed under local anesthesia by the senior neuroradiologists. A 6-French sheath was placed in the femoral artery and systemic heparinization with activated clotting time of 2-3 times the baseline was maintained during the procedure. Then, A 6-French guiding catheter (Cordis, Miami Lakes, FL) was placed in the subclavian artery over a .035-in. guide wire. Next, stenotic lesions were crossed with .014-in. guidewires (Cordis) under road-map fluoroscopy. The appropriate stent was subsequently used to the lesion. The diameter of the deployed stent was based on the diameter of the distal normal vessel and the length of the stent had to cover 3-5 mm of normal lumen on either side of the lesion. Balloon-expandable bare-metal stents (BMS) (Express Vascular SD; Boston Scientific Corporation, Natick, MA) were deployed as the first choice. Drug-eluting stents (DES) (sirolimus-eluting stent [SES] Firebird2 stent; MicroPort Medical, Shanghai, China) as coronary stents were used only when BMS implantation was predicted to be challenging due to the tortuosity of the proximal vertebral artery. Finally, angiography was performed to evaluate the residual stenosis. Dual antiplatelet drugs (aspirin and clopidogrel) were continued for at least 6 months and then switched to aspirin for lifelong. All patients were given a standardized prevention program, including smoking cessation, alcohol restriction, management of blood pressure, blood glucose, and serum lipid.

Clinical and Angiographic Follow-up

The clinical follow-up was performed by telephone interview or clinic visits at 1, 3, 6, 12 months and yearly thereafter post procedure. The clinical events including TIA, stroke (both anterior and posterior circulation), myocardial infarction or any death were recorded as clinical outcomes.

The digital subtraction angiography (DSA) follow-up was performed usually at 6 months after the surgery. The angiographic assessment was performed according to the decision of the physicians once the patient had recurrent stroke or TIA. ISR was defined as greater than 50% stenosis within or immediately (within 5 mm) adjacent to the stent[11]. Patients with ISR but no occlusion were treated with balloon angioplasty alone or stent re intervention.

Statistical Analysis

The data analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). ISR and clinical events during follow-up were evaluated using Kaplan-Meier analysis. To evaluate the differences between the ISR group and no ISR group, categorical data were compared using Pearson's chi-square or Fisher exact tests; continuous variables were analyzed by student *t* tests for normal distributed data or Mann-Whitney *U* tests for skewed data. Significant variables in the univariate analyses were further put into a multivariate Cox regression analysis with backward elimination modeling. *P* less than .05 was considered statistically significant.

Results

A total of 206 patients (age range, 42-82 years) who had undergone 229 stents implantation were included in the analysis. Table 1 summarizes the baseline characteristics.

Clinical and Angiographic Outcomes during Follow-up

With mean clinical follow-up of 32.7-month (range: 4-29 months), 23 patients (23/206, 11.2%) had clinical events. Of those, 4 patients died of nonstroke related diseases; 1 patient had TIA; 5 patients suffered from cerebral hemorrhage; and the other 13 patients experienced cerebral infarction. Kaplan-Meier curve for clinical event was constructed (Fig. 1), which showed that the cumulative clinical event-free survival was 98% at 12 months and 94% at 24 months after stent placement.

The ISR was identified in the 30 patients (30/206, 14.6%) with 31 lesions (31/ 229, 13.5%) with the mean follow-up duration of 11.1-month (range: 3-92 months). In our study, Kaplan-Meier curve for ISR (Fig. 2) showed that the cumulative ISR rate was 7%, 21% and 34% at 6, 12 and 24 months after the procedure, respectively. Among 30 patients with ISR, three (10.0%) had clinical events. Of those, 1 patient died of stroke; 1 patient died of nonstroke related diseases; and 1 patient experienced cerebral infarction.

Predictors for ISR

Table 2 shows the comparisons of clinical, demographic, and procedure characteristics between the two groups. Stent diameter, stent type, smoking, and diabetes