JoS JOURNAL OF STROKE

Journal of Stroke 2019;21(1):101-104
https://doi.org/10.5853/jos.2018.00479

Letter to the Editor

Cerebrovascular Drug-Eluting Stent versus Bare-Metal Stent in the Treatment of Vertebral Artery Stenosis: A Non-Inferiority Randomized Clinical Trial

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Dear Sir:

Drug-eluting coronary stents have been used for patients with vertebral artery stenosis to prevent the occurrence of in-stent restenosis which affects the therapeutic efficacy of angioplasty and stenting. However, the results are inconsistent.[1] A new cerebrovascular sirolimus-eluting stent system (Maurora, Alain Biotechnology Co. Ltd., Beijing, China),[2] different from the Apollo stent systems (Apollo, MicroPort Scientific Corp., Shanghai, China) made of 316L stainless steel,[3] adopts L605 cobalt-chromium alloy that offers a higher yield and has tensile strength characteristics allowing for thinner thickness while maintaining adequate strength and flexibility suitable for a curved artery of the brain, and the sirolimus can reduce the cell proliferation. This trial was to evaluate the safety and efficacy of this new drug-eluting stent.

Table 1. The inclusion and exclusion criteria

Inclusion criteria
1. Aged 18 years or older
2. Intracranial vertebral artery stenosis of at least 70% with a vertebral transient ischemic attack or ischemic stroke who had at least one antiplatelet drug in the previous 6 months, or extracranial vertebral artery stenosis of at least 70%.
3. Target vessel reference diameter must be measured to be 2.00 to 5.00 mm; the length of the target stenotic lesion is ≤20 mm.
4. Only one target artery needs one stent.
5. mRS ≤3
6. At least one atherosclerotic risk factor, such as hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia and smoking history.
7. Patients understand the purpose and requirements of the study and have signed the informed consent form.
Exclusion criteria
1. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is proximal or distal to the target intracranial lesion.
2. Non-atherosclerotic stenosis.
3. Intracranial (subarachnoid, subdural, or epidural) hemorrhage within 6 weeks.
4. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation. In addition, other cardiac sources of emboli such as left ventricular aneurysms, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcified aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma.
5. Intracranial aneurysm, tumors, or any intracranial vascular malformations.
6. Allergic reaction to any of the medical therapy, including aspirin, clopidogrel, heparin, sirolimus, contrast agents, and local or general anesthetics.
7. Recent gastrointestinal bleed that would interfere with antiplatelet therap.
8. Active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelets <100,000, hematocrit <30, international normalized ratio >1.5, clotting factor abnormality that increases the risk of bleeding, current alcohol or substance abuse, uncontrolled severe hypertension (systolic pressure >180 mm Hg or diastolic pressure >115 mm Hg), severe liver impairment aspartate transaminase or alanine transaminase >3×normal, cirrhosis, or creatinine >265.2 mmol/L (unless on dialysis).
9. Major surgery (including open femoral, aortic, or carotid surgery) within previous 30 days or planned in the next 90 days after enrollment.
10. Calcified plaque difficult to be diluted, or embolism in target lumen.

Table 2. Baseline and procedure-related characteristics

Parameter	DES-G (n=20)	BMS-G (n=20)	Difference (95% CI)	*P*
Age (yr)	58.6±10.6	61.6±8.4	−3.0 (−9.1 to 3.2)	0.335
Male sex	16 (80.0)	16 (80.0)	0 (−24.8 to 24.8)	1.000
BMI	24.4±2.7	25.4±2.9	−1.0 (−2.9 to 0.7)	0.240
Hypertension	13 (65.0)	18 (90.0)	−25.0 (−49.7 to −0.3)	0.127
Hyperhomocysteinemia	7 (35.0)	6 (30.0)	5.0 (−24.0 to 34.0)	1.000
Hyperlipidaemia	3 (15.0)	3 (15.0)	0 (−22.1 to 22.1)	1.000
Diabetes mellitus	4 (20.0)	7 (35.0)	−15.0 (−42.3 to 12.3)	0.480
Smoker	9 (45.0)	9 (45.0)	0 (−30.8 to 30.8)	1.000
Coronary artery disease	4 (20.0)	3 (15.0)	5.0 (−18.5 to 28.5)	1.000
Peripheral artery atherosclerosis	7 (35.0)	10 (50.0)	−15.0% (−45.3 to 15.3)	0.523
Recent qualifying event			NA	0.005
Stroke	5 (25.0)	11 (55.0)		
TIA	5 (25.0)	8 (40.0)		
Others	10 (50.0)	1 (5.0)		
Location of the target stenosis in the vertebral artery				
V1-V3*	17 (85.0)	8 (40.0)	45.0 (18.4 to 71.6)	0.008
Time from qualifying event to procedure	35 (15–36)	19 (9–25)	NA	0.488
mRS score			NA	0.742
1	16	16		
2	4	3		
3	0	1		
Arterial target stenosis (%)	80 (75–85)	82.5 (70–90)	NA	0.535
Referenced normal artery diameter (mm)	3.8±0.8	3.4±0.6	0.4 (−0.05 to 0.86)	0.078
MORI			NA	0.823
A	11	9		
B	5	10		
C	4	1		
Stent length	12 (12–14)	13 (10.5–13)	NA	0.236
Balloon expansion time (sec)	20 (15–30)	30 (20–34)	NA	0.158
Residual stenosis	10 (2.5–10)	7.5 (2.5–10)	NA	0.822

Values are presented as mean±SD, number (%), or median (range).
DES-G, drug-eluting stent group; BMS-G, bare-metal stent group; CI, confidence interval; BMI, body mass index; NA, not applicable; TIA, transient ischemic attack; mRS, modified Rankin Scale; MORI, Mori type.
*V1-V3, the extracranial segments of the vertebral artery.

This was a single center, open-label, prospective, non-inferiority, randomized, controlled trial (ChiCTR-IIR-16009115).[2] Inclusion and exclusion criteria were based on the Endovascular Interventional Treatment for Ischemic Stroke Guideline of China (Table 1). Patients aged 18 years or older with intracranial vertebral artery stenosis of at least 70% and presence of transient ischemic attack or ischemic stroke were enrolled. And, for the patients with extracranial vertebral artery stenosis of at least 70%, presence of symptoms was not necessary. The sample size of this non-inferiority trial was calculated based on our previous retrospective data[4] and the non-inferiority margin[2] (Δ =6%). Patients were randomized in a 1:1 ratio to undergo stenting with Maurora stents or Apollo stents between September 2014 and September 2015.

Primary outcomes included surgical complications within 30 days after procedure and the incidence of in-stent restenosis within 6 months after operation. Secondary outcomes included stroke ipsilateral to the target vertebral artery cerebrovascular and cardiovascular events, and serious adverse events within 12 months after operation. In-stent restenosis was defined as

 https://doi.org/10.5853/jos.2018.00479

Table 3. Primary and secondary outcomes 30-day and 1-year after procedure

Outcome	DES-G (n=20)	BMS-G (n=20)
Primary outcomes (%) (95% CI)		
Procedure complications within 30 days	0/20 (0) (0–13.9)	0/20 (0) (0–13.9)
In-stent restenosis	1/20 (5) (0.1–24.9)	5/20 (25) (8.7–49.1)
No. of secondary outcomes		
All adverse events within 30 days	0	0
All adverse events beyond 30 days	2	12
Death	0	0
Stroke	0	2
In-stent restenosis	1	5
Symptomatic	0	2
Angina	1	1
Dizziness	0	2
Lower limbs paresthesia	0	1
Gum bleeding	0	1
Post hoc outcomes after complete follow-up (%) (95% CI)		
Stroke in target vertebral artery territory	0/20 (0) (0–13.9)	2/20 (10) (1.2–31.7)

DES-G, drug-eluting stent group; BMS-G, bare-metal stent group; CI, confidence interval.

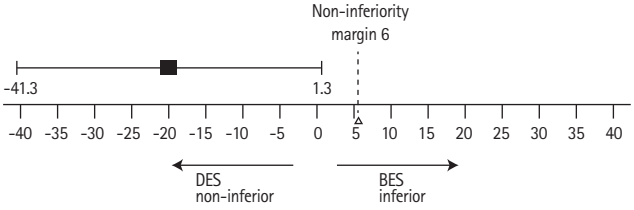

Figure 1. The non-inferiority text for restenosis. DES, drug-eluting stents; BMS, bare-metal stents.

a lesion demonstrating more than 50% stenosis (within or immediately [within 5 mm] adjacent to the stent) and more than 30% absolute luminal loss at 6-month angiographic follow-up imaging (30% increase in posttreatment stenosis).

As a result, 40 enrolled patients were randomly divided into the two groups to receive stenting with either Maurora stent (drug-eluting stent group [DES-G], n=20) or Apollo stent (bare-metal stent group [BMS-G], n=20), with no cross-over. Though the study groups were well balanced with regards to the baseline and procedure-related demographics data, which showed no significant differences (P>0.05), recent qualifying event (P=0.005) and location of target stenosis in the vertebral artery (P=0.008) showed statistical significance (Table 2). All the primary and secondary outcomes can be seen in Table 3. No procedure-related complications occurred within 30 days after procedure. The median angiography follow-up time was 6.5 months in DES-G and 6.4 months in BMS-G. In-stent restenosis rates were 5% in the DES-G and 25% in BMS-G with a difference of −20% (P=0.182), demonstrating non-inferiority (Figure 1).

The mean clinical follow-up was 18.0 months for DES-G and 18.8 months for BMS-G. Serious adverse events occurred in one patient in the DES-G and three in the BMS-G (P=0.605). The 1-year incidence rates for cerebrovascular and cardiovascular events were 5% in DES-G and 15% in BMS-G (log-rank test, P=0.317). The 1-year incidence rates for ipsilateral stroke were 0% in DES-G and 10% in BMS-G (log-rank test, P=0.152).

In this study, two strokes occurred all due to in-stent restenosis, which demonstrated that in-stent restenosis was one important factor that affected the stenting efficacy. Non-inferiority test used in the study reduced the the need of large sample size, but the basic characteristics between the two groups were not well balanced, and it failed to obtain a superior result in the decrease in the in-stent stenosis. However, as far as we know, this study was the first randomized controlled trial that used special cerebrovascular drug-eluting stent for treating vertebral artery stenosis. The results showed that the cerebrovascular drug-eluting stent for the treatment of vertebral artery stenosis was safe, and was not inferior to the bare metal stent in reducing the restenosis rate. Although statistically insignificant, it showed a tendency to reduce the incidence of restenosis (5% and 25%). This study has laid the foundation for phase III multicenter clinical trial in the future.

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Received: February 12, 2018
Revised: March 15, 2018
Accepted: April 6, 2018

This study has received funding by The National Natural Science Foundation of China (No. 81601583), The Technology Research Project of Henan Province (No. 162102310268 and 172102310509) and Aboard Research Project of Henan Provincial Health Commission (2016054).

https://doi.org/10.5853/jos.2018.00479