Japanese Registry of Neuroendovascular Therapy: Extracranial Steno-occlusive Diseases except for Internal Carotid Artery Stenosis

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Abstract

Although utilization of endovascular treatment of extracranial steno-occlusive lesions except for internal carotid artery stenosis continues to increase, there is no consensus regarding the natural course and standard treatment of these lesions. The aim of this study was to characterize the utility of endovascular treatment for extracranial steno-occlusive lesions except for internal carotid artery stenosis. A total of 1249 procedures for extracranial steno-occlusive lesions were identified from the Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2. Excluding the cases of carotid lesions (290 cases), endovascular procedures were performed for 471 (37.7%) subclavian artery stenoses, 404 (32.3%) extracranial vertebral artery stenoses, and 38 (3.0%) innominate artery stenoses with a technical success rate of 97.2%. A stent was placed for 783 lesions and percutaneous transluminal angioplasty was performed for 183 lesions. Forty complications were reported in this cohort. Among these, ischemic complications were the most frequent (12 cases). Comparison between JR-NET1 and JR-NET2 demonstrated a marked increase in the number of procedures, a change in the utilization of antiplatelet therapy, and an increased rate of favorable outcome. We conclude that the endovascular treatment for extracranial steno-occlusive lesions is relatively safe. Continuous efforts should be made to reduce the complication rate, and further trials are needed to validate the beneficial effect of this procedure.

Key words: Japanese Registry of Neuroendovascular Therapy (JR-NET), subclavian artery stenosis, vertebral artery stenosis, stent

Introduction

Stenosis and occlusion of the extracranial subclavian and vertebral arteries are frequent findings among patients who undergo cerebrovascular imaging.1,2 While there is no clear consensus on the natural course and best management of these lesions, recent reports have demonstrated that these lesions can cause vertebrobasilar ischemic events.3,4 Recent advancements in medical therapy and endovascular devices have resulted in an increased utilization of these modalities for the management of extracranial steno-occlusive lesions.5,6 The aim of this study was to characterize the utility of endovascular treatment for extracranial steno-occlusive lesions except for internal carotid artery stenosis in Japan.

Methods

The database of the Japanese Registry of Neuroendovascular Therapy (JR-NET) and the Japanese Registry of Neuroendovascular Therapy 2 (JR-NET2) were used...
to identify the patients. All patients who underwent endovascular procedures performed by the Japanese Society of Neuroendovascular therapy specialists from January 2005 to December 2006 (JR-NET) and from January 2007 to December 2009 (JR-NET2) were included in these registries. Patients who had extracranial steno-occlusive diseases except for internal carotid artery stenosis were extracted from these registries and analyzed. Patient demographics, procedural parameters, and 30-day outcomes were investigated. Favorable outcome was defined as a modified Rankin Scale (mRS) score of 0 or 1 at 30 days after the procedure. Statistical analyses were performed using the R version 2.15.1 software package (R Core Team, 2012; Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; URL: http://www.R-project.org/). The chi-square test was used to compare categorical variables between groups. A value of $p < 0.05$ was considered to indicate statistical significance.

**Results**

**I. General review**

A total of 1477 percutaneous transluminal angioplasty (PTA) or stenting procedures for extracranial steno-occlusive lesions (except for internal carotid artery stenosis) were identified from JR-NET and JR-NET2 (660 procedures in JR-NET and 817 procedures in JR-NET2). Among these cases, detailed information was available for 442 JR-NET patients and 807 JR-NET2 patients. These 1249 cases were subjected to subsequent analysis. In this cohort, there were 471 (37.7%) cases of subclavian artery stenosis, 38 (3.0%) cases of innominate artery stenosis, 404 (32.3%) cases of extracranial vertebral artery stenosis, and 290 (23.2%) cases of carotid artery stenosis (Fig. 1). We excluded cases of carotid artery stenosis because this group might share common characteristics with internal carotid artery stenosis. As a result, 959 cases were subjected to the later analysis. The technical success rate was 97.2% (324 cases in JR-NET and 608 cases in JR-NET2). Periprocedural complications were documented in 4.2% (20 cases in JR-NET and 20 cases in JR-NET2).

**II. Detailed analysis**

**Patient characteristics:** In JR-NET and JR-NET2, a total of 900 patients (93.8%) had atherosclerotic lesions. A total of 19 patients (2.0%) were treated for lesions associated with aortitis and 12 patients

![Fig. 1 Distribution of lesion that was treated among patients registered with Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2. na: not available.](image1)

![Fig. 2 Symptoms of the patients harboring extracranial stenoses (vertebral artery, subclavian artery, and innominate artery lesions) at presentation. TIA: transient ischemic attack.](image2)
(1.3%) were treated for dissections related to iatrogenic, traumatic, or idiopathic causes. Half of these cases were asymptomatic (459 cases, 47.9%) while the remaining had minor stroke (192 cases, 20.0%) and transient ischemic attack including amaurosis fugax (133 cases, 13.9%) (Fig. 2). Timing of the treatment was available only for patients registered with JR-NET2; symptomatic cases were treated within 24 h in 12 cases (4.0%); within 14 days in 49 cases (18.0%); and at more than 15 days after the events in 214 cases (78.0%). The degree of stenosis was documented as 100% (occluded) in 82 cases (8.6%), 70–99% in 728 cases (75.9%), and 50–69% in 121 cases (12.6%).

**Procedures:** Stenting was attempted for 783 lesions. The PTA alone was attempted for 183 lesions. Protection against distal embolism was used in 334 cases (34.8%). In this group, distal balloon protection was used in 287 procedures (85.9%). Other protection was used in 44 procedures (16 procedures in JR-NET and 28 procedures in JR-NET2). The details of the “other protection method” were available only for patients registered with JR-NET2. Distal filter protection was used in 17 procedures (7.7%), and proximal protection was used in 6 procedures (2.7%). A total of 775 stents were placed. In this stented group, poststenting dilatation was performed in 455 procedures (59.3%). The stents used in JR-NET were balloon expandable in 141 cases (53.4%), self-expandable/closed cell in 14 cases (5.3%), self-expandable/open cell in 37 cases (14.0%), and coronary stents in 62 cases (23.5%). In JR-NET2, an open-cell stent was used in 317 cases (62.0%), and a closed-cell stent was used in 159 cases (29.0%). More detailed information regarding stent characteristics was not available for patients registered with JR-NET2.

**Antithrombotics:** Anticoagulants were administered postoperatively in 468 cases (48.0%). The anticoagulant was argatroban in 306 cases (54.4%) and heparin in 256 cases (45.6%). Antiplatelets were administered preoperatively in 921 cases for both before and after procedures. Single antiplatelet therapy was administered in 134 cases (14.5%), dual antiplatelet therapy was administered in 36 cases (3.9%) preoperatively. The number of antiplatelet agents was not significantly different when comparing patients preoperatively vs. postoperatively (p = 0.317). The preoperative combination of antiplatelets most frequently employed was aspirin and thienopyridine (443 cases, 48.1%) followed by aspirin and cilostazol (210 cases, 22.8%). Details of the antiplatelet use are included in Fig. 3.

**Outcomes:** The mRS of 959 patients at 30 days after treatment was 0 in 660 patients (69.5%), 1 in 159 patients (16.7%), 2 in 69 patients (7.3%), 3 in 46 patients (4.8%), 4 in 11 patients (1.2%), 5 in 2 patients (0.2%), and 6 in 3 patients (0.3%). The overall outcome was good (mRS 0–1) in 85.4% of the patients. The mRS did not differ significantly between the preoperative and postoperative assessments (p = 0.128). Death occurred in three cases; one of them [a case of vertebral artery (VA) stenosis in JR-NET] was deemed as possibly related to the procedure. The mRS deteriorated after the procedures by more than 2 points in 22 patients (2.3%, Fig. 4A).

**Complications:** A total of 40 complications were documented (4.2%). The most common complication...
was distal embolism (12 cases, 30.0%) followed by vessel dissection (10 cases, 25.0%). Details regarding these complications were available only for patients registered with JR-NET2. In JR-NET2, complications occurred during the procedure in 12 cases (60.0%) and occurred within 24h postoperatively in 7 cases (35.0%). Although most patients (13 of 20 cases, 65.0%) experiencing complications were treated conservatively, endovascular treatment (three cases of subclavian artery stenosis, one case of VA stenosis, one case of innominate artery stenosis) or direct surgery (one case of subclavian artery stenosis) was needed for some patients. Morbidity (including transient symptoms, 19 patients) and mortality (3 patients) related to the procedure were calculated as 2.0% and 0.3%, respectively.

III. Differences according to the location of the lesion

Comparison between groups of patients (VA stenosis, subclavian artery stenosis, and innominate artery stenosis) revealed a significant effect of the lesion location in several survey items. Aortitis as a cause of steno-occlusive lesion was seen more frequently in innominate artery (0.2% in VA stenosis, 2.1% in subclavian artery stenosis, and 13.2% in innominate artery stenosis, p < 0.001). In the group of VA stenosis, more patients have minor or major stroke than in the group of subclavian or innominate stenosis (p < 0.001, Fig. 5A). Revascularization for chronic total occlusion was performed more frequently in the group of subclavian artery stenosis (0.5% in VA stenosis, 15.9% in subclavian artery stenosis, and 5.3% in innominate artery stenosis, p < 0.001). Protection against distal embolism was performed more frequently in the group of innominate artery stenosis (p < 0.001, Fig. 5B). The mRS deteriorated more frequently after the revascularization for VA stenosis (p < 0.001). There was no apparent effect of lesion location in other survey items.

IV. Comparison between JR-NET and JR-NET2

The number of registered cases of extracranial PTA or stenting was markedly higher in JR-NET2 (622 cases) than in JR-NET (337 cases). The distribution of lesion sites treated in JR-NET and JR-NET2 was not significantly different (p = 0.151). For procedures, the number of patients who received preoperative antiplatelets did not differ significantly (p = 0.275). The type and combination of antiplatelet agents used was significantly different when comparing the two
registries ($p < 0.001$). For example, a single use of cilostazol was significantly lower in JR-NET2 (5 of 601 patients, 0.8%) than in JR-NET (12 of 320 patients, 3.8%) ($p = 0.004$), while triple antiplatelet therapy (5 of 320 patients [1.6%] in JR-NET and 31 of 601 patients [5.2%] in JR-NET2, $p = 0.012$) was significantly higher in JR-NET2 than in JR-NET (Fig. 3). The rate of utilization of protection against distal embolism was similar when comparing the two registries (113 of 337 patients [33.5%] in JR-NET and 221 of 622 patients [35.5%] in JR-NET2, $p = 0.502$). The distal balloon protection was the most popular method in both JR-NET (83.2%) and JR-NET2 (87.3%). The rate of the favorable outcome was significantly higher in JR-NET2 than in JR-NET (271 of 337 patients [80.4%] in JR-NET and 548 of 622 patients [88.1%] in JR-NET2, $p < 0.001$, Fig. 4B) but the rate of patients whose mRS deteriorated by more than two points was similar when comparing the two registries (8 patients [2.3%] in JR-NET1 vs. 14 patients [2.3%] in JR-NET2, $p = 0.867$).

The complication rate (5.9% in JR-NET vs. 3.2% in JR-NET2, $p = 0.066$) and the variation of complications were not significantly different when comparing JR-NET and JR-NET2. Embolic complications, the most frequent complication both in JR-NET and JR-NET2, occurred in 4 out of 20 patients and in 8 out of 20 patients ($p = 0.493$).

**Discussion**

The results of JR-NET and JR-NET2 suggest that stenting and PTA of extracranial steno-occlusive lesions are relatively safe. Postprocedural morbidity and mortality were low (2.0% and 0.3%, respectively) and the rate of periprocedural complications was within the acceptable limits (5.0%). These results are consistent with the previous reports concerning extracranial VA and subclavian stenoses.

Although the ability of PTA or stenting to prevent vertebrobasilar ischemic events is an important goal, the follow-up period in JR-NET and JR-NET2 (30 days after procedures) was too short to investigate this issue. In patients with VA stenosis, the CAVATAS study suggested that there was a very low rate of recurrent vertebrobasilar ischemic event irrespective of whether the patient received medical treatment alone or endovascular treatment in combination with medical treatment. According to the analysis of lesion location effect in our study, a patient having VA stenosis is likely to have higher rate of mRS deterioration after the procedure than a patient having subclavian artery stenosis or innominate artery stenosis. There is a possibility that the event risk...
concerning these lesions might even be lower than the morbidity risk reported in our study. Further studies are needed to clarify the natural course of these lesions and to lower the morbidity and mortality of this procedure.

The rate of the favorable outcome was higher in JR-NET2 when compared to JR-NET but the rate of complications and the rate of worsening mRS after the procedure was similar when comparing the two groups. The improved outcomes in JR-NET2 likely reflect the changes in treatment strategies based on advances in devices and antiplatelet therapy, while the rate of complications and deteriorating mRS after procedure did not significantly changed. These results indicate the indication of endovascular treatment as a preventive measure increased, while recent development of endovascular treatment did not necessarily connect with the improvement of safety of this treatment. Clinicians should keep in mind that patients with extracranial stenotic lesion might have a favorable outcome, even in the absence of the treatment, and that the endovascular treatment for such lesions is still associated with a risk of complications (albeit low). Continuous efforts should be made to reduce the complication rate, and further trials are needed to validate the beneficial effect of this procedure.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in this article. All authors who are members of the Japan Neurosurgical Society (JNS) have registered online self-reported COI Disclosure Statement Forms through the website for JNS members.

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