Parent artery occlusion (PAO) is an alternative to surgical clipping or endovascular endosaccular coil embolization for the management of cerebral aneurysms. Most giant and fusiform aneurysms are not amenable to endosaccular coil embolization due to anatomical considerations, such as a broad-neck. However, majority of reports regarding the safety of PAO are based on case series involving a relatively small number of patients. In the present study, a total of 381 consecutive patients with unruptured cerebral aneurysms who were treated with PAO were extracted from the Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and JR-NET2 database, which are nationwide surveys conducted by the Japanese Society of Neuroendovascular Therapy. The mean age of the 381 patients was 58.1 years, and 59.3% were female. The aneurysmal location included the vertebral artery (42%) and the cavernous portion of internal carotid artery (32%). The aneurysm size and shape consisted of fusiform (45%), giant (25%), and large (22%). Symptomatic lesions were present in 59.8% of the population. Technical success was achieved in 98.4%. The 30-day morbidity and mortality rates were 3.1% and 1.0%, respectively. The most frequent procedure-related complication was ischemic stroke, which occurred in 12.9% (distal embolism, 6.0%; branch occlusion, 3.9%). The 30-day morbidity and mortality rates related to ischemic strokes were 2.1% and 0.3%, respectively. PAO for unruptured aneurysms is feasible with a high technical success rate. Peri-procedural management of ischemic stroke is the key to enhance the safety of this treatment option.

Key words: unruptured cerebral aneurysm, parent artery occlusion, Japanese Registry of Neuroendovascular Therapy (JR-NET)
the high rate of recanalization following embolization remains problematic despite the use of a stent-assisted technique.4) Parent artery occlusion (PAO) with or without extracranial-intracranial (EC-IC) bypass represents another form of treatment. The available literature on PAO for unruptured aneurysms mostly consists of case series with relatively small numbers of patients,5–8) primarily because giant and fusiform aneurysms are far less common when compared to small aneurysms in patients undergoing coil embolization.

The Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and JR-NET2 are nationwide surveys conducted by the Japanese Society of Neuroendovascular Therapy (JSNET) in 2007 and 2010, respectively, to determine the status of neuroendovascular therapy (JSNET) in 2007 and surveys conducted by the Japanese Society of Neuroendovascular Therapy (JR-NET) 1 and JR-NET2 are nationwide surveys conducted by the Japanese Society of Neuroendovascular Therapy (JSNET) in 2007 and 2010, respectively, to determine the status of neuroendovascular therapy in Japan and to standardize endovascular procedures and plan education for Japanese neurointerventionists based on outcomes. The primary endpoint in these registries in the 30-day clinical outcome (modified Rankin Scale, mRS), and secondary endpoints include technical success, adverse events arising within 30 days, and procedure-related complications arising after 30 days.

The purpose of the present study was to analyze the safety and outcomes of PAO among 381 patients with unruptured cerebral aneurysms within the JR-NET1 and JR-NET2 databases.

Materials and Methods

I. JR-NET1 and JR-NET2 protocols

All EVT specialists certified by JSNET were recommended to register their consecutive endovascular procedures online in the JR-NET1 and JR-NET2 databases, which are strictly protected from unauthorized access. Clinical and procedural data were entered through the website managed by the Translation Research Informatics Center (Kobe) and were anonymously reviewed by the principal investigators. In the JR-NET1 study, patients were registered from 122 Japanese neurovascular centers with 200 EVT specialists. The inclusion criteria comprised of patients who underwent EVT performed by EVT specialists between January 2005 and December 2006. Overall, 10,715 patients who underwent 11,174 EVT procedures were registered. Similarly, in JR-NET2, 255 EVT specialists from 150 neurovascular centers registered 20,272 patients with 20,854 procedures performed between January 2007 and December 2009. In all, 32,028 EVT procedures were registered in the JR-NET1 and JR-NET2 databases.

II. Data collection

Each JR-NET1 and JR-NET2 dataset of cerebral aneurysms included the following parameters: patient demographics (age and gender), EVT procedure (date, technical success, and angiographical outcome), clinical data (status at pre-procedure and 30-day post-procedure), complication data (procedure-related, adverse events, and outcomes), aneurysm data (symptomatic, size, shape, and location), and antithrombotic regimen [antiplatelet (AP) and anticoagulant therapy]. Because categorization criteria for aneurysm size and shape differed from the JR-NET1 and to JR-NET2 surveys, a part of two datasets was not able to be merged for analysis. Concerning aneurysm shape and size, only the JR-NET2 dataset was analyzed in the present study.

Procedure-related complications were classified as hemorrhagic stroke, ischemic stroke, systemic disease, puncture-site trouble, and others. Aneurysm rupture was also documented. Ischemic stroke was further categorized into distal embolism, branch occlusion, and others. Each complication was documented along with the information on clinical outcome. Pre-procedural and post-procedural clinical statuses were assessed by the mRS score. Morbidity and mortality were, respectively, defined as deterioration of 2 or more points on the mRS and as any death at 30 days post-EVT.

III. Data extraction and patient demographics

We identified 4,473 patients with cerebral aneurysms in the JR-NET1 database and 8,562 patients with cerebral aneurysms in the JR-NET2 database. Of these, patients with ruptured aneurysms and unruptured aneurysms treated with endosaccular embolization were excluded from the present study. Patients with dissecting aneurysms were also excluded due to different nature of the pathogenesis of this condition. Moreover, unexpected PAO procedures in patients who were originally planned to undergo endosaccular embolization were also eliminated, leaving only intentional and elective PAO in the final analysis. Consequently, 93 patients in the JR-NET1 database and 288 patients in the JR-NET2 database (a total of 381 patients with 381 unruptured aneurysms) who were treated with elective PAO were identified and analyzed in the present study. The mean age of the patients was 58.1 years. Two hundred and twenty-six patients (59.3%) were female.

IV. Statistical analysis

Mean and frequency data were compared using Student’s t-test and the χ² test or Fisher’s exact test, respectively. All data were statistically analyzed using JMP version 10.0 software (SAS Institute, Cary, North Carolina, USA). The significance threshold was established at P < 0.05.
Results

I. Aneurysm characteristics

Figure 1 shows the anatomical location of the aneurysms treated with PAO. The most common location was the vertebral artery (VA; 160, 42%), followed by cavernous portion of internal carotid artery (ICA; 120, 32%) and the ICA paraclinoid (29, 8%). Two hundred and twenty-eight (59.8%) of 381 aneurysms were symptomatic (e.g., due to aneurysm mass effect). Figure 2 shows the data on size and shape of the aneurysms registered in the JR-NET2 database. One hundred and thirty aneurysms (45%) were fusiform. Seventy three (25%) and 62 (22%) were giant (> 25 mm) and large (> 10 mm), respectively.

II. EVT procedures

Procedural success was achieved in 375 of 381 cases (98.4%). Procedure-related complications were noted in 68 cases (17.8%). Ischemic stroke, including transient symptoms, was documented in 49 patients (12.9%). Hemorrhagic stroke was found in four patients (1.0%) while aneurysm rupture was not documented either in the JR-NET1 or JR-NET2 survey (0%). Puncture site trouble requiring blood transfusion occurred in four patients (1.0%).

III. Clinical outcomes

Figure 3 shows pre-procedural and 30-day post-procedural mRS. The details of clinical outcomes in JR-NET1 and JR-NET2 are shown in Table 1. The pre-procedural mRS score was as follows: 0 in 236 (61.9%) patients; 1 in 93 (24.4%) patients; 2 in 29 (7.6%) patients; 3 in 12 (3.1%) patients; 4 in 9 (2.4%) patients; 5 in 2 (0%) patients; and 6 in 0 (0%) patients. The 30-day post-procedural mRS score was as follows: 0 in 222 (58.3%) patients; 1 in 89 (23.4%) patients; 2 in 33 (8.7%) patients; 3 in 15 (4.0%) patients; 4 in 14 (3.7%) patients; 5 in 6 (1.6%) patients; 6 in 4 (1.0%) patients; and unavailable in 3 (0.8%) patients. The 30-day morbidity and mortality rates were 3.1% and 1.0%, respectively. Nine patients suffered neurological deficits from ischemic stroke within 30 days, and one patient died from hemorrhagic stroke. Ischemic stroke was the most common complication. Table 2 shows the detailed information on ischemic complications. Distal embolism...
and branch occlusion accounted for 6.0% and 3.9% of all cases of ischemic stroke, respectively. The cause was unknown or unavailable in 11 patients (2.9%). The 30-day morbidity and mortality rates related to ischemic complications were 2.1% and 0.3%, respectively.

IV. Antithrombotic therapy

For the purpose of preventing ischemic complications, AP medicine was pre-procedurally administered in 301 of 381 patients (79.0%). The rate of use of AP therapy increased from 71.0% in JR-nEt1 to 81.6% in JR-nEt2. Double AP therapy was used in 31.2% of patients in JR-nEt1 and in 43.8% of patients in JR-nEt2 (40.7% of patients in JR-nEt1 and JR-nEt2).

Intra-procedural systemic heparinization was used in 98.4% while post-procedural anticoagulation therapy using heparin or argatroban was used in 75.3%. Post-procedural anticoagulation was used in 77.4% in JR-nEt1 and in 74.7% of patients in JR-nEt2. Table 3 shows the rates of ischemic stroke and 30-day morbidity in patients with and without AP therapy.
ischemic stroke were not significantly different between the AP and non-AP groups. Other factors including patient’s age, post-operative anticoagulant therapy, and aneurysm location were not found to be statistically involved with the incidence of ischemic complications by multivariate analysis.

V. Ischemic complications according to aneurysm location

The rate of ischemic complication by anatomical location is shown in Table 4. Seventeen (10.2%) of 166 aneurysms in the anterior circulation were complicated by periprocedural major/minor ischemic stroke, including transient symptoms. By contrast, ischemic events occurred in 32 (14.9%) of 214 aneurysms in the posterior circulation. Patients with aneurysms in the VA, the most common aneurysm location, experienced ischemic stroke at a rate of 12.5% (20 of 160). Compared to the VA, PAO for ICA-cavernous aneurysms caused less ischemic complication (5.8%) primarily because none of them experienced branch occlusion.

Table 4 Ischemic complications by anatomical location of the aneurysms

<table>
<thead>
<tr>
<th>Aneurysm location</th>
<th>n</th>
<th>Branch occlusion</th>
<th>Distal embolism</th>
<th>All ischemic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>160</td>
<td>12 (7.5%)</td>
<td>8 (5.0%)</td>
<td>20 (12.5%)</td>
</tr>
<tr>
<td>ICA-cavernous</td>
<td>120</td>
<td>0 (0%)</td>
<td>7 (5.8%)</td>
<td>7 (5.8%)</td>
</tr>
<tr>
<td>ICA-paraclinoid</td>
<td>29</td>
<td>0 (0%)</td>
<td>3 (10.3%)</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>PCA</td>
<td>16</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>BA-bif</td>
<td>10</td>
<td>0 (0%)</td>
<td>1 (10.0%)</td>
<td>1 (10.0%)</td>
</tr>
</tbody>
</table>


Discussion

Despite endovascular remodeling techniques, endosaccular embolization for large, giant, or fusiform aneurysms is usually challenging and also ineffective, due to a high recanalization rate.\(^1\)\(^-\)\(^3\) Neck-bridging stents such as Enterprise (Codman Inc., Raynham, Massachusetts, USA) and Neuroform (Stryker Corp., Kalamazoo, Michigan, USA) can be used to assist endosaccular embolization for those aneurysms, but recanalization remains problematic.\(^4\) A flow-diverting (FD) stent, such as the Pipeline Embolization Device (Covidien Inc., Mansfield, Massachusetts, USA), might overcome this limitation of endosaccular treatment.\(^5\) Although introduction of FD treatment has been long awaited among Japanese EVT specialists, complications related to FD treatment, such as delayed in-stent stenosis and aneurysm rupture, are serious enough to temper the enthusiasm for such therapy.\(^10\)\(^,\)\(^11\) Therefore, PAO remains the most common treatment modality for management of aneurysms that are not amenable to coil embolization. Although EC-IC bypass should be added prior to PAO in a patient without tolerance to balloon test occlusion (BTO), endovascular PAO procedure itself is feasible from a technical standpoint.

The present study showed that PAO was performed with a high rate of technical success (98.4%) but with a significant rate of ischemic stroke (12.8%). Almost half of periprocedural ischemic strokes were caused by distal embolism, although most appeared transient or minor. The 30-day morbidity rate related to ischemic stroke was 2.1%.

Analysis according to the location of the aneurysms showed that the rate of ischemic complications was 10.2% in the anterior circulation and 14.9% in the posterior circulation. The aneurysm location with the highest rate of ischemic events was the VA.

Previous studies have demonstrated that ischemic events, including transient ischemic attack, occurs in 0–12.3% of the patients and that the permanent morbidity rate ranges from 0% to 8.3%.\(^7\)\(^,\)\(^8\)\(^,\)\(^12\)\(^-\)\(^14\) The present study demonstrated a higher rate of ischemic events, most probably because 42% of registered aneurysms were in the VA. Causes of ischemic events include (1) hypoperfusion, (2) distal embolism, and (3) branch occlusion (perforator occlusion, etc.). Careful evaluation, including pre-procedural BTO, is an important consideration in the efforts to prevent hypoperfusion by PAO.\(^6\) In contrast to the anterior circulation, where BTO can cause clear neurological symptoms, BTO in the posterior circulation may result in only subtle symptoms. Tolerance to PAO should be carefully evaluated particularly in the posterior circulation. The rate of ischemic events secondary to distal embolism may be reduced by the use of pre-procedural AP therapy and intraprocedural systemic heparinization.

It is also important to evaluate whether important perforating arteries arise from the arterial segment to be occluded by PAO. BTO should be carefully repeated by changing the location of a balloon catheter to find a perforating artery to be occluded by PAO. If a patient presents a neurological sign in BTO, it should be carefully determined whether the symptom is caused by perforator occlusion or hemodynamic insufficiency of a parent artery. High-resolution computed tomography angiography and flow-sensitive black-blood magnetic resonance angiography (MRA) may be useful to detect small perforating arteries.\(^15\)\(^,\)\(^16\) Ultrahigh-field MRA with 7.0T may be promising with respect to visualizing.
these small vessels.\textsuperscript{17}

The utilization of AP therapy in PAO has increased over time (from 71.0\% in JR-NET1 to 81.6\% in JR-NET2). Moreover, the use of double AP therapy has also increased (from 31.2\% in JR-NET1 to 43.8\% in JR-NET2). However, the rate of peri-procedural ischemic stroke has not changed significantly (12.9\% in JR-NET1 and 12.8\% in JR-NET2). Moreover, no statistically significant difference in the rate of ischemic stroke and 30-day morbidity was found whether or not AP therapy was used. Large prospective studies are necessary to determine if there is any benefit to AP and antiocoagulation therapy in patients undergoing PAO.

Finally, we acknowledge several limitations in the present study. First, although all JSNET-certified EVT specialists were invited to participate in the JR-NET1 and JR-NET2 study, not all EVT cases were enrolled in this study. We do not have data on the exact number of EVT cases performed in the same period in Japan, but we estimate that approximately 40\% of EVT cases were included in the present study. Second, due to the retrospective nature of the study, further detailed information was not retrievable. For example, we assume that surgical bypass was performed in several cases prior to or following PAO treatment. Either the JR-NET1 or JR-NET2 database did not include the data on additional surgical treatment. This may have significant impact on the post-procedural mRS. Third, dissecting aneurysms that presented with subarachnoid hemorrhage or ischemic stroke were registered in a different data table. However, some of the unruptured asymptomatic dissecting aneurysms may be included in the present study because etiology was unknown in those cases.

**Conclusion**

Review of the nationwide JR-NET1 and JR-NET2 Japanese surveillance databases showed that PAO for unruptured cerebral aneurysms was feasible and was associated with a high technical success rate. Peri-procedural management of ischemic stroke is the key to enhance the safety of this treatment modality.

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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 the article. All authors who are members of the Japan Neurosurgical Society (JNS) have registered self-reported conflict of interest disclosure statement forms online through the website for JNS members.

**References**


Address reprint requests to: Akira Ishii, MD, Department of Neurosurgery, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho Syogoin, Sakyo-ku, Kyoto, Kyoto 606-8507, Japan.

e-mail: ishii@kuhp.kyoto-u.ac.jp