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Recent Trends in Neuro-endovascular Treatment for Acute Ischemic Stroke, Cerebral Aneurysms, Carotid Stenosis, and Brain Arteriovenous Malformations

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Abstract

The efficacy of mechanical thrombectomy with stent retrievers for emergent large vessel occlusion has been proved by randomized trials. Mechanical thrombectomy is increasingly being adopted in Japan since stent retrievers were first approved in 2014. An urgent clinical task is to offer structured systems of care to provide this treatment in a timely fashion to all patients with emergent large vessel occlusion. Treatment with flow-diverting stents is currently a preferred treatment option worldwide for large and giant unruptured aneurysms. Initial studies reported high rates of complete aneurysm occlusion, even in large and giant aneurysms, without delayed aneurysmal recanalization and/or growth. The Pipeline Embolic Device is a flow diverter recently approved in Japan for the treatment of large and giant wide-neck unruptured aneurysms in the internal carotid artery, from the petrous to superior hypophyseal segments. Carotid artery stenting is the preferred treatment approach for carotid stenosis in Japan, whereas it remains an alternative for carotid endarterectomy in Europe and the United States. Carotid artery stenting with embolic protection and plaque imaging is effective in achieving favorable outcomes. The design and conclusions of a randomized trial of unruptured brain arteriovenous malformations (ARUBA) trial, which compared medical management alone and medical management with interventional therapy in patients with an unruptured arteriovenous brain malformation, are controversial. However, the annual bleeding rate (2.2%) of the medical management group obtained from this study is worthy of consideration when deciding treatment strategy.

Key words: endovascular therapy, acute thrombectomy, cerebral aneurysm, carotid artery stenting, brain arteriovenous malformation

Introduction

Endovascular treatment for vascular diseases of the brain and spinal cord has gradually developed as a less invasive treatment and is now widely applied worldwide. Advances have been achieved through the development of device and imaging technology alongside an increased understanding of disease pathophysiology. Evidence obtained from milestone randomized controlled trials comparing conventional treatment and endovascular treatment has changed treatment strategies.[1–7] Breakthroughs in neuro-endovascular treatment for acute ischemic stroke have occurred in recent years,[8–12] accompanied by reliable progress in treating other diseases. This study examines recent trends and advancements in neuro-endovascular therapy.

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Acute thrombectomy

Endovascular therapy for emergent large vessel occlusion began with intra-arterial fibrinolytic therapy in the 1980s.[13] However, despite refinement and sophistication of newly developed devices and imaging technology, its efficacy remained unproven. In 2015, the results of five randomized trials (medical therapy alone versus medical therapy with endovascular therapy), MR CLEAN,[8] ESCAPE,[9] EXTEND-IA,[10] SWIFT PRIME,[11] and REVASCAT[12] were published, all of which demonstrated the positive effect of endovascular therapy for patients with emergent large vessel occlusion.

As a consequence of these trials, the European Stroke Organization (ESO) in collaboration with the European Society for Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) released their consensus statement on

mechanical thrombectomy in acute ischemic stroke (http://www.esmint.eu/sites/default/files/Consensus_thrombectomy_ESO_Karolinska_ESMINT_ESNR_final.pdf). The Standards and Guidelines Committee of the Society of NeuroInterventional Surgery (SNIS) published their guideline "Embolectomy for stroke with emergent large vessel occlusion".[14] In 2015 the American Heart Association/American College of Cardiology (AHA/ASA) also published a focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment.[15] AHA/ASA recommends endovascular therapy with a stent retriever for patients who meet all of the following criteria (Class I; Level of Evidence A): (a) pre-stroke modified Rankin Scale (mRS) score 0–1; (b) acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator within 4.5 h of onset according to guidelines from professional medical societies; (c) causative occlusion of the internal carotid artery (ICA) or proximal middle cerebral artery (M1); (d) age ≥18 years; (e) National Institute of Health Stroke Scale (NIHSS) score of ≥6; (f) Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6; and (g) treatment initiated (groin puncture) within 6 h of symptom onset. The Japan Stroke Society, the Japan Neurosurgical Society, and the Japanese Society of Neuroendovascular Therapy also produced their Guideline for proper usage of percutaneous transluminal thrombectomy devices, which was published in Japanese (*Jpn J Stroke* 37: 259–279, 2015).

Goyal et al. designed the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration for the meta-analysis of individual patient data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) including 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to medical therapy.[16] Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted common odds ratio [OR] 2·49, 95% confidence interval [CI] 1.76–3.53; $P < 0·0001$). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2.6, which means that thrombectomy is a highly effective treatment compared with other treatments for stroke.[17] Campbell et al. also pooled 787 patients (401 randomized to endovascular thrombectomy and 386 to standard care) from trials in which the Solitaire (Medtronic, Irvine, CA, USA) (Fig. 1) was the only or the predominant device (SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT) (SEER Collaboration).[18] The common OR for mRS improvement was 2.7 (2.0–3.5). The number needed to treat to reduce disability was 2.5, and successful revascularization occurred in 77% treated with the Solitaire device. The onset-to-TICI (Thrombolysis In Cerebral Infarction) 2b/3 time was a significant predictor of outcome (OR 0.99 per minute; $P = 0.011$) with the probability of independent functional outcome declining 1% per 23-min delay. From the subanalysis of MR CLEAN, for every hour of reperfusion delay the initially large benefit of thrombectomy decreased the absolute risk difference for a good outcome by 6% per hour of delay, and the treatment effect was not significant beyond 6 h 18 min from onset.[19] Subanalysis of ESCAPE showed that every 30-min increase in computed tomography (CT)-to-reperfusion time reduced the probability of achieving a functionally independent outcome (90-day mRS 0–2) by 8.3% ($P = 0.006$).[20] Subanalysis of REVASCAT also showed that longer onset to recanalization time was associated with a reduced likelihood of a good outcome (OR for 30-min delay 0.74; 95% CI 0.59–0.93).[21] The influence of treatment delay on the treatment effect was remarkable.

Endovascular thrombectomy is now the standard treatment for patients with acute ischemic stroke caused by occlusion of the proximal anterior circulation with class I evidence. Therefore, we should provide this treatment for all patients who suffer acute ischemic stroke on transport to hospital or transfer the patient to a hospital providing this treatment as soon as possible. Our aim should be to offer structured systems of care to provide this treatment in a timely fashion to all patients with acute ischemic stroke caused by large vessel occlusion.

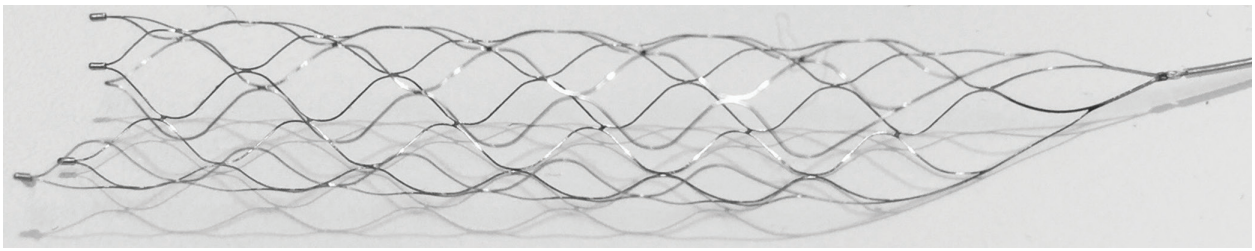

Fig. 1 Solitaire FR (Medtronic, Irvine, CA, USA). Stent-like retriever for acute thrombectomy.

Endovascular therapy with flow diverter for intracranial aneurysm

A flow diverter (FD) is a stent-like device with more metal coverage and less porosity than neck-bridge stents for aneurysmal coiling. An FD disrupts the intra-aneurysmal flow, thus favoring intra-aneurysmal thrombosis and neointimal remodeling. The Pipeline Embolic Device (PED; Medtronic, Irvine, CA, USA) (Fig. 2) is the first FD for the treatment of cerebral aneurysms.[22] The device consists of a braided mesh cylinder composed of 48 microfilaments. Initial studies reported high rates of complete aneurysm occlusion, even in large and giant aneurysms, without delayed aneurysmal recanalization and/or growth.[22–26] The PED received the CE mark of approval in 2008, followed by the US Food and Drug Administration approval in 2011. In Japan, the PED was approved in 2015 for the treatment of large and giant wide-neck unruptured aneurysms in the ICA, from the petrous to superior hypophyseal segments. The Japan Neurosurgical Society, the Japan Stroke Society, and the Japanese Society of Neuroendovascular Therapy formulated the Guideline for the proper usage of flow-diverter stent (http://www.jsnet.umin.jp/sozai/info-shonin/150403FD_shishin.pdf). The PED is now increasingly being used in 23 institutions across Japan in accordance with this guideline.

Kallmes et al. reported results of an international retrospective study of the PED registry including 793 patients with 906 aneurysms.[27] The neurological morbidity and mortality rate was 8.4%, the highest being in the posterior circulation group (16.4%) and the lowest in the group with ICA < 10 mm (4.8%) ($P < 0.01$). Use of the PED for posterior circulation aneurysms is considered higher risk and is beyond approved indication in Japan. The rate of spontaneous rupture and intracranial hemorrhage were reported as 0.6% and 2.4%, respectively. The cause of these hemorrhagic complications is yet to be completely elucidated.[28]

The PED for ICA aneurysms usually covers some branches such as the ophthalmic artery and anterior choroidal artery (AChA). Patients treated with the PED for large and giant ICA aneurysms had excellent neuro-ophthalmological outcomes 6 months after the procedure in the PUFS trial,[25] with deficits improving in most of the patients (64%), very few deficits worsening (2.6%), and few new deficits developing (5%).[29] Neki et al. retrospectively analyzed 20 consecutive patients with unavoidable covering of the AChA with a single PED.[30] No patient complained of transient or permanent symptoms related to an AChA occlusion. In all cases, the AChA remained patent without any flow changes during follow-up.

Treatment with an FD is currently the preferred option for large and giant unruptured aneurysms in the ICA. However, delayed ischemic complications due to in-stent thrombosis or covered vessel occlusion during long-term follow-up are a concern. Therapeutic ICA occlusion after test occlusion was historically the standard treatment for this disease. Bechan et al. reported in 2015 that this strategy is safe, effective, and still the preferred treatment because most aneurysms shrunk, and most cranial nerve dysfunctions were cured or improved without antiplatelet therapy.[31] Several ongoing randomized trials of FDs are under way in North America and Europe[32] and will help to more rigorously determine the efficacy of this new technology in the near future.

Carotid artery stenting

Recently, the Asymptomatic Carotid Trial (ACT) I, involving asymptomatic patients with severe carotid stenosis who were not at high risk for carotid endarterectomy (CEA), proved that carotid artery stenting (CAS) was not inferior to CEA with regard to the primary composite end point (event rate 3.8% and 3.4%, respectively; $P = 0.01$ for non-inferiority).[7] However, CAS remains an alternative treatment for CEA in Europe and the United States because of the

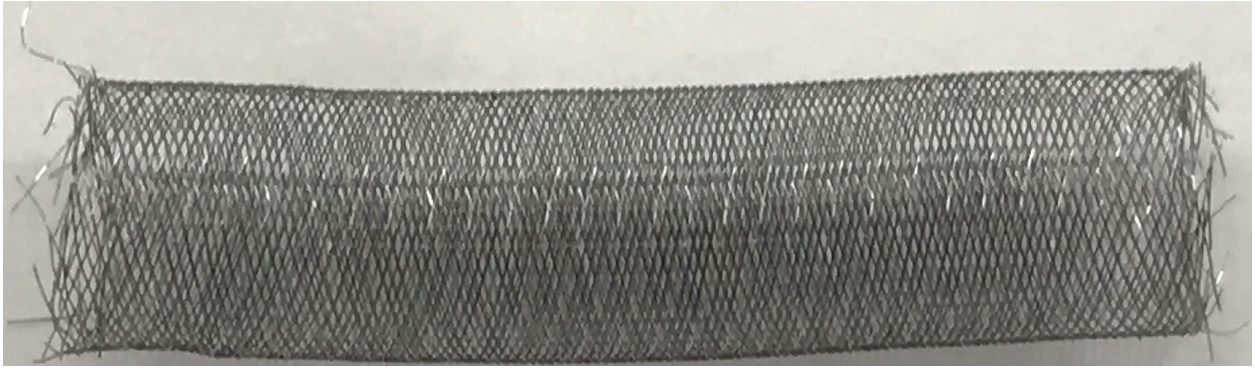

Fig. 2 Pipeline Embolic Device (Medtronic, Irvine, CA, USA). Flow-diverter stent for cerebral aneurysms.

negative results of randomized trials of symptomatic patients.[4–6,33] In Japan, CAS seems to be the preferred treatment because of its favorable results. The Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2, which are retrospective nationwide multicenter surveillances, reported a low clinically significant complication rate (3.2%) among 7134 procedures (1943 for JR-NET1 and 5191 for JR-NET2).[34] Multivariate logistic analysis revealed that age (OR 1.04 per year; 95% 1.02–1.07; $P = 0.0004$), symptomatic lesion (OR 1.87; 95% CI, 1.31–2.71; $P = 0.0004$), and the use of a closed-cell type stent (OR 0.58; 95% CI 0.32–1.00; $P = 0.05$) were independently associated with clinically significant complications.

CAS with embolic protection is effective in obtaining favorable outcomes. However, difficult vascular anatomy such as type III or diseased aortic arch, carotid tortuosity, difficult peripheral access, and difficult distal landing may lead to complications. Fanous et al. developed a scoring system using demographics and vascular anatomy that predicts complications,[35] whereby patients with a high score should avoid CAS. Furthermore, improved imaging techniques such as CT, magnetic resonance imaging, and ultrasonography have enabled us to understand not only the degree of carotid artery stenosis but also the vulnerability of the plaque, which stratify the risk of patients or treatments.[36]

With recently developed devices and imaging technology, CAS has become a safer revascularization procedure. However, the best available medical treatment, including lifestyle modification, blood pressure and diabetes control, antiplatelet agents, and lipid-lowering therapy is the cornerstone of the management of patients with either asymptomatic or symptomatic carotid artery stenosis.[37] Stroke rates for asymptomatic carotid patients with best medical treatment alone have decreased to approximately 0.5% per year.[38]

Endovascular treatment for brain arteriovenous malformations (BAVM)

Liquid embolic materials are mainly used for embolization of BAVM. Onyx (Medtronic, Irvine, CA, USA) is the latest agent in addition to n-butyl cyanoacrylate (NBCA). A meta-analysis of Onyx and NBCA including 103 studies comprising 3593 patients was performed.[39] Complete obliteration of AVM was seen in 13.7% in the NBCA group and 24% in the Onyx group (OR 1.9). However, neurological outcomes for NBCA and Onyx were only 5.2% and 6.8%, respectively (OR 1.4; $p = 0.56$). Onyx appeared to increase the cure rate of AVMs but with a possible increase in permanent neurological deficits and mortality.

A randomized trial of unruptured brain arteriovenous malformations (ARUBA) is a multicenter, non-blinded, randomized trial comparing medical management alone and medical management with interventional therapy in patients with unruptured BAVM. Randomization was stopped in mid-study because of the superiority of the medical management group, and the authors concluded that the risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group (hazard ratio 0.27, 95% CI 0.14–0.54).[40] The ARUBA trial was followed by many reports delivering favorable results of interventional therapy, especially surgical removal for ARUBA eligible patients, which showed a high cure rate and excellent functional outcomes.[41–47]

The ARUBA trial includes some limitations such as a low randomization rate, bias toward non-surgical therapies, shortage of surgical expertise, lower rate of complete AVM obliteration, higher rate of delayed hemorrhage, and short study duration. Its design and conclusions remain controversial. However, the annual bleeding rate (2.2%) of the medical management group obtained by prospective study is worthy of consideration when deciding upon treatment strategy.

BAVM was believed previously to be a congenital lesion attributable to developmental failure of embryos. Recently, reports have appeared of de novo BAVM in disease-free patients with no previous diagnosis,[48,49] with hereditary hemorrhagic telangiectasia,[50] after radiation therapy,[51] and after implantation of genetically modified allogeneic mesenchymal stem cells in the brain.[52] The fact that the average age at the initial diagnosis of BAVM is about 30–40 years old contradicts its congenital nature[53] or presence at birth, in contrast to vein of Galen aneurysmal malformations.[54] Komiyama mentioned on reviewing their pathogenesis that BAVMs are "dynamic" lesions that can grow, remodel, and regress in addition to rupture.[55]

Conclusion

Neuro-endovascular treatment makes use of new technology to expand indications and improve results, with further development expected. The impact of mechanical thrombectomy is potentially formidable. However, as new treatments with new devices currently lack long-term results, detailed observational study of long-term follow-up data and scientific evaluation of new treatments are warranted.

Conflicts of Interest Disclosure

YM received honoraria from Medtronic Japan and Stryker Japan for lecture fees. EI, TY, and AM

have no conflicts of interest. The authors registered online Self-reported COI Disclosure Statement Forms through the website for Japan Neurosurgical Society members.

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