Endovascular Treatment for Ischemic Stroke

MUNETAKA YAMAMOTO*, HIDENORI OISHI*, HAJIME ARAI*

*Department of Neurosurgery, Juntendo University Faculty of Medicine, Tokyo, Japan

In Japan, out of the total number of deaths classified by cause in 2013, 120,000 deaths were due to strokes, making up 9.3% of the total and putting stroke in 4th position. On the other hand, strokes are the number one cause that requires long-term nursing care and comprise 20% of the total. Strokes are broadly classified into cerebral infarctions, intracerebral hemorrhages, and subarachnoid hemorrhages. A cerebral infarction is caused by the occlusion of a blood vessel in the brain. The most important form of treatment for cerebral infarction is prevention. The purpose of performing recanalization therapy for acute ischemic stroke, in which the occluded vessel has reopened, is minimizing the extent of possible cerebral infarction. Intravenous administration of thrombolytic drugs to treat acute ischemic stroke within three hours of onset started being performed in Japan in 2005. In 2010, a spiral-shaped device, Merci Retrieval System, became available for use in Japan for thrombi retrieval and heralded the era of mechanical thrombectomy. In 2011, a thrombus aspiration device that used a catheter, Penumbra System, was introduced. In 2014, stent thrombectomy devices, Solitaire Flow Restoration device and Trevo ProVue Retriever, were successively introduced, which allowed for a full range of treatment selections for full-scale endovascular treatment for acute ischemic stroke.

Key words: ischemic stroke, cerebral infarction, mechanical thrombectomy, endovascular treatment

Introduction

The mortality rate for strokes in Japan has been reduced due to treatment of hypertension and an increase in the standard of treatment. According to the Summary of Vital Statistics (Ministry of Health, Labour and Welfare (MHLW)), out of the total number of deaths classified by cause in 2013, 120,000 deaths were due to strokes, making up 9.3% of the total and putting stroke in 4th position. On the other hand, according to the Summary of the Comprehensive Survey of Living Conditions (MHLW), strokes are the number one cause that requires long-term nursing care and comprise 20% of the total. According to the Summary of the Patient Survey (MHLW), the number of stroke patients is over 1.3 million and strokes occur in 300,000 individuals annually. The rate of stroke onset per 100,000 members of the population during the past decade was approximately 1,000, indicating that although the mortality rate has decreased, prevalence has hardly decreased. The breakdown for strokes has not been revealed in the national statistics, but when calculated based on a report from the Hisayama Study 1), 65% were cerebral infarctions, 25% were intracerebral hemorrhages, and 10% were subarachnoid hemorrhages. The number of stroke patients whose lives are saved but who are left with severe sequelae is increasing.

Cerebral infarction

A cerebral infarction is caused by the occlusion of a blood vessel in the brain. Cerebral infarction occurs in 200,000 people annually, and in terms of the prognosis in the 5 years after onset, the mortality rate is 40%, 20% of patients require long-term care including bedridden patients and the condition improves in 40% of patients. The
mechanism of blood vessel occlusion is classified into 3 types.

1. Lacunar infarction
   Lacunar infarcts occur when the arterioles that supply blood to the deep parts of the brain parenchyma are affected by hypertension and develop atherosclerosis, leading to occlusion. These infarctions, which comprise about 30% of all cerebral infarctions, are on the decline, with advances in the treatment of hypertension.

2. Atherothrombotic cerebral infarction
   Atherothrombotic cerebral infarctions are caused by vascular atherosclerosis (plaque). Atherosclerosis is caused by damage to the vascular intima, which causes the infiltration of leukocytes and accumulation of lipid components into the arterial wall. Furthermore, vascular smooth muscle cells migrate into the vascular intima and proliferate. This results in the formation of plaque when the deposition of fibrous components and lipids coat the internal intimal surface. Risk factors include hypertension, diabetes mellitus, dyslipidemia, and smoking. Intraluminal occlusion is caused by plaque enlargement and rupture and dispersion of the ruptured plaque or the thrombus that has formed results in occlusion of the peripheral cerebral blood vessels, resulting in cerebral infarction. Thirty percent of all cerebral infarctions are atherothrombotic cerebral infarctions.

3. Cardioembolic stroke
   Cardioembolic strokes are caused by emboli that originate in the heart and occlude the flow of blood to cerebral blood vessels; they comprise 28% of all strokes. The most common condition that causes emboli to form in the heart is atrial fibrillation. The sudden occlusion near the center of the previously normal blood vessel means that no collateral circulation develops and because the resulting strokes are usually extensive, they tend to be serious. There are said to be 1,000,000 patients with atrial fibrillation, and in recent years, the frequency of cardioembolic stroke onset has been increasing.

Treatment of cerebral infarctions

1. Primary prevention
   The most important form of treatment for cerebral infarction is prevention. Primary prevention includes drug treatment of hypertension, diabetes mellitus, dyslipidemia, and arrhythmia, as well as the improvement of lifestyle habits, such as dietary therapy, exercise therapy, quitting smoking, or avoiding alcohol consumption. In addition, stenosis of the internal carotid artery in the neck due to atheroma (internal carotid artery stenosis) is an indication for surgical treatment (carotid endarterectomy or carotid artery stenting), if severe stenosis is present.

2. Secondary prevention
   Secondary prevention is the prevention of recurrence. As a rule, treatment similar to that used for primary prevention is selected, but there is stricter monitoring and the expansion of the indications for surgical treatment or endovascular treatment is being investigated. In addition to surgical treatment for carotid artery stenosis, cerebrovascular bypass surgery and endovascular treatment (percutaneous transluminal angioplasty) are sometimes also used to treat vascular occlusion of the intra- and extra-cranial vessels, and intracranial vessel stenosis. The preventive effects of surgical treatment have only been verified in combination with sufficient internal medical therapy. Furthermore, there are strict standards for the cerebrovascular conditions that are eligible for surgical treatment so sufficient care must be taken with determining whether a case is eligible.

Recanalization therapy for acute ischemic stroke

The purpose of performing recanalization therapy for acute ischemic stroke, in which the occluded vessel has reopened, is minimizing the extent of possible cerebral infarction. This is a completely different concept to the treatment used to date for primary and secondary prevention. This can be achieved by either advancing a catheter into the occluded blood vessel and performing thrombolysis through the injection of thrombolytic drugs or using a balloon catheter to physically widen the occluded lesion. However, as these techniques are
complex and their effects are insufficient, they have not come into widespread use.

Intravenous administration of thrombolytic drugs to treat acute ischemic stroke within three hours of onset started being performed in Japan in 2005. There is a drug known as Alteplase, which is a recombinant tissue plasminogen activator (rt-PA); treatment with this drug can be performed at several institutions because it can be administered through normal intravenous infusion. In 2012, the administration criteria were expanded to include any patient within 4.5 hours of stroke onset. When administering thrombolytic drugs, the most frequent complication is hemorrhage. This could involve a cerebral hemorrhage caused by reperfusion of blood into the area affected by cerebral infarction or a hemorrhage at the location of extracranial systemic pathology (gastric ulcer or aortic vascular dissection), and there could be hemorrhage at both sites. In all cases, once hemorrhage has occurred, the effects of the thrombolytic drug are catastrophic and it is difficult to achieve hemostasis, meaning that these cases are often severe. Therefore, the administration criteria for this drug include various strict conditions in addition to the time from onset. Reports indicate that in clinical practice, administration of thrombolytic drugs is only possible for 4%-5% of patients who have suffered a cerebral infarction. In addition, improvement of symptoms is obtained in 10% of cerebral infarction patients treated with these drugs. Furthermore, it is now known that if occlusion occurs in the carotid vessels or in the main intracranial arteries, known as the thick vessels, achieving recanalization using thrombolytic drugs is likely to be difficult.

Mechanical thrombectomy

In 2010, a spiral-shaped device, Merci Retrieval System (Stryker Neurovascular, Fremont, CA, USA) (Figure-1), became available for use in Japan for thrombi retrieval and heralded the era of mechanical thrombectomy. Thereafter, in 2011, a thrombus aspiration device that used a catheter, Penumbra System (Penumbra, Alameda, CA, USA) (Figure-2), was introduced. In 2014, stent thrombectomy devices, Solitaire Flow Restoration device (Covidien, Dublin, Ireland) (Figure-3) and Trevo ProVue Retriever (Stryker Neurovascular, Fremont, CA, USA) (Figure-4), were successively introduced, which allowed for a full range of treatment selections for full-scale endovascular treatment for acute ischemic stroke.

Reports of the efficacy of stent thrombectomy devices in particular have come from the US and Europe as the result of randomized controlled trials (RCT) focusing on the Merci, which was developed first (SWIFT³, TREVO 2⁴), and prospective single-group trials (STAR⁵), with high expectations centered on their introduction. Meanwhile, results of 3 RCTs reported in 2013 (IMS-III⁶, SYNTHESIS Expansion⁷, MR RESCUE⁸) that compared IV rt-PA monotherapy to use in combination with endovascular treatment were not able to show efficacy in all cases that used rt-PA in combination with endovascular treatment, and the significance of endovascular treatment when treating acute ischemic stroke was called into question. However, when these RCT findings were analyzed in detail, results actually revealed an effective means of endovascular treatment rather than denying the significance of this treatment. In addition, the results of an RCT from the Netherlands reported in 2014 (MR CLEAN⁹) indicated favorable outcomes for
combination with endovascular treatment. Thus, recanalization via endovascular treatment almost stopped being performed; however, is now once again being promoted.

Conditions increasing the outcomes of endovascular treatment

Clinical outcomes for recanalization by endovascular treatment for acute ischemic stroke were different in each RCT mainly because of the rate of recanalization and the time until recanalization.

1. IMS-III

The rate of recanalization in the IMS-III was clearly low at 23%-44%. This appears to be the reason why stent devices with a high rate of recanalization are currently not used. In other words, because the data is based on techniques before new devices were released onto the market, it should not be used to rule out the efficacy of current new devices. In addition, the time from onset to recanalization was 317.5 min, which is more than 60 minutes longer than the STAR, which will be mentioned later.

The recanalization rate in MR RESCUE is 67%, which appears high, but the definition of recanalization is a problematic point. Compared to groups where sufficient recanalization was achieved, groups in which a sufficient extent of recanalization was not achieved had unfavorable clinical outcomes, as was previously shown in the aforementioned IMS-III. The low value of the effective recanalization rate may have caused the unfavorable clinical outcomes. There was no mention of the time from onset to recanalization, but the time from onset until the angiography was started was 360 minutes or more, demonstrating that the time up to recanalization was quite a bit longer than in IMS-III.

2. STAR

The data in STAR was obtained using a stent...
device, Solitaire FR. The effective recanalization rate was high at 79.2%. In addition, the time from onset to recanalization was 256 minutes, which was shorter than in the other reports. During a subanalysis, for each one hour that the time from onset to recanalization was prolonged, the percentage of patients with a good clinical outcome decreased by 38%, and irrespective of the rate of recanalization, the time to recanalization was again verified to greatly influence the clinical outcome.

3. MR CLEAN
An RCT study comparing IV rt-PA monotherapy and concomitant use of endovascular treatment was conducted at an institution in the Netherlands. The device used for endovascular treatment was a stent in 97% of cases, and the time from onset to recanalization was 360 min, with an effective recanalization rate of 58.7%. The clinical outcomes in the concomitant endovascular treatment group were also favorable.

4. ESCAPE/EXTEND-IA/SWIFT-PRIME study
During the International Stroke Conference 2015, the results of three RCTs were reported. Usefulness for all endovascular treatments when using any of the stent devices was reported.

The clinical outcomes after 90 days were favorable: in the ESCAPE trial, 53% in the concomitant endovascular treatment group and 29% in the monotherapy group; in the EXTEND-IA trial, 71% in the concomitant endovascular treatment group and 40% in the monotherapy group; and in the SWIFT PRIME trial, 60.2% in the concomitant endovascular treatment group and 35.5% in the monotherapy group. In all groups, the outcomes in the concomitant endovascular treatment groups were better. Details from forthcoming papers are awaited.

Thrombectomy device

1. Merci Retrieval System (Stryker Neurovascular, Fremont, CA, USA)
In 2004, approval was obtained from the American FDA for the first thrombectomy device. This device is made up of a spiral-shaped coil and a filament that are advanced to the distal end of the thrombus, entangled in the thrombus, and then used to pull it out. It was the first thrombectomy device introduced in Japan in 2010. With the commercialization of new devices with a high rate of thrombectomy, it is no longer used, but it was a ground-breaking device that allowed us to switch from the local thrombolysis that had been performed to date to a new method of treatment known as mechanical thrombectomy.

2. Penumbra System (Penumbra, Alameda, CA, USA)
Approved by the FDA in 2008 and introduced in Japan in 2011, this device is used for aspiration and removal of thrombi. It is made up of a reperfusion catheter for aspiration, and an attached aspiration pump, as well as a separator to prevent occlusion of the inside of the catheter. The device is being continuously improved and has evolved into a device with a wider catheter that is better for aspiration. Currently, the thrombus is aspirated without using the separator and the ADAPT technique\(^\text{10}\), which involves the thrombus being wedged onto the tip of the catheter and aspirated, is the most popular.

If there is occlusion of the anterior cerebral artery, middle cerebral artery, or the intracranial internal carotid artery, a guiding catheter with an attached balloon is inserted and placed. If the occlusion starts from the origin of the internal carotid artery, the device is placed in the common carotid artery. If there is occlusion in the vertebro-basilar arterial system, a guiding catheter is inserted and placed into the vertebral artery; however, if the vertebral artery is occluded, it is usually difficult to insert a guiding catheter with attached balloon. In such cases, a normal guiding catheter with the maximum diameter that can be inserted is selected. A reperfusion catheter with the maximum diameter suitable for the occlusion diameter is advanced to just before the occluded region, and aspiration with the pump is attempted for 90 s. If aspiration is unsuccessful, we employ the ADAPT technique. The balloon on the guiding catheter is proximally clamped, and the reperfusion catheter is slowly withdrawn while continuing to aspirate using the pump. In this case, it is more effective to concomitantly use manual aspiration with a syringe from the guiding catheter.
3. Solitaire Flow Restoration device (Covidien, Dublin, Ireland)

This is a stent thrombectomy device approved by the FDA in 2012 and introduced in Japan in July 2014. The device is made up of a single-sheet, self-expandable stent designed in a cylindrical shape. The stent was designed to capture the thrombus, and the thrombus is interlocked while the sheet that makes up the stent maintains its overlapping structure. This device demonstrates an extremely high ability to capture thrombi. The stent itself cannot be confirmed radiographically, and only the markers at either end are radiopaque.

4. Trevo ProVue Retriever (Stryker Neurovascular, Fremont, CA, USA)

This is a stent thrombectomy device approved by the FDA in 2012 and introduced in Japan in July 2014. This is a self-expandable stent with vertical struts directed perpendicular to the vessel wall. When the central portion, which has the ability to effectively capture thrombi, is advanced into the site where the thrombus is located, the struts, which are unique structures, become entangled in the thrombus and grip tightly. Because the overall stent of the Trevo, unlike the Solitaire, is radiopaque, it offers the advantage of clearly showing the positional relationships between the stent and thrombus.

Irrespective of which stent thrombectomy device is used, the thrombectomy rate is currently at its highest, with extremely high recanalization rate and good clinical outcomes have been reported [3-5].

The selection of the guiding catheter is similar to that of the Penumbra system. After advancing the microcatheter to a point distal to the occlusion site, we use an image of both the microcatheter and guiding catheter to gain an initial understanding of the site of occlusion. The part of the stent that is effective at grasping thrombi is extended into the occlusion. In most cases, temporary recanalization of the site of occlusion is confirmed immediately after the stent is advanced. At this point in time, the thrombus is pressing on and distorting the outside of the stent and is not properly grasped. We wait for a few minutes, and then confirm that the stent is placed within the occlusion, at which time it is determined that the stent has grasped the thrombus. The guiding catheter balloon is dilated, and the proximal end is clamped, while blood is simultaneously aspirated from the guiding catheter during stent retrieval. Immediately after the stent is withdrawn from the body, the guiding catheter is sufficiently aspirated and care is taken to ensure that no thrombus remains inside the guiding catheter [11].

Personal experience

Even in our experience, there has been an obvious increase in recanalization rates through the commercialization of stent thrombectomy devices and improvement of the Penumbra system. Eighteen acute ischemic stroke cases were treated under mechanical thrombectomy in Juntendo University Hospital from December 2011 to January 2015. Five cases were treated by Merci Retrieval System (TICI 2b; 2 cases, TICI 0; 3 cases), 5 cases by Penumbra System (TICI 3; 2 cases, TICI 2b; 3 cases), 5 cases by Trevo ProVue Retriever (TICI 3; 2 cases, TICI 2b; 2 cases, TICI 0; 1 cases), 3 cases by Solitaire Flow Restoration device (TICI 3; 1 cases, TICI 2b; 2 cases). As a result, although we have experienced cases in which symptoms have improved dramatically, there are also cases in which achieving recanalization is not associated with an improvement in clinical symptoms. In addition, even if recanalization is achieved within 3 hours of onset, there are also cases that we have treated who experience no improvement in clinical symptoms.

Conclusions

To make various techniques for shortening time until recanalization possible, improvements to surgeon skill supported by advances in devices are necessary. Moreover, infrastructure for rapid emergency treatment for each facility and the cooperation of each related department are also vital. The rapid progression of endovascular intervention to treat acute cerebral infarction is likely to have a major influence on the establishment of regional cooperation for stroke treatment in the acute phase.
References