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厚生労働科学研究委託費

厚生労働科学研究委託事業（循環器疾患・糖尿病等生活習慣病対策実用化研究事業）

（委託業務題目）循環器疾患の新たな治療法の開発に関する研究

平成２６年度　委託業務成果報告書

業務主任者　吉村　紳一

平成２７（２０１５）年　３月

本報告書は、厚生労働省の厚生労働科学研究委託事業による委託業務として、学校法人兵庫医科大学 医学部 教授 吉村紳一が実施した平成２６年度「循環器疾患の新たな治療法の開発に関する研究」の成果を取りまとめたものです。

目　　次

厚生労働科学研究委託費（循環器疾患・糖尿病等生活習慣病対策実用化研究事業）
委託業務成果報告（総括）

循環器疾患の新たな治療法の開発に関する研究

業務主任者　吉村　紳一　兵庫医科大学医学部・教授

研究要旨:本研究においては発症後 4.5 時間以内の脳主幹動脈急性閉塞症における脳血管内治療の有効性確認のため無作為化比較試験（RESCUE-Japan RCT）を企画した。また同時に発症後 24 時間以内の脳主幹動脈閉塞症の前向き登録調査（RESCUE-Japan Registry2）も並行して行うこととした。RESCUE-Japan RCT の基本デザインは多施設共同、無作為化、非盲検、標準治療対照、並行群間比較試験であり、適応基準に合致し、除外基準のいずれにも抵触しない症例をランダムに介入群と対照群の２群に割り付けた。主要評価項目は発症 90 日後の modified Rankin scale（mRS)の違いで、目標症例数は 200 例（各群 100 例)、研究期間は 2014 年 9 月 1 日～2017 年 1 月 31 日(入院および追跡期間)とした。一方、RESCUE-Japan Registry2 では RCT の適応基準に合致しない症例が前向きに登録される。本研究は計画通りに症例登録が開始されたが、2015 年 1 月にオランダの RCT の結果が報告され、さらに 2015 年 2 月の国際脳卒中学会で、さらに 3 つの RCT で治療効果が確認されたため、独立モニタリング委員の判断にて RCT の症例登録を一旦停止し、登録された 18 例の 3 ヶ月後の転帰を解析することとなった。一方、RESCUE-Japan Registry2 については登録数がすでに 400 例を超えており、年内に中間解析が行われる予定である。

吉村紳一・兵庫医科大学医学部
教授

A．研究目的

主幹動脈急性閉塞例の治療成績は全体に不良であり、tPA 静注療法が行われたとしても予後例が多い。我が国においても血管内治療が行われているが、2013年に報告された欧米の３つのRCTはいずれもその有効性を証明できなかった。そこで発症後4.5時間以内の脳主幹動脈急性閉塞症の無作為化比較試験（randomized controlled tria l: RCT）を企画した。また同時に発症後24時間以内の脳主幹動脈閉塞症の前向き登録調査(Registry)も行うこととした。

B．研究方法

RESCUE-Japan RCT の基本デザインは多施設共同、無作為化、非盲検、標準治療対照、並行群間比較試験。適応基準に合致し、除外基準のいずれにも抵触しない症例をランダムに以下の２群に割り付けた；介入群（rt-PA 静注療法を含む標準的治療に血内治療を追加する)、対照群（rt-PA 静注療法を含む標準的治療のみ)。主要評価項目は発症 90 日後の modified Rankin scale（mRS）の違いで、目標症例数は 200 例（各群 100 例)、研究期間は 2014 年 9 月 1 日～2017 年 1 月 31 日（入院および追跡期間）とした。

一方、RESCUE-Japan Registry2 では適応基準に合致しない症例を前向きに登録する。発症後 24 時間以内に来院した全症例が対象で、目標症例数は 1,000 例、研究期間は RCT と同期間で、2014 年 9 月 1 日～2017 年 1 月 31 日（入院および追跡期間）とした。

（倫理面への配慮）

本研究に関与するすべての者は「世界医

師会ヘルシンキ宣言」、「疫学研究に関する倫理指針」および「臨床研究に関する倫理指針」に従う。本研究は通常診療下で行う研究であり、被験者全員がrt-PA 静注療法を受けることができる。一方、脳血管内治療は、研究開始時点では科学的に有効性が確認されておらず、先行研究ではその有益性が否定されていた。このため被験者が血管内治療を受けないことにより不利益を被るか否かは不明と判断した。本研究においては別に定める同意説明文書に基づき、研究に参加する前に十分に説明し、被験者または代諾者からインフォームド・コンセントを受け、当該者本人・代諾者の自由意思による試験参加の同意を文書で得ることとした。

C．研究結果

本研究は研究計画通り進行し、症例登録が開始された。その後、2015年1月にオランダのRCT（MR CELAN）の結果が報告されたが、本研究の独立モニタリング委員は全参加施設に連絡の上、研究の継続を決定した。しかし、2015年2月の国際脳卒中学会で、さらに3つのRCTで治療効果が確認されたため、RESCUE-Japan RCTにおいては症例登録を一旦停止し、登録された18例の3ヶ月後の転帰を解析することとなった。一方、RESCUE-Japan Registry2については研究を継続することとなり、登録数はすでに400例を超えており、年内に中間解析を行う予定である。

D．考察

急性期脳梗塞に対する治療については世界的に極めて大きな注目が集まっており、今後もRCTの結果が報告されると考えられる。一方、我が国では人種の違いや併用するrt-PA 静注療法の用量の違いなどがあるため、独自に血管内治療の有効性を確認する必要があると考えられる。このため、RESCUE-Japan RCTの初期症例の解析とともに、前向き登録研究であるRESCUE-Japan Registry2によって我が国の治療実態とその解析を行い、国民に有益な情報を発信したいと考えている。

E．結論

我が国における急性期脳梗塞に対する血管内治療の有効性確認のための比較試験であるRESCUE-Japan RCTは予定通り開始された。欧米のRCTの報告によりRESCUE-Japan RCTにおいては症例登録を一旦停止し、登録された18例の3ヶ月後の転帰を解析することとなった。一方、前向き登録研究であるRESCUE-Japan Registry2については登録進行中である。

F．健康危険情報

本研究に関する健康被害などの報告はない。

G．研究発表

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H. 知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

様式第１９

学　会　等　発　表　実　績

委託業務題目「循環器疾患の新たな治療法の開発に関する研究」

機関名　学校法人兵庫医科大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Carotid artery stenting. (Educational Lecture)	Yoshimura S	Kuala Lumpur, Malaysia (WFNS Course & Workshop 2014)	2014	国外
Acute endovascular thrombectomy. (Educational Lecture)	Yoshimura S	Kuala Lumpur, Malaysia (WFNS Course & Workshop 2014)	2014	国外
IVR Workshop. (Hans-on)	Yoshimura S	Xi'an, China (2nd International Congress on Minimally Invasive Technique in Neurosurgery)	2014	国外
機械的血栓回収療法の現状. (プレナリーセッション)	吉村紳一，白川学，内田和孝，田中康恵	大阪（第34回日本脳神経外科コングレス総会）	2014	国内
超急性期再開通療法の展望. (共催シンポジウム)	吉村紳一	和歌山（第20回日本血管内治療学会総会）	2014	国内
海外のon going trialと国内の試み. （レクチャー）	吉村紳一	神戸（脳血管内治療ブラッシュアップセミナー）	2014	国内
Solitaire™FR国内導入. （共催セミナー）	吉村紳一	神戸（脳血管内治療ブラッシュアップセミナー）	2014	国内
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頚動脈ステント留置術における脳循環代謝画像の意義と対策. (シンポジウム)	吉村紳一，白川学，内田和孝，進藤誠悟，榎本由貴子，江頭裕介，岩間亨	盛岡（第33回The Mt. Fuji Workshop on CVD）	2014	国内
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Imaging necessary for neuroendovascular therapy from a neurosurgeon's view. (シンポジウム)	吉村紳一	神戸（第50回日本医学放射線学会秋季臨床大会）	2014	国内
脳梗塞急性期マネジメント ～血管内治療と抗凝固療法～. (アフタヌーンセミナー)	吉村紳一	東京（日本脳神経外科学会第73回学術総会）	2014	国内
二刀流医師が考える脳血管障害治療. （アフタヌーンセミナー）	吉村紳一	東京（日本脳神経外科学会第73回学術総会）	2014	国内

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頚動脈ステント留置術におけるpitfall. (ランチョンセミナー)	吉村紳一	横浜 (第30回NPO法人日本脳神経血管内治療学会学術総会)	2014	国内
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Big debate2「脳血管解離」(日本脳卒中の外科学会／日本脳神経血管内治療学会 合同生涯教育セミナー・パネリスト)	吉村紳一	広島 (STROKE2015 (第40回日本脳卒中学会総会／第44回日本脳卒中の外科学会学術集会／第31回スパズム・シンポジウム))	2015	国内
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２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Efficacy of endovascular treatment for acute cerebral large-vessel occlusion: analysis of nationwide prospective registry.	Yoshimura S, Sakai N, Okada Y, Kitagawa K, Kimura K, Tanahashi N, Hyogo T, Yamagami H, Egashira Y; Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism (RESCUE)-Japan Registry Investigators	J Stroke Cerebrovasc Dis 23:1183-1190	2014	国外
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Efficacy of Endovascular Treatment for Acute Cerebral Large-Vessel Occlusion: Analysis of Nationwide Prospective Registry

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Background: The aim of this nationwide, prospective registry of acute cerebral large-vessel occlusion was to assess the efficacy of endovascular treatment (EVT) on outcome in the "real-world" settings. *Methods:* Medical information of the patients was anonymized and registered prospectively through a Web site from 84 medical centers in Japan. Reperfusion of the affected arteries was evaluated by the Thrombolysis in Cerebral Infarction grade on cerebral angiography or by the modified Mori grade on magnetic resonance angiography. Clinical outcome was evaluated by modified Rankin Scale (mRS) at 90 days after onset. Symptomatic intracranial hemorrhage and procedure-related complications were also analyzed. *Results:* Among intravenous tissue plasminogen activator (IV t-PA)–failed patients, no significant difference in favorable outcome was seen with or without EVT overall (41.7% versus 36.8%, $P = .55$). However, EVT significantly increased favorable outcomes (mRS score 0-2) in patients with internal carotid artery (ICA)/middle cerebral artery M1/basilar artery (BA) occlusion (41.3% versus 20.5%, $P = .019$). In contrast, among t-PA–ineligible patients, EVT significantly increased favorable outcomes overall (29.1% versus 19.5%; odds ratio, 1.70; $P = .007$). Furthermore, favorable outcomes were more common in patients with ICA/M1/BA occlusion (29.0% versus 10.3%; odds ratio, 3.56; $P < .0001$). Multivariate analysis also confirmed the efficacy of IV t-PA, EVT, and their combination for favorable outcome. *Conclusions:* EVT significantly improved clinical outcomes in IV t-PA–failed and t-PA–ineligible patients with ICA/M1/BA occlusion. These findings support the introduction of EVT for acute proximal artery occlusion. **Key Words:** Acute stroke—large-vessel occlusion—endovascular treatment—tissue plasminogen activator—national registry.

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Introduction

Although the introduction of intravenous (IV) administration of recombinant tissue plasminogen activator (t-PA) has had a significant impact on the treatment of acute stroke, problems with its use have become apparent. For example, IV t-PA is reportedly used in less than 5% of all ischemic stroke cases, and the rate of early recanalization of the affected artery, which reportedly correlates with better clinical outcomes, appears low.[1-3] The rate of recanalization is known to be higher with intra-arterial (IA) treatments, such as thrombolysis and mechanical procedures than with IV t-PA.[2] Endovascular treatment (EVT), such as mechanical thrombectomy, balloon angioplasty, or thrombolysis, has been associated with higher rate of reperfusion,[4-10] but recent randomized, controlled trials have failed to confirm its clinical efficacy compared with IV t-PA or standard care.[11-13]

As the first nationwide, prospective registry of acute cerebral large-vessel occlusion, this study was conducted to assess the impact of EVT on clinical outcome following approval of a mechanical clot retriever in Japan.

Methods

The registry covered all patients with acute stroke because of large-vessel occlusion who were admitted to 84 participating medical centers within 24 hours after onset between July 1, 2010, and June 30, 2011. Medical information of the patients was anonymized and registered prospectively through a Web site (http://www.rescue-japan.jp). Factors related to treatment selection and outcomes were investigated as follows: time to admission, type of stroke, occluded vessel, National Institutes of Health Stroke Scale (NIHSS) score on admission, modified Rankin scale (mRS) score 3 months after onset, and treatments including various devices for EVT, medications, and laboratory data. The methods, results, and complications of EVT were precisely recorded. The study was approved by the local institutional review committee in each hospital, and its protocol was registered (University Hospital Medical Information Network: UMIN000003412). The register of patients was monitored to rule out selection bias by monitoring committee.

Primary and Secondary Outcomes

The primary outcome was the rate of an mRS score of 0-2 at 90 days after onset. Secondary outcomes were (1) recanalization of the target vessel (immediately after treatment and 24 hours after onset), (2) rate of an mRS score of 0-1 at 90 days after onset, (3) NIHSS score on admission and 7 days after onset, (4) relationship between recanalization and prognosis, (5) symptomatic intracranial hemorrhage within 24 hours after onset, (6) death within 90 days after onset, and (7) other adverse events.

Neurologic Evaluation

NIHSS score was evaluated on admission, 1 hour after bolus injection of t-PA, immediately after EVT, 24 (±8) hours after onset, and 7 (±2) days after onset.

Computed Tomography and Magnetic Resonance Imaging

All patients underwent repeated computed tomography (CT) or magnetic resonance imaging (MRI) with MR angiography at 24 (±8) hours after onset, except for patients admitted 16-24 hours after onset.

Intravenous Tissue Plasminogen Activator

IV t-PA was performed as the first-line treatment within 3 hours of symptom onset, in accordance with the standard protocol in Japan (.6 mg/kg dose, 10% bolus, 90% continuously infused over 60 minutes).[14]

Endovascular Treatment

EVT was performed basically IV t-PA–failed or t-PA–ineligible patients within 8 hours after onset. EVT was defined as IA catheter procedures such as clot removal/aspiration, balloon angioplasty, stenting, and IA thrombolysis using a microcatheter.

Reperfusion Analysis

Neuroimaging studies at baseline with CT or MR angiography were performed for proving large arterial occlusion. When IV t-PA was performed, reperfusion of the affected artery was evaluated on cerebral angiography or MR angiography at 1-3 hours after t-PA bolus injection and at 24 (±8) hours after onset. In cases of EVT, reperfusion of the affected artery was evaluated on final angiography and on MR angiography at 24 (±8) hours after onset.

On cerebral angiography, reperfusion was classified according to the modified Thrombolysis in Cerebral Infarction (TICI) grade.[15] Grade 0, no perfusion; grade 1, perfusion past the initial obstruction, but limited distal branch filling with little or slow distal perfusion; grade 2, penetration with minimal perfusion; grade 2A, perfusion of less than half of the vascular distribution of the occluded artery; grade 2B, perfusion of half or greater of the vascular distribution of the occluded artery; and grade 3, full perfusion with filling of all distal branches.

On MR angiography, reperfusion was evaluated according to the modified Mori grade.[16] Grade 0, no reperfusion; grade 1, movement of thrombus not associated with any flow improvement; grade 2, partial (branch) recanalization in less than 50% of the branches in the occluded arterial territory; and grade 3, nearly complete recanalization with reperfusion in >50% of the branches in the occluded arterial territory.

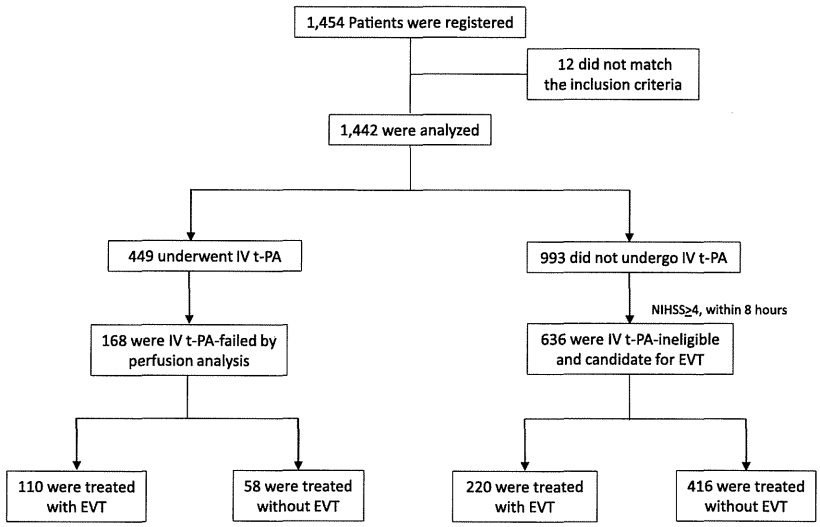

Figure 1. *Flowchart of patients. Abbreviations: EVT, endovascular treatment; IV t-PA, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.*

Successful reperfusion in this study was defined as grades 2B and 3 using TICI grading or grade 3 using modified Mori's grading.

IV t-PA–failed patients were defined as those patients whose vessel was not significantly reperfused, that is, showing modified Mori's grade 0-1 on MR angiography or TICI grade 0-1 on cerebral angiography at 1-3 hours after the bolus injection of t-PA.

Evaluation of Clinical Outcome

Patient outcomes were evaluated using the mRS on admission and 90 (±10) days after onset. A favorable outcome was defined as an mRS score of 0-2.

Evaluation of Symptomatic Hemorrhage

In this study, intracranial hemorrhage within 24 ± 8 hours after onset was evaluated on follow-up imaging. Symptomatic hemorrhage was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition,[17] local or remote parenchymal hematoma type 2 on follow-up imaging, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or lowest value between baseline and 24 hours or hemorrhage leading to death.

Statistical Analysis

Statistical analysis was performed using commercially available software (JMP 7; SAS Institute, Cary, NC). The statistical significance of intergroup differences was assessed using the t test for quantitative scales, Pearson χ^2 test for categorical scales, and the Mann–Whitney U test or Wilcoxon signed-rank test for ordinal scales. Values of P less than .05 were considered significant. Statistical analysis was carried out by members of the writing committee.

Results

Backgrounds and Characteristics of Patients

Of the 1454 registered patients, 1442 patients (99.2%) met the inclusion criteria and were analyzed in this study (Fig 1, Table 1). Median baseline NIHSS score on admission was 16 (interquartile range, 9-21), and median time from onset to admission was 125 minutes (interquartile range, 60-300 minutes). In this study, 849 patients (58.9%) arrived within 3 hours and 312 patients (21.6%) arrived 3-8 hours after onset.

Cardioembolic infarction was diagnosed in 1023 patients (71.0%), and atherothrombotic infarction was diagnosed in 288 (20.0%). The occluded vessel was the internal carotid artery (ICA) in 407 patients (28.2%), the MCA in 760 (52.7%), the basilar artery (BA) in 99 (6.9%), and multiple in 57 patients (4.0%).

Reperfusion after IV t-PA and Clinical Outcome

In the 449 patients who received IV t-PA, 318 underwent a reperfusion study: 147 patients (46.2%) underwent cerebral angiography alone, 119 patients (37.4%) underwent repeated MR angiography alone, and 52 patients underwent both (16.3%).

On cerebral angiography, reperfusion was judged 1-3 hours after IV t-PA by the TICI grade.[15] Successful reperfusion, defined as grade 2B or 3, was obtained in 11% of ICA cases, 29.2% of proximal M1 cases, 37.8% of distal M1 cases, 40.7% of M2 or distal cases, and 23.6% of BA cases (Fig 2).

Clinical outcomes of patients were also analyzed by location of vessel occlusion (Table 2). Overall, a significant difference in the rate of successful reperfusion was evident between patients treated by IV t-PA alone and IV t-PA + EVT (43.5% versus 62.8%, OR 2.19, P = .006), but clinical outcome showed no significant difference (42.2% versus 44.5%, OR 1.09, P = .65). In

Table 1. *Baseline characteristics of patients*

	Median (IQR) or n (%)
Total number of munched patients	1442
Mean age, y	75.5 (67-83)
Sex, female	634 (44.0)
Hypertension	818 (56.7)
Diabetes mellitus	282 (19.6)
Hyperlipidemia	283 (19.6)
Atrial fibrillation	853 (59.2)
Congestive heart failure	170 (11.8)
Smoking	203 (14.1)
Systolic BP, mm Hg	157 (139-174)
Diastolic BP, mm Hg	84 (72-97)
Serum glucose, mg/dL	127 (109-154.5)
Baseline NIHSS score	16 (9-21)
Onset to admission, min	125 (60-300)
Within 3 h	849 (58.9)
3-8 h	312 (21.6)
More than 8 h	192 (13.3)
Unknown	89 (6.2)
Stroke subtype	
Cardioembolic infarction	1023 (71.0)
Atherothrombotic infarction	288 (20.0)
Others/unclassified	131 (9.1)
Occluded vessel	
ICA	407 (28.2)
Extracranial ICA	195 (13.5)
Intracranial ICA	186 (12.9)
ICA (unknown)	26 (1.8)
MCA	760 (52.7)
Proximal M1	263 (18.2)
Distal M1	223 (15.5)
M1 (unknown)	5 (.3)
M2 or distal	269 (18.7)
BA	99 (6.9)
PCA	52 (3.6)
VA	32 (2.2)
ACA	17 (1.2)
Multiple	57 (4.0)
Others	104 (7.2)
Unknown	15 (1.0)

Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; BP, blood pressure; ICA, internal carotid artery; IQR, interquartile range; M1, middle cerebral artery M1 portion; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery.

the ICA, successful reperfusion and favorable outcome (mRS score 0-2) were more common after IV t-PA + EVT than after IV t-PA alone (reperfusion: 56.0% versus 18.8%, OR 5.51, P = .0006; favorable outcome: 43.8% versus 21.4%, OR 2.85, P = .015). However, other vessels such as the M1 and BA showed no significant differences in rate of successful reperfusion or favorable outcome.

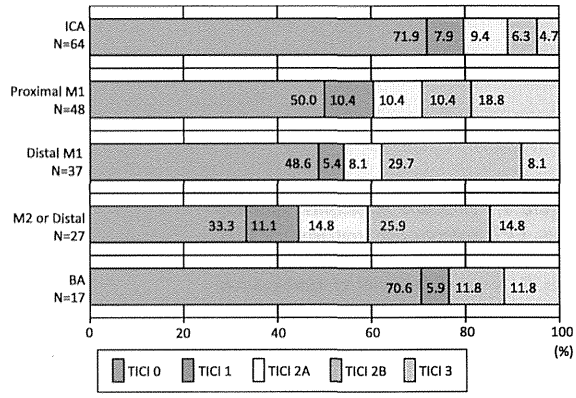

Figure 2. *Reperfusion of the affected arteries on cerebral angiography after intravenous tissue plasminogen activator. Reperfusion of the affected arteries was evaluated by the TICI grade on cerebral angiography; grade 0, no perfusion; grade 1, perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion; grade 2, penetration with minimal perfusion; grade 2A, perfusion of less than half of the vascular distribution of the occluded artery; grade 2B, perfusion of half or greater of the vascular distribution of the occluded artery; and grade 3, full perfusion with filling of all distal branches. Successful reperfusion, defined as grade 2B or 3, was obtained in 11% of ICA cases, 29.2% of proximal M1 portion of middle cerebral artery cases, 37.8% of distal M1 cases, 40.7% of M2 or distal cases, and 23.6% of BA cases. Abbreviations: BA, basilar artery; ICA, internal carotid artery; TICI, Thrombolysis in Cerebral Infarction.*

Effect of EVT for IV t-PA–Failed Patients

Next, the effect of EVT for IV t-PA–failed patients was analyzed. Of the 168 IV t-PA-failed patients, 110 were treated with EVT. The EVT group was younger (71.5 versus 76 years, P = .024) and contained fewer patients with hypertension (52.7% versus 69%, P = .041), but neurologic grade was significantly worse (median NIHSS score: 17 versus 14, P = .0019). Median duration to EVT was 210 minutes (range, 180-245 minutes) after onset.

A difference was seen in the rate of successful reperfusion (88.3% versus 42.0%, P < .0001, Table 3), but no significant difference in favorable outcome was seen between patients with or without EVT overall (41.7% versus 36.8%, P = .55). EVT significantly increased favorable outcomes (mRS score 0-2) in patients with ICA/M1/BA occlusion (41.3% versus 20.5%, P = .019, Table 3, Fig 3, A). These results suggest that EVT was effective to obtain better clinical outcomes for IV t-PA–failed patients with ICA/M1/BA occlusion.

Effect of EVT for IV t-PA–Ineligible Patients

The effect of EVT for IV t-PA–ineligible patients was then evaluated. Among 993 patients who did not undergo IV t-PA, 636 patients with NIHSS score of 4 or more and arrived within 8 hours after onset were judged as candidates for EVT (Fig 1). Among these 636 patients, 220 were treated with EVT. The EVT group was significantly younger (73 versus 78 years, P < .0001) and included fewer women (37.7% versus 50.2%, P = .0025), although

Table 2. *Analysis of reperfusion and outcome by location of vessel occlusion*

	Reperfusion analysis (n = 318)			Outcome analysis (n = 442)		
	Successful reperfusion*, n (%)	OR (95% CI)	*P*	Favorable outcome†, n (%)	OR (95% CI)	*P*
Total	167 (52.5%)			190 (43.0%)		
IV t-PA alone	74 (43.5%)	2.19 (1.40-3.46)	.006	125 (42.2%)	1.09 (.74-1.64)	.65
IV t-PA + EVT	93 (62.8%)			65 (44.5%)		
ICA	34 (41.5%)			33 (31.7%)		
IV t-PA alone	6 (18.8%)	5.51 (2.03-17.0)	.0006	12 (21.4%)	2.85 (1.23-6.87)	.015
IV t-PA + EVT	28 (56.0%)			21 (43.8%)		
M1	73 (58.6%)			70 (39.3%)		
IV t-PA alone	36 (51.4%)	1.40 (.70-2.81)	.34	42 (36.2%)	1.45 (.77-2.72)	.25
IV t-PA + EVT	37 (59.7%)			28 (45.2%)		
BA	19 (79.2)			13 (43.3)		
IV t-PA alone	7 (70.0)	2.57 (.35-23.4)	.35	7 (43.8)	.96 (.22-4.15)	.96
IV t-PA + EVT	12 (85.7)			6 (42.9)		
Others	64 (50.8%)			106 (54.6%)		
IV t-PA alone	42 (47.7%)	1.51 (.70-3.28)	.29	88 (56.4%)	.70 (.34-1.42)	.32
IV t-PA + EVT	22 (57.9%)			18 (47.4%)		

Abbreviations: EVT, endovascular treatment; IV t-PA, intravenous tissue plasminogen activator; M1, middle cerebral artery M1 portion; OR, odds ratio; CI, confidence interval.

*Successful reperfusion, Thrombolysis in Cerebral Infarction grades 2B and 3 or modified Mori's grade 3.

†Favorable outcome, modified Rankin Scale score 0-2 at 90 days after onset.

neurologic score was not different (NIHSS: 18 versus 17, $P = .52$). Median duration to EVT was 240 minutes (range, 179-346 minutes) after onset.

Against this background, EVT increased the rates of successful reperfusion (78.5% versus 44.5%, OR 4.54, $P < .0001$, Table 3) and favorable outcomes (29.1% versus 19.5%, OR 1.70, $P = .007$). Furthermore, favorable outcomes were more common in patients with ICA/M1/BA occlusion (29.0% versus 10.3%, OR 3.56, $P < .0001$, Fig 3, B).

These results suggest that EVT was effective for obtaining better clinical outcomes in IV t-PA–ineligible patients, particularly when the occlusion involved proximal arteries.

Symptomatic Intracranial Hemorrhage

Of the 1360 patients who underwent repeated CT or MRI at 24 ± 8 hours after onset, symptomatic hemorrhage was observed in 46 (3.4%) overall, comprising 13 of 644 patients (2.0%) in the conservative group treated without IV t-PA or EVT, 11 of 292 patients (3.8%) with IV t-PA, 8 of 148 patients (5.4%) with IV t-PA and EVT, and 13 of 264 patients (4.9%) with EVT only. The rate of symptomatic intracranial hemorrhage (sICH) in patients treated with IV t-PA alone was comparable with that seen in the Japanese postmarketing trial of alteplase.[16] No significant increase in sICH was observed in either the IV t-PA

Table 3. *Analysis of reperfusion and outcome in IV t-PA–failed or t-PA–ineligible patients*

IV t-PA–failed patients	With EVT (n = 110)	Without EVT (n = 58)	*P*	OR (95% CI)
Successful reperfusion	68/77 (88.3)	21/50 (42.0)	<.0001	10.4 (4.42-26.7)
Favorable outcome				
Overall	45/108 (41.7)	21/57 (36.8)	.55	1.22 (0.64-2.39)
ICA/M1/BA occlusion	38/92 (41.3)	8/39 (20.5)	.019	2.73 (1.17-6.96)
IV t-PA–ineligible patients	**With EVT (n = 220)**	**Without EVT (n = 416)**	***P***	**OR (95% CI)**
Successful reperfusion*	135/172 (78.5)	110/247 (44.5)	<.0001	4.54 (2.94-7.14)
Favorable outcome†				
Overall	64/220 (29.1)	80/410 (19.5)	.007	1.70 (1.16-2.48)
ICA/M1/BA occlusion	51/176 (29.0)	29/282 (10.3)	<.0001	3.56 (2.17-5.95)

Abbreviations: BA, basilar artery; CI, confidence interval; EVT, endovascular treatment; ICA, internal carotid artery; M1, middle cerebral artery M1 portion; OR, odds ratio.

*Successful reperfusion, Thrombolysis in Cerebral Infarction grades 2B and 3 or modified Mori's grade 3.

†Favorable outcome, modified Rankin Scale score 0-2 at 90 days after onset.

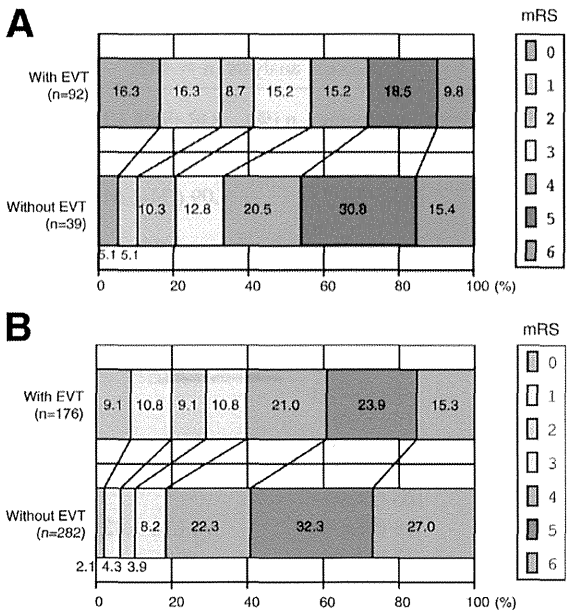

Figure 3. *Functional outcome at 90 days in the patients with ICA/M1/BA occlusion. (A) Functional outcome at 90 days in the IV t-PA–failed patients with or without EVT. Shown are 90-day mRS scores in patients undergoing additional EVT or receiving standard medical care for the IV t-PA–failed patients with ICA/M1/BA occlusion. The percentages of patients are shown in, above, or below each cell. Additional EVT was superior to standard medical care in IV t-PA–failed patients with ICA/M1/BA occlusion (P = .019). (B) Functional outcome at 90 days in the IV t-PA–ineligible patients with or without EVT. EVT was superior to standard care in IV t-PA–ineligible patients with ICA/M1/BA occlusion (P < .0001). Abbreviations: BA, basilar artery; EVT, endovascular treatment; ICA, internal carotid artery; IV t-PA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale.*

and EVT group or EVT-alone group compared with the IV t-PA group (P = .42 and P = .50, respectively).

Procedure-Related Complications after EVT

Procedure-related complications were observed in 32 of 268 procedures (11.9%) in the EVT-alone group, of which 9 (3.4%) were clinically significant. On the other hand, procedure-related complications were seen with 16 of 148 procedures (10.8%) in the IV t-PA and EVT group, of which 4 (2.7%) were clinically significant. There was no significant difference between the EVT-alone group and IV t-PA and EVT group.

Characteristics for Favorable Outcome at 90 Days

Multivariate regression analysis indicated that higher baseline NIHSS and higher age were significantly related to unfavorable outcome, whereas IV t-PA + EVT, IV t-PA, and EVT were all associated with favorable outcome significantly (Table 4). Odds ratio was highest in combination with IV t-PA + EVT, IV t-PA alone, and EVT alone in order.

Table 4. *Characteristics associated with favorable outcome at 90 d*

Characteristic	*P*	OR (95% CI)
Baseline NIHSS, per 1-point increase	<.0001	.876 (.858-.894)
Age, per 1-y increase	<.0001	.963 (.951-.975)
Sex, male (0) vs female (1)	.534	.914 (.688-1.214)
IV t-PA + EVT	<.0001	3.244 (2.055-5.120)
IV t-PA alone	<.0001	2.971 (2.097-4.209)
EVT alone	.007	1.699 (1.156-2.498)

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

Discussion

In this nationwide registry study of acute large-vessel occlusion, EVT significantly increased the rate of favorable outcomes in patients with ICA occlusion but not with other vessel occlusion. Among IV t-PA–failed patients, EVT increased the rate of favorable outcomes in patients with ICA/M1/BA occlusion but not overall. In contrast, among IV t-PA–ineligible patients, EVT increased the rate of favorable outcomes regardless of the affected vessels, and favorable outcomes were more common in patients with ICA/M1/BA occlusion. The reason for better outcomes involving these proximal vessels might be that catheter interventions were feasible, and successful reperfusion by IV t-PA alone was rare. In fact, a significant increase in successful reperfusion was seen with addition of EVT in both IV t-PA–failed and t-PA–ineligible patients with ICA/M1/BA. Patient selection based on preprocedural vessel imaging is thus key to obtain a favorable effect with EVT.

On the other hand, recent randomized, controlled trials failed to show the efficacy of EVT for acute stroke.[11-13] For example, the Interventional Management of Stroke III trial was performed to determine whether a combined approach with IV t-PA and EVT is more effective than IV t-PA alone. However, that trial did not show any benefit in terms of functional outcome from the use of EVT.[11] The Synthesis Expansion and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial likewise failed to show any efficacy of EVT.[12,13] The failure of these trials might be attributable to delayed initiation of EVT and/or insufficient reperfusion using first-generation devices. In this registry, EVT was started much earlier (210 minutes after onset in RESCUE-Japan versus more than 360 minutes in MR RESCUE), and the reperfusion rate was much higher than that of MR RESCUE (TICI IIb-III: 52.5% in RESCUE-Japan versus 26% in MR RESCUE).[13] The reason for the higher rate of reperfusion in the present study might be because of unlimited use of endovascular devices such as stents and balloons. These

differences should be considered when designing future comparative studies.

The disadvantages of EVT also need to be kept in mind. For example, the device may injure the vessel, resulting in intracranial hemorrhage or infarction. The incidence of clinically significant procedure-related complications was 3.4% with EVT alone and 2.8% with IV t-PA and EVT in the present study, comparable with the 5.5% in the Multi MERCI trial.[8] Furthermore, symptomatic hemorrhage was not significantly elevated by EVT after IV t-PA in this study. The incidence of complications with current EVT, thus, seems acceptable.

This study had some limitations. In this study, baseline characteristics were not balanced because the study was not a randomized trial. Also, treatment selection was made in each institute independently, which might have affected the clinical outcomes. To clarify the real clinical impact of EVT for acute stroke, randomized trials applying new-generation devices such as stent retrievers with appropriate patient selection using vessel imaging should be performed in the near future.

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