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The selections of acute stroke patients for catheter based intervention

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SOUHRN

Intravenózní podání trombolytik během prvních 4,5 hodiny od vzniku příhody představuje již po řadu let spolehlivý způsob léčby pacientů s akutní ischemickou cévní mozkovou příhodou. Vzhledem k vysokému výskytu komplikací a nízké úspěšnosti trombolytické léčby, zvláště u pacientů s uzávěrem proximálních tepen, je však nutno vypracovat účinnější léčebné postupy. Podle výsledků nejnovějších randomizovaných kontrolovaných studií jsou endovaskulární výkony ve spojení s intravenózním podáním trombolytik nedílnou součástí léčby tohoto onemocnění. Endovaskulární léčba stent-retrievery zajistila vyšší úspěšnost výkonu a rychlejší rekanalizaci, tedy i lepší výsledky, zvláště u nemocných, u nichž byl uzávěr proximálních tepen bez rozsáhlejšího postižení tkáně prokázán zobrazovacími metodami.

Keywords:
Acute stroke
Endovascular treatment
Imaging
Mechanical thrombectomy

ABSTRACT

Administration of intravenous thrombolytic agents within the first 4.5 h after initial presentation has been used as a reliable therapy for many years in patients with acute ischemic stroke. However, more efficient therapeutic strategies are warranted due to high complication and low treatment success rate with thrombolytic agents, particularly in patients with proximal arterial occlusion. After the completion of the most recent randomized controlled trials, endovascular treatments in conjunction with intravenous thrombolytic agents have been regarded as an integral part of management in this condition. Endovascular treatments with retrievable stents have resulted in higher and faster recanalization rates, hence better clinical outcomes, particularly in patients in whom presence of proximal arterial occlusion and absence of large core tissue have been demonstrated using imaging modalities.

Introduction

Ischemic stroke results from impaired cranial perfusion due to total blockade or slowing of cranial blood flow in at least one of the cerebral vessels. Together with impaired cerebral blood flow, an area referred to as the "core zone" surrounded by another zone, i.e. "penumbra" develop [1,2]. Core is characterized by tissue necrosis occurring due to decline in blood flow below a critical threshold, and even successful reperfusion does not lead to tissue repair in this area. On the other hand, penumbra around the core is still viable despite reduced blood flow and impaired functions [1–3]. Penumbra may regain normal functions if reperfusion can be achieved; however, acute stroke is a dynamic process in which the necrotic core zone expands and salvageable penumbral zone contracts with time, resulting in the formation of an infarction zone composed of necrotic tissue within hours [4,5].

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The target of management in ischemic stroke is to restore functionality in the penumbra zone, which is considered as the "salvageable" zone; in other words, the stroke treatment targets reducing infarct size and saving penumbra [4,5]. In this regard, the only treatment modality with proven efficacy is recanalization in the occluded vessel. NINDS was the first study to demonstrate significant improvement in patient functions – despite the absence of a decline in mortality as compared to controls – with IV tissue plasminogen activator (tPA) treatment administered within the first 3 hours. As a result of this study, IV tPA was approved by the FDA in USA [6,7]. The treatment window was expanded to include the first 4.5 h period after stroke onset following the publication of ECASS III study which showed that the benefits of IV tPA may continue up to 4.5 h in selected patients [8] In patients eligible for IV tPA according to national and international guidelines, this treatment results in improved functional outcomes within 3 to 6 months. Since earlier treatment is associated with more significant benefits, an effort should be made to eliminate potential delays in initiation of treatment [6–8]. Despite considerable success of IV tPA in patients with acute ischemic stroke, this treatment is also associated with a number of problems. The therapeutic window of IV tPA in patients with acute ischemia stroke is narrow and many patients present to the emergency room after the initial 4.5 h period. Also, delayed IV tPA treatment is associated with increased risk of intracranial hemorrhage. Furthermore, the efficacy of IV tPA in proximal vessels in patients with acute ischemic stroke is considerably low [9–11].

PROACT II study published in 1999 showed that intra--arterial pro-urokinase (a specific thrombolytic agent) administered with heparin within the first 6 h resulted in better functionality as compared to those treated with heparin only. However, intra-arterial thrombolytic agent has never been approved by FDA and has never become a standard therapeutic approach [12]. In particular, IMS I study showed no recanalization of proximal occlusion after IV thrombolytic agents, as demonstrated by post--treatment angiography [13].

Although relatively successful recanalization rates were achieved in proximal arterial occlusion using the first-generation thrombectomy and thrombo-aspiration devices (e.g. Merci, CATCH, Penumbra), this did not translate much into clinical improvement [14–16]. In the pivotal Penumbra study involving a total of 125 patients with acute ischemic stroke and NIHS score >8, although thrombo-aspiration performed within the first 8 h period resulted in TIMI 2–3 patency in the occluded vessel in 81.6% of the patients, mRS score at 3 months was <2 in only 25% of the patients. An analysis of the potential causes of this clinical failure showed that recanalization did not result in clinical improvement, particularly in patients in whom recanalization was performed after 300 minutes and in those who had a large core-infarct at the initial CT imaging [17]. These results clearly emphasized two important issues. Firstly, acute ischemic stroke should be promptly treated and advanced instruments should be utilized for quick recanalization. Secondly, patient selection for endovascular treatment should be performed meticulously, since patients with established injury do not benefit from reperfusion [17].

In 2013, three multi-center, randomized studies have been published that compared endovascular treatment and IV thrombolytic treatment. In all three studies, i.e. MR RESCUE, SYNTHESIS and IMS III trials, no superiority of endovascular treatment over IV tPA could be demonstrated in acute ischemic stroke patients [18–20]. In IMS III study 900 patients from 58 study centers with suspected vascular occlusion and an NIH score equal to or greater than 10 were enrolled. All patients received tPA for 40 min and then were randomized to either complete IV tPA or underwent endovascular treatment. Due to slow enrollment rate in the study, small modifications were made in the study schedule as to include patients with an NIH score ≥8 in addition to demonstration of vessel occlusion in CT angiography. Furthermore, toward the end of the study, full dose of IV tPA was administered in those subjects randomized to endovascular treatment. The choice of devices used for endovascular treatment was left at the discretion of the clinician (mostly first generation). The study was prematurely terminated after enrollment of 656 patients due to the absence of significant difference between the two groups. Also, pre-defined primary and secondary end-points did not differ between the study groups [18]. Similarly, no superiority of endovascular treatment over IV tPA could be demonstrated in MR RESCUE and SYNTHESIS [19,20].

Factors implicated for the observed failure included the inadequate technology of endovascular devices, inability to achieve re-canalization at adequate rates and speed, and particularly the inclusion of inappropriate patients. For instance, of the 656 patients included in IMS III, only 306 had a vascular imaging study prior to randomization. In 80 patients randomized with CTA or MRA, in other words in nearly 20% of the patients, there was no vascular occlusion. An analysis including only patients with CTA-confirmed occlusion, patients undergoing endovascular treatment had more successful outcomes in terms of the proportion of patients with a 3-month mRS score of ≤2, than IV tPA patients ($p = 0.0114$) [18].

The recently introduced retrievable stents resulted in higher and quicker recanalization rates in patients with acute ischemic stroke. In SWIFT study (Solitaire flow restoration device versus the Merci Retriever in patients with acute ischemic stroke), a retrievable device, i.e. solitaire, was compared with Merci. Patents over 22 years of age with a TIMI 0 or 1 flow as demonstrated by DSA (MCA M1 or M2 branch, ICA, basilar or vertebral artery) who failed IV tPA within the first 8 h or who had no IV tPA were included. At the end of the study, retrievable stents were more successful both in terms of successful recanalization rate (61% vs. 24%) and also in terms of the proportion of patients with a 3-month mRS score below 2 (58% vs. 33%) [21]. Similarly, in TREVO 2 (Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke) where another retrievable stent device, i.e. Trevo, was utilized, the rate of successful recanalization with retrievable stents was higher as compared to first-generation thrombectomy devices (86% vs. 60%) [22].

Lessons learned from the failures in randomized controlled studies as well as the data emerging from clinical studies examining the role of new generation thrombec-

tomy devices suggested that in appropriately selected patients, promptly administered endovascular treatment with higher success rates could give a light of hope. In more recent randomized clinical studies, all these factors were taken into consideration to solely include newer generation thrombectomy and thrombo-aspiration devices, as well as to include patients with a small core zone and proximal occlusion established prior to randomization. Subsequently, recently completed studies in patients with acute stroke who were shown to have proximal arterial occlusion and limited core zone in imaging studies demonstrated the superiority of endovascular treatment over IV tPA alone [18–20].

In MR CLEAN study, a total of 445 patients with proven proximal occlusion in the anterior circulation (CTA, MRA) and acute ischemic stroke, were randomized to receive EV after IV tPA within the first 6 h. Of the 233 intra-arterial interventions, 190 were performed using retrievable stents. The two groups were comparable in terms of mortality and hematoma frequency, while there was a net 13.5% difference between endovascular treatment group and IV tPA alone with respect to ability to lead an independent life (OD 1, 67) [23]. Following the success seen in MR CLEAN, other studies such as ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT were published successively [24–27].

It is likely that the successful outcomes observed in these randomized controlled studies are not only associated with the use of newer generation thrombectomy devices, but also with the criteria used for patient inclusion and with the imaging modalities used for patient selection. Of these inclusion criteria used in above-mentioned studies, age is depicted in Table 1, time to puncture in Table 2, severity of stroke in Table 3, prerequisites for occlusion sites in Table 4, and the requirement for imaging modalities prior to randomization in Table 5. Also, Table 6 and 7 show the devices used and the proportion of subjects undergoing IV tPA along with endovascular treatment, respectively.

In the recently published AHA-ASA guidelines [28], the patient selection criteria for endovascular treatment in patients with acute ischemic stroke are as follows:

1. Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered (Class I; Level of Evidence A).
2. Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A). (New recommendation):
   (a) Prestroke mRS score 0 to 1,
   (b) Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
   (c) Causative occlusion of the internal carotid artery or proximal MCA (M1),
   (d) Age ≥18 years,
   (e) NIHSS score of ≥6, (f) ASPECTS of ≥6, and
   (g) Treatment can be initiated (groin puncture) within 6 h of symptom onset
3. As with intravenous r-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 h of stroke onset (Class I; Level of Evidence B-R).
4. When treatment is initiated beyond 6 h from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the internal

Table 1 – Limit of age in randomized controlled trials

MR CLEAN	>18
EXTEND-IA	>18
ESCAPE	>18
SWIFT Prime	18–80 (initially 18–85)
REVASCAT	18–80
THRACE	18–80
THERAPY	18–80

Table 2 – Time to puncture in randomized controlled trials

IMS III	6 h
MR CLEAN	6 h
EXTEND-IA	6 h
ESCAPE	12 h (84% first 6 h)
SWIFT Prime	6 h
REVASCAT	8 h (90% first 6 h)
THRACE	tPA 4 h, endovascular treatment 5 h
THERAPY	5 h

Table 3 – Severity of stroke in randomized controlled trials

	Limit	Mean
IMS III	>10 (if CTA shows occlussion >8)	17
MR CLEAN	>2	18
EXTEND-IA	No	15
ESCAPE	>6	17
SWIFT Prime	>8	17
REVASCAT	>6	17
THRACE	10–25	18
THERAPY	>8	17.5

Table 4 – Prerequisites for occlusion sites in randomized controlled trials

IMS III	NA
MR CLEAN	ICA, M1, M2, A1, A2
EXTEND-IA	ICA, M1, M2
ESCAPE	ICA, M1, M2, A1, A2
SWIFT Prime	ICA, M1
REVASCAT	ICA, M1
THRACE	ICA, M1, BAZİLER
THERAPY	ICA, M1, M2

Table 5 – The requirement for imaging modalities prior to randomization	
IMS III	Noncontrast CT
MR CLEAN	CT, CTA
EXTEND-IA	CT, CTA, CTP
ESCAPE	CT, CTA – collateral scores
SWIFT Prime	CT, CTA ± BTP or MRI
REVASCAT	CT, CTA ± CTP
THRACE	CT, CTA, MRA
THERAPY	CT, CTA – length of clot

Table 6 – Devices used in randomized controlled trials	
IMS III	Any devices which FDA approved (only 5 stentrievers)
MR CLEAN	Any devices (82% stentrievers)
EXTEND-IA	Solitaire
ESCAPE	Any devices (79 % stentrievers, 62% solitaire)
SWIFT Prime	Solitaire
REVASCAT	Solitaire
THRACE	Any devices
THERAPY	Penumbra

Table 7 – The proportion of subjects undergoing IV tPA along with endovascular treatment in randomized controlled trials	
IMS III	100%
MR CLEAN	89%
EXTEND-IA	100%
ESCAPE	76%
SWIFT Prime	100%
REVASCAT	73%
THRACE	100%
THERAPY	100%

carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence C). Additional randomized trial data are needed.

5. In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa; Level of Evidence C). There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or nontime based (e.g., prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).

Conclusion

In patients with acute ischemic stroke who have proximal arterial occlusion and limited core tissue as established by imaging studies, endovascular treatment with IV tPA should be administered within the first 6 h unless contraindicated. Presence of good collaterals can be investigated, provided that the imaging studies are not associated with therapeutic delay, since achievement of prompt reperfusion is the primary priority.

Conflict of interest
None declared.

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Ethical statement
Authors state that the research was conducted according to ethical standards.

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