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Review article – *Special issue: Acute Ischemic Stroke*

The selections of acute stroke patients for catheter based intervention

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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.

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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

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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].

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 h. 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 3–6 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 min 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, Syntesis 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 Syntesis [19,20].

Factors implicated for the observed failure included the inadequate technology of endovascular devices, inability to achieve recanalization 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 vs. 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 vs. Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke) where another retrievable