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REVIEW

Pharmacological recanalization therapy in acute ischemic stroke — , Evolution, current state and perspectives of intravenous and intra-arterial thrombolysis

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Summary Stroke ranges third in mortality in industrialized nations and is the leading cause of disability in older people. Ischemic stroke following thrombotic or embolic vessel occlusion accounts for more than 80% of cerebrovascular events. Immediate restoration of cerebral blood flow is crucial in order to salvage brain tissue. Experimental thrombolytic treatment was introduced into the clinical setting in the late 1950s and required more than 30 years of intense research till its breakthrough and subsequent routine clinical use by the presentation of the NINDS trial results in 1995. To date, intravenous thrombolysis with tissue plasminogen activator up to 4.5 h after symptom onset is the only proven reperfusion therapy for acute ischemic stroke. In this review, we summarize the evolution of intravenous and intra-arterial pharmacological recanalization therapies in acute ischemic stroke and present current clinical practice as well as its promising perspectives.

Abbreviations: ACA, anterior cerebral artery; AHA, American Heart Association; BA, basilar artery; BI, Barthel Index; CT, computed tomography; ECASS, European Cooperative Acute Stroke Study; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GOS, Glasgow Outcome Scale; i.a., intra-arterial; ICA, internal carotid artery; ICH, intracerebral hemorrhage; i.v., intravenous; MRI, magnetic resonance imaging; NNT, number needed to treat; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; r-pro-UK, recombinant pro-urokinase; RCT, randomized controlled trial; rtPA, recombinant tissue plasminogen activator; sICH, symptomatic intracerebral hemorrhage; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register; UK, urokinase; SK, streptokinase; vs., versus.

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Introduction

Despite a decrease in stroke incidence over the past years in the United States and Europe [1,2], stroke remains the second most common cause of mortality [3] and the third most common reason for disability worldwide [4]. Hereby, ischemic stroke accounts for about 87% of cases, whereas 13% is attributable to rupture of a blood vessel resulting in hemorrhagic stroke (intracerebral or subarachnoid hemorrhage) [5].

In ischemic stroke, early restoration of perfusion is crucial and has a significant impact on favorable outcome [6]. Hence, in the last decades, various treatment modalities have been developed to restore fast cerebral blood supply. In this review, we summarize the evolution of pharmacological thrombolysis in acute ischemic stroke.

First steps of thrombolytic therapy in patients with stroke

Already in the late 1950s and early 1960s, treatment with thrombolytic agents was applied intravenously (i.v.) and intra-arterially (i.a.) in patients with cerebral arterial occlusion [7,8]. First trials with randomized and non-randomized control groups followed in the subsequent years and decades with administration of the thrombolytic agent within 72 hours after symptom onset [9—14]. The initial wide range of time from symptom onset to thrombolytic treatment tended to decrease with the following studies to 6 hours [11]. However, despite more than 60 studies till the early 1990s, thrombolytic therapy for stroke has not been tested in large randomized controlled trial (RCT) and strong evidence for its efficacy was lacking [11].

Intravenous thrombolysis in acute ischemic stroke

The 1995 published ECASS trial was the first large, randomized and double-blinded study for treatment with i.v. thrombolysis in patients with acute ischemic stroke [15] (Table 1). A total of 620 patients with acute ischemic hemispheric stroke from 14 countries were recruited between 1992 and 1994. Out of these, 313 patients were randomized to treatment with the recombinant tissue plasminogen activator (rtPA) alteplase (1.1 mg/kg bw, maximum 100 mg) within the first 6 hours from onset of symptoms. The remaining patients received placebo. Protocol violations were documented in a large proportion of patients ($n = 109$). Thus besides the whole group (intention to treat [ITT]), a subgroup (target population [TP]) without these protocol-violation patients was analyzed. The results of the TP analysis showed a significant increase in favorable outcome (modified Rankin Scale, mRS ≤ 1 at day 90) in the rtPA group (median mRS of 2 in the rtPA group and 3 in the placebo group, $P = 0.035$). There was no statistically significant difference concerning mortality rate at day 30 as well as in the incidence of all intracererbal hemorrhages (ICH, hemorrhagic infarction and parenchymal hemorrhage). However, a statistically significant increase of parenchymal hemorrhage events was apparent in the rtPA treated groups and mortality at day 90 was also higher in the rtPA ITT treatment arm (22.4% vs. 15.8%, $P = 0.04$). It was concluded that the positive impact on functional outcome did not outweigh the higher mortality rate and the increase in parenchymal hematoma in patients treated with rtPA.

After the disappointing results of the first ECASS trial, a turnaround was achieved with the only 2 months later published NINDS study [16]. In this two-part study, 624 patients, chosen according to strict inclusion/exclusion criteria, were randomized and treated either with i.v. rtPA or with placebo. In contrast to the ECASS trial, treatment was performed within 3 hours of symptom onset with a reduced dose of 0.9 mg/kg bw, maximum 90 mg. In part one, 291 patients were enrolled for the investigation of neurological improvement within the first 24 hours. A significant clinical improvement measured by the National Institute of Health Stroke Scale (NIHSS) score could not be shown. The remaining 333 patients were classified in part two for the assessment of clinical outcome at three months. In this second part, a significant increase in favorable outcome in the rtPA group compared to the placebo group could be clearly demonstrated ($P = 0.008$). The increase in favorable outcome was demonstrated in several scores: mRS (odds ratio [OR]: 1.7 [1.1—2.6]), NIHSS (OR: 1.7 [1.0—2.8]), Barthel Index (BI; OR: 1.6 [1.1—2.5]) as well as in the Glasgow Outcome Scale (GOS; OR: 1.6 [1.1—2.5]). Favorable outcome was defined by mRS and NIHSS ≤ 1, a BI score of 95 to 100, or GOS = 1. Symptomatic ICH (sICH) occurred more often in the rtPA group within 36 hours after stroke onset. No difference in mortality was noted between the two groups (17% in rtPA group and 21% in placebo group, $P = 0.30$) at 3 months. Moreover, the benefit of rtPA treatment was confirmed 1 year after stroke [17]. As a result, treatment with i.v. rtPA within 3 hours of symptom onset was approved by the US FDA in 1996 [18].

A post hoc analysis of the 1998 published ECASS II trial confirmed a positive treatment effect of rtPA with an absolute increase in independent patients (mRS 0—2) at day 30 of 8.3% ($P = 0.024$) [19]. However, this study failed to show significant improvement in terms of its primary outcome (mRS ≤ 1).

Time is brain

Pilot studies suggested an increased benefit with early therapy initiation [20,21]. In a subgroup analysis of the NINDS trial, the positive clinical effect of early treatment was confirmed [22]. Treatment onset within 90 minutes resulted in an OR for favorable outcome at 3 months of 2.11 [1.33—3.35] whereas delayed rtPA treatment (90—180 min) was associated with an attenuated benefit (OR: 1.69 [1.09—2.62]). Consequently, the question arose about treatment efficacy with prolongation of time window for rtPA application after onset of symptoms. The beneficial effect in the NINDS trial in patients treated within 91—180 minutes was challenged, as a higher number of patients with a baseline NIHSS score <5 in the rtPA (19%) group compared to the placebo group (4%) was detected. Baseline NIHSS is a strong predictor for