Medical Therapy for Ischemic Stroke: Review of Intravenous and Intra-Arterial Treatment Options

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Key words
- Acute cerebral ischemia
- Fibrinolytic therapy
- Stroke
- Thrombolysis

Abbreviations and Acronyms
CT: Computed tomography
FDA: U.S. Food and Drug Administration
ICH: Intracerebral hemorrhage
MCA: Middle cerebral artery
mRS: Modified Rankin Scale
NINDS: National Institute of Neurological Disorders and Stroke
r-proUK: Recombinant pro-urokinase
r-tPA: Recombinant tissue plasminogen activator
UK: Urokinase

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BACKGROUND: **Thrombolytic therapy is of proven and substantial benefit for select patients with acute cerebral ischemia. Diagnostic options and medical treatment options for acute stroke ischemia have undergone enormous changes in the past decades. Whereas initially stroke treatment was reduced to prevention, management of symptoms, and rehabilitation, nowadays a multitude of different fibrinolytic drugs are available. The wide availability of computed tomography in the late 1980s made thrombolysis a real therapeutic option because it allowed a fast and accurate differentiation between ischemic and hemorrhagic stroke.**

METHODS: **This study reviews these developments and how they have shaped our current use and understanding of thrombolytics in the treatment of acute ischemic stroke.**

RESULTS: **Patient selection remains a central aspect of thrombolytic treatment, and to date, the use of different fibrinolytics has been studied in over 20 large randomized trials for different clinical settings, time windows, and routes of administration. These studies included over 7000 patients, and led to our current understanding of the use of thrombolysis in acute stroke.**

CONCLUSIONS: **Intravenous fibrinolytic therapy within the first 3 hours of ischemic stroke onset offers substantial benefits for virtually all patients with potentially disabling deficits. In the 3- to 4.5-hour treatment window, intravenous fibrinolytic therapy has been shown to offer moderate net benefits when applied to all patients with potentially disabling deficits. Intra-arterial fibrinolytic therapy in the 3- to 6-hour window offers moderate net benefits when applied to all patients with potentially disabling deficits and large-artery cerebral thrombotic occlusions.**

INTRODUCTION

The management, including the diagnosis and possible treatment, of acute cerebral ischemia has undergone enormous changes in the past decades (16).Thrombolytic characteristics of bacteria were discovered in the 1930s, and since then, the concept of clot-busting drugs has held enormous promise and potential in the treatment of acute cardiac and cerebral ischemia (60). In the case of stroke, however, efforts have largely been hindered by inadequate diagnosis, which resulted in patients with acute hemorrhage being given fibrinolytic drugs (10). As a result, stroke management focused mostly on the management of the symptoms, antiplatelet therapy, secondary stroke prevention, and rehabilitation (7). With the wide availability and improved technology of computed tomography (CT) scanners, a rapid distinction between hemorrhagic and ischemic strokes became possible. Thrombolysis became a real therapeutic option in the setting of acute cerebral ischemia. The concept of an ischemic penumbra gave further power to the use of thrombolytics with the idea that brain tissue can be salvaged once reperfusion is achieved (17). Beginning in the 1990s, thrombolysis for ischemic stroke was systematically studied in large randomized trials. To date, thrombolytic therapy for ischemic stroke has been investigated in 21 randomized controlled clinical trials enrolling more than 7000 patients (65). Historically, 3 different thrombolytic agents were studied most extensively, which included streptokinase, urokinase, and recombinant tissue plasminogen activator (r-tPA), all of which share the same pharmacological function of converting plasminogen to plasmin to break down fibrin in blood clots (65). These agents were studied in different clinical settings and trials, applying different windows of time and routes of administration (intravenous vs. intra-arterial). In this article, we discuss these developments and how they have shaped our current use and understanding of thrombolytics in the treatment of acute ischemic stroke.

INITIAL EXPERIENCES WITH STREPTOKINASE

Streptokinase was the first thrombolytic agent to be discovered in the 1930s, and an

initial in vitro study revealed its characteristic of dissolving experimentally produced thrombi (60). Whereas streptokinase proved beneficial in the treatment of cardiac ischemia, a randomized trial in 1964 showed no benefit for patients with cerebral ischemia (42). In this trial, patients were included up to 72 hours after onset of symptoms and treated by anticoagulation alone (36 patients), or anticoagulation and streptokinase (27 patients). Patients receiving streptokinase fared worse compared with the control group. Three large randomized controlled trials analyzed the use of streptokinase in ischemic stroke after the wide accessibility of computed tomography. All demonstrated an increase in the rate of symptomatic intracranial hemorrhage with no improvement in functional outcome and were terminated prematurely due to increased mortality in the streptokinase treatment arm (12, 15, 23, 25). In these trials, streptokinase was used in doses of 1.5 million units intravenously within 4 or 6 hours of stroke onset. A pooled meta-analysis of the streptokinase trials including 653 treatment patients and 639 control patients failed to show a benefits of treatment because of its very narrow therapeutic window and significant rates of morbidity (mainly intracranial hemorrhage) and systemic hemorrhage, as well as mortality (12). No improved outcome was seen in patients receiving therapy earlier ($<$ 3 hours). A number of possible explanations for the negative effect of streptokinase on outcome in these studies have been discussed, with the main ones being the high streptokinase dose and its hypotensive effect, which may have caused cerebral hypoperfusion in patients with cerebral ischemia (12). As a result, the American Academy of Neurology sees no indication for the administration of intravenous streptokinase in the clinical setting of an acute ischemic stroke, according to their Quality Standards Statement (1).

EXPERIENCE WITH INTRAVENOUS AND INTRA-ARTERIAL UROKINASE

The administration of another plasminogen activator, urokinase, was first studied in 1976 by Fletcher et al. in a feasibility study analyzing 3 different urokinase intravenous dosage regimens (18). Urokinase has some distinct advantages over streptokinase in its pharmacological characteristics. Because it has no antigenic properties, its thrombolytic activity in plasma can be predicted, thus making it safer, and its thrombolytic activity is faster with higher clot-lysis rates (46). Trials using intravenous urokinase in the 1980s and 1990s, however, showed no clear clinical benefits with higher rates of symptomatic intracranial hemorrhages and mortality when compared with control groups (57, 65). Yet, initial results from its intra-arterial administration were promising, with a complete or partial recanalization rate in 12 of 15 patients (51). Furthermore, recanalization was correlated with improved clinical status in all but 2 patients.

Intra-arterial thrombolysis seemed a logical step in the evolvement of thrombolytic therapy of stroke. Compared with intravenous therapies, it delivers a high concentration of the thrombolytic agent to the clot target, causing lower systemic exposure to the drug and thus possibly enhancing recanalization rates (65). Together with developments in endovascular techniques, which allowed rapid access and navigation through the intracranial vascular tree by microcatheters, local intra-arterial infusion of thrombolytics became a real treatment option. Along with the development of second-generation thrombolytics such as prourokinase, this led to the evaluation of intra-arterial thrombolysis in large randomized controlled trials (14, 34). A phase II trial, the PROACT I, tested the safety and the recanalization rates after intra-arterial prourokinase in 40 patients with acute ischemic stroke (25 patients receiving prourokinase vs. 14 patients receiving placebo only) (**Table 1**). The study involved 37 centers, and its results were reported in 1998 (13). A high recanalization rate was significantly associated with the administration of prourokinase. Hemorrhagic transformation causing neurological deterioration within 24 hours of treatment occurred in 15.4% of the recombinant pro-urokinase (r-proUK)–treated patients and 7.1% of the placebo-treated patients, a trend that was not statistically significant. This led to PROACT II (reported in 1999), which randomized 180 subjects within 6 hours of middle cerebral artery (MCA) occlusion onset to receive 9 mg of intra-arterial prourokinase and heparin or intravenous heparin only (11). The primary outcome, analyzed by intention to treat, was based on the proportion of patients with slight or no neurological disability at 90 days as defined by a modified Rankin score of 2 or less. Secondary outcomes included MCA recanalization, the frequency of intracranial hemorrhage with neurological deterioration, and mortality. For the primary analysis, 40% of r-proUK patients and 25% of control patients had a modified Rankin score of 2 or less ($P = 0.04$). Mortality was 25% for the r-proUK group and 27% for the control group. The recanalization rate was 66% for the r-proUK group and 18% for the control group ($P < 0.001$). Intracranial hemorrhage with neurological deterioration within 24 hours occurred in 10% of r-proUK patients and 2% of control patients ($P = 0.06$). Despite an increased frequency of early symptomatic intracranial hemorrhage, treatment with intra-arterial r-proUK within 6 hours of the onset of acute ischemic stroke caused by MCA occlusion significantly improved clinical outcome at 90 days (11). This benefit in outcome could be shown by Nedeltchev et al. in a matched-cohort study of patients after intra-arterial thrombolysis with urokinase to have a significant long-term effect after 2 years (44). Despite the positive results of PROACT I and II, prourokinase has not been approved by the U.S. Food and Drug Administration (FDA), yet large case series using other fibrinolytic agents in an intra-arterial route, such as tPA (recombinant tissue plasminogen activator), urokinase, and reteplase have demonstrated outcomes and results in comparison with PROACT II (4, 8, 43, 44, 48, 49, 59).

Results of the Japanese MELT trial were published in 2007. Its study objective was to determine the clinical efficacy and safety of intra-arterial urokinase in patients with acute MCA stroke of less than 6 hours duration (45). The study design largely paralleled PROACT II, enrolling only patients with M1 or M2 MCA occlusions; however, technically, it allowed manipulation and disruption of the clot by use of a guidewire, and as such, is not a pure pharmacological thrombolysis trial (45). After approval of intravenous r-tPA in Japan, the study was stopped by the steering committee. By that time, 114 patients had been randomized. Complete ($n = 3$) or partial ($n = 39$) recanalization was achieved in 42 of 57 of the patients (73.7%). The study did formally not reach its specified primary end point of the proportion of patients with nondisabled outcome (modified Rankin Scale [mRS] $\leq$2) at 3 months, with an absolute increase of 10.5%. However, for the specified sec-