Trombolysis in acute stroke

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Abstract

Background: Rapid restoration of cerebral blood flow is the principle goal of acute ischemic stroke therapy. Intravenous recombinant tissue plasminogen activator is an effective therapy for acute ischemic stroke. It has been available in the United States for over a decade and was approved for use in Israel at the end of 2004.

Objectives: To assess the implementation of intravenous rt-PA in routine clinical care at our center after its formal approval in Israel, and the therapeutic and logistic implications for reperfusion therapy for acute ischemic stroke in Israel.

Methods: Patients with acute ischemic stroke admitted between January 2005 and June 2006 who were treated with intravenous rt-PA or endovascular-based reperfusion were reviewed. Implementation, timing, safety and clinical outcomes were assessed.

Results: Forty-six patients received reperfusion therapy (37 with intravenous rt-PA and 9 with endovascular-based therapy), corresponding to 4.0% of ischemic stroke patients in 2005 and a projection of 6.2% in 2006. The mean age of intravenously treated patients was 67 years (range 22–85 years), median baseline NIHSS score was 14 (25–75%, 10–18) and the median 'onset to drug time' was 150 minutes (25–75%, 120–178). Symptomatic intracerebral hemorrhage and orolingual angioedema each occurred in one patient (2.7%). Significant clinical improvement occurred in 54% of treated patients, and 38% of patients were independent at hospital discharge.

Conclusions: The use of reperfusion therapy for acute ischemic stroke has increased in our center after the formal approval of rt-PA therapy to over 5%, with 'onset to drug time', safety and outcome after intravenous rt-PA treatment comparing favorably with worldwide experience. A prerequisite for the implementation of effective reperfusion therapy and expansion of the proportion of patients treated nationwide is the establishment of a comprehensive infrastructure.

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Urgent reperfusion therapy, aimed at restoring artery patency and brain perfusion, is the principle goal of early ischemic stroke therapy [1-5]. Rapidity and completeness of recanalization is a powerful determinant of clinical outcome [3,6]. It is estimated that every minute in which a large-vessel ischemic stroke is left untreated, the average patient loses about 1.9 million neurons, and that within an hour of treatment failure this amounts to the number of neurons lost during 3.6 years of normal aging [7]. Unlike normal aging, however, the acute extinction of an enormous number of neurons in a distinct area of the brain may lead to devastating functional consequences. The main target of reperfusion is the penumbra, ischemic but still viable brain tissue that is potentially salvageable if restoration of blood flow can be achieved in time. Failure of timely reperfusion triggers a biochemical and metabolic cascade ultimately leading to irreversible brain injury by progressive transformation of the penumbra into infarcted tissue: the infarct core expands as the penumbra becomes extinct.

We previously reported the initial experience with intravenous recombinant tissue plasminogen activator for acute ischemic stroke in Israel [8]. Intravenous rt-PA, approved for use in the United States since 1995, was approved in Israel for acute stroke therapy at the end of 2004. We now extend our report on its implementation in routine clinical care at our center after its formal approval in Israel and discuss therapeutic and logistic implications for reperfusion therapy nationwide.

Patients and Methods

Patients with acute ischemic stroke admitted between January 2005 and June 2006 who received reperfusion therapy were reviewed. Patients' characteristics, stroke presentation and in-hospital course were evaluated. Stroke onset to computed tomography time and onset-to-drug time were determined. Stroke severity was assessed by the National Institutes of Health Stroke Scale score and functional outcome by the modified Rankin scale [9]. Clinical subtypes of ischemic stroke were classified by the Oxfordshire Community Stroke Project criteria. Main outcome and safety parameters were similar to those used in the ongoing SITS trial (Safe Implementation of Thrombolysis in Stroke: a multinational, multi-center monitoring study of safety and efficacy of thrombolysis in stroke) [10]. Significant early improvement was defined as NIHSS decrease of at least 4 points or full recovery (NIHSS = 0) between baseline and 24–48 hours. Independence at hospital discharge was defined as mRS 0–2. Symptomatic intracerebral hemorrhage was defined

rt-PA = recombinant tissue plasminogen activator

NIHSS = National Institutes of Health Stroke Scale
mRS = modified Rankin scale

as a parenchymal hematoma type 2 according to the European Cooperative Acute Stroke Study (ECASS) criteria accompanied by NIHSS deterioration ≥ 4 from baseline. The rates of annual admissions for acute ischemic stroke were derived from a large prospective survey of acute cerebrovascular diseases conducted at our medical center [11].

Results

Between January 2005 and June 2006, 46 patients received reperfusion therapy (37 with intravenous rt-PA and 9 with endovascular-based therapy). Overall 26 patients were treated in 2005 and 20 patients from January until June 2006, corresponding to 4.0% of ischemic stroke patients in 2005 and a projection of 6.2% in 2006.

Baseline characteristics of patients treated with intravenous rt-PA are summarized in Table 1. Mean age was 67 years (range 22–85), and 27% of patients were female. The median stroke onset to CT time was 67 minutes (25–75%, 51–94) and the median onset-to-drug time was 150 minutes (25–75%, 120–178). The most frequent stroke subtype classified by the Oxfordshire Community Stroke Project criteria were anterior circulation infarcts (total anterior circulation 44% and partial anterior circulation 19%).

Presentation and in-hospital course of intravenous rt-PA treated patients are summarized in Table 2. The median NIHSS score on admission was 14 (25–75%, 10–18), implying moderate stroke severity and it decreased to 10.5 (25–75%, 3–16) after 24–48 hours. Significant clinical improvement (≥ 4 points in NIHSS score) occurred in 54% of the treated patients. At hospital discharge 38% of the patients were independent. Complications related to rt-PA included symptomatic intracerebral hemorrhage and orolingual angioedema occurring in one patient (2.7%) each. The only symptomatic intracerebral hemorrhage, which subsequently proved to be fatal, occurred in an 85 year old patient.

Table 1. Baseline characteristics of intravenous rt-PA treated patients (n=37)

Age (mean ± SD) yrs	67 ± 12 (range 22–85)
Females	27%
Hypertension	68%
Diabetes	43%
Dyslipidemia	62%
Atrial fibrillation	27%
Smoker	38%
Prior transient ischemic attack/ stroke	8%
Prior angina	32%
Prior antiplatelet use	40%
Prior statin use	35%
Prior ACE/ARB use	27%

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blockers

Table 2. Presentation and in-hospital course of intravenous rt-PA treated patients

Stroke severity	
NIHSS score (baseline)	
Median (25–75%)	14 (10–18)
NIHSS score (24–48 hrs)	
Median (25–75%)	10.5 (3–16)
Baseline measurements	
Systolic BP (mmHg)	134 ± 25
Diastolic BP (mmHg)	81 ± 12
Glucose (mg/dl)	153 ± 66
Clinical classification	
Total anterior circulation	44%
Partial anterior circulation	19%
Posterior circulation	5%
Lacunar infarct	30%
Timing	
Onset to CT time (min)	
Median (25–75%)	67 (51–94)
Onset to drug time (min)	
Median (25–75%)	150 (120–178)
Outcome	
Significant early improvement (≥ 4 points in NIHSS)	54%
Independence at hospital discharge (mRS 0–2)	38%
rt-PA related complications	
Symptomatic intracecerebral hemorrhage	1 (2.7%)
Orolingual angioedema	1 (2.7%)

Discussion

Since approval of rt-PA in Israel the use of reperfusion therapy at our center has gradually increased from 2.6% as reported previously [8] to 4.0% in 2005 and a projection of 6.2% in 2006. Nationwide, reperfusion therapy was delivered in Israel, before formal approval was granted, at a rate of 0.5% [12] and was limited to only two medical centers. Currently, intravenous rt-PA has been administered, at least sporadically, in about 10 centers, whereas complementary endovascular-based intervention is becoming available in three centers. Availability, however, does not mean adequate accessibility, since this requires an appropriate infrastructure including medical expertise and facilities available 24 hours a day. Worldwide experience demonstrates that proper infrastructure allows an increase in the implementation rate of recanalization therapy to over 10% based on current guidelines [13,14]. In addition, pharmacological, mechanical and imaging advancements may likely offer better treatment options to a higher proportion of patients.

Reperfusion strategies

For patients with acute ischemic stroke presenting within the first 3 hours of onset, the basis of reperfusion therapy is intravenous thrombolysis [1,4,5]. Intravenous rt-PA within 3 hours of onset is the only proven therapy, with an estimated number needed to treat of 3.1 for any improvement in outcome [15]. Transcranial

Doppler, apart from being a useful bedside tool to monitor recanalization and re-occlusion, has been shown to effectively enhance rt-PA-induced recanalization [16]. We found in our patient series that after formal approval of rt-PA in Israel, time to treatment, safety and effectiveness of implemented reperfusion therapy compare favorably with other series worldwide. The proportion of treated patients exceeded a 5% threshold, yet falls short of rates achieved at other medical centers that have a comprehensive infrastructure for the treatment of acute ischemic stroke [13,14].

Despite its proven benefit, intravenous rt-PA therapy has important shortcomings, such as a limited time window, a relatively low recanalization and high re-occlusion rate, as well as an inherent risk of hemorrhage. Novel fibrinolytic agents with a potentially better risk/benefit profile are currently under investigation [17-19]. In addition, combined pharmacological approaches aim to further enhance and accelerate reperfusion, since hemostatic activation observed after thrombolysis may reduce its efficacy [19,20].

Early reperfusion therapy is evolving into a multi-faceted treatment, in which endovascular based reperfusion is a valuable complementary modality to standard intravenous-based therapy, comprising a wide range of rapidly developing pharmacological and mechanical treatment options aimed to achieve artery patency [21,22]. Intraarterially delivered, pharmacological thrombolysis is effective in middle cerebral artery occlusion within 6 hours of symptom onset and in acute basilar thrombosis [2]. Novel mechanical endovascular interventions are emerging, designed to mechanically disrupt the clot, retrieve the embolus or augment fibrinolysis [21,23]. They share the advantages of avoiding pharmacological fibrinolysis with its inherent risk of hemorrhage, and represent an alternative treatment option for patients with contraindications for the latter [22]. A key disadvantage of endovascular-based therapy is the critical delay in initiation of therapy ("time is brain"). In addition, its high cost and labor intensity, in combination with the high level of expertise required, render it less accessible compared to intravenous-based reperfusion therapy.

Imaging-guided patient selection: a tool to expand patient eligibility

The availability of modern magnetic resonance imaging technology, including perfusion-weighted imaging and diffusion-weighted imaging, enables the identification of the ischemic penumbra and thus represents a powerful tool in assisting patient-tailored therapeutic decisions beyond 3 hours. Penumbral imaging (that may be MR or CT based) can provide a physiologic 'tissue clock' in individual patients, and thus application beyond 3 hours may allow a substantially greater number of patients to be treated [19,24,25].

A comprehensive infrastructure for reperfusion therapy in Israel

Whether the goal of prompt restoration of cerebral perfusion will be achieved or not will not only depend on the appropriate choice of drug or recanalization technique. It requires a set-up to ensure that the patient is speedily processed through the 'acute stroke' critical pathway, that therapy is implemented as early as possible, that patient-tailored therapeutic decisions are made and patients appropriately monitored. A multifaceted approach is more likely to be successful in reducing delays to therapy and improving the efficiency of brain reperfusion.

Given that intravenous rt-PA was approved for use in the U.S. already over a decade ago, and compared to the western world, implementation of reperfusion therapy for acute ischemic stroke in Israel is lagging behind. Moreover, the availability of infrastructure, resources and implementation of reperfusion therapy in acute stroke contrasts strikingly with that of acute coronary syndrome in Israel, despite the very high cost saving achieved by dedicated stroke units and rt-PA therapy in Israel (Ginsberg GM, cost-utility analysis of stroke units and rt-PA in Israel, Dept. of Medical Technology Assessment, Ministry of Health).

An essential prerequisite for adequate reperfusion therapy in acute stroke is widespread accessibility to intravenous-based rt-PA therapy throughout the country [5]. It can be delivered in primary centers, requiring mainly 24 hours daily availability of a neurologist and CT, a written protocol and an appropriate setting for monitoring. Several referral comprehensive stroke centers are required for neuro-endovascular-based reperfusion therapy with availability of penumbral imaging for patient selection beyond 3 hours. Given the increasing complexity of a comprehensive approach for reperfusion and the urgency of treatment, such centers require availability 24 hours a day of a stroke neurologist and a neuro-interventionalist, as well as an appropriate stroke unit/intensive care infrastructure.

In conclusion, the use of reperfusion therapy for acute ischemic stroke increased in our center (after it was officially approved) to over 5%, with safety and outcome after intravenous rt-PA comparing favorably with worldwide experience. Nationwide, the number of centers offering thrombolysis is gradually increasing since its approval in Israel, yet the overall rate of implementation is still low. In an era of quickly expanding treatment options the rate of implementation of reperfusion therapy should be considerably higher. A prerequisite for the implementation of effective reperfusion therapy and expansion of the proportion of patients treated is the establishment of a comprehensive infrastructure nationwide.

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