

Review articles

Intravenous rtPA thrombolysis in acute ischemic stroke

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Abstract

Early intravenous thrombolysis within the first three hours has been considered in the United States as the first proven treatment in acute ischemic stroke. However, not all patients will respond to this therapy which is also associated with a risk of symptomatic, including fatal, intracranial hemorrhage. This overview addresses the issue of efficacy and safety of intravenous alteplase (tPA) in acute cerebral ischemia. The rationale for thrombolytic therapy and its limits are described. The controlled studies show that intravenous tPA is effective and safe when given under restrictive conditions within 3 hours after stroke onset, but the data for a larger therapeutic window between 3 and 6 hours remain controversial. The expected functional improvement and the risk of intracranial hemorrhage greatly depend on selective clinical and imaging criteria. For this purpose, MRI, using the diffusion- and perfusion-weighted sequences combined with MR-angiography, should be preferred to CT scan in the next future. Applicability of tPA thrombolysis in current neurological practice in Belgium is discussed. Before its generalization, this therapy should be restricted to specialized stroke centers and all treated patients should be recorded in a central data bank to guarantee continued surveillance.

Key words : Thrombolysis ; alteplase ; stroke ; cerebral ischemia ; therapy.

After the publication of the American study on tPA, intravenous thrombolysis has been considered as the first proven treatment in acute ischemic stroke and has been licensed by the Food and Drug Administration for this indication. By contrast, thrombolysis using intravenous urokinase or streptokinase is not currently recommended in acute stroke patients because either clinical evidence of efficacy is lacking (urokinase) or the rate of intracranial symptomatic (including fatal) hemorrhage is unacceptably high (streptokinase). This overview addresses the issue of efficacy and safety of rtPA and the way of selecting the patients who are the best candidates for this therapy.

Rationale for thrombolytic therapy

The occluding thrombus may lyse spontaneously due to the activity of endogenous thrombolytic

system, but this occurs very rarely within the first hours after stroke onset: 4.3% within 6 hours (Yamaguchi *et al.*, 1993) and 20% within 24 hours (Dalal *et al.*, 1965). Thus, the main goal of thrombolytic treatment is to allow and speed up the recanalization process to salvage the ischemic penumbra area against its transformation into definite infarct. Improved outcome is indeed significantly correlated with arterial recanalization (Yamaguchi *et al.*, 1993 ; von Kummer *et al.*, 1995). The reperfusion window, the period during which cerebral recirculation will allow full recovery, has been estimated to be 4 hours in humans (Pulsinelli, 1995).

Limits of thrombolytic therapy

Failure of thrombolysis may be due to the absence of recanalization, the delayed reopening of occluded arteries beyond the therapeutic window, and the lack of tissue reperfusion when recanalization is incomplete, when emboli have dislodged in distal branches, or when a 'no-reflow' phenomenon is operative (Davis *et al.*, 1993 ; Okada *et al.*, 1993). Another important issue is the individual variation of the cytoprotective and reperfusion window which is dependent on the duration and degree of ischemia and the presence and quality of collateral blood supply (Baron *et al.*, 1995). The therapeutic window may be shorter (< 4 hours) or longer (up to 6 hours) in some patients. The reperfusion injury (Ames *et al.*, 1968) is another potential factor of poor recovery, because return of blood flow in the post-ischemic period may lead to interactions between blood and the damaged tissue yielding further tissue injury (Weisfeldt, 1987). Furthermore, after long or severe ischemia, reperfusion may enhance the development of edema in the irreversibly damaged cerebral tissue (Ito *et al.*, 1979 ; Branston *et al.*, 1980). As a result, new therapeutic trials, based on experimental evidences with NMDA- (MK801) (Phillips *et al.*, 1988) and AMPA-receptor antagonists (NBQX) (Overgaard *et al.*, 1993a), should implicate counteraction of putative mediators of reperfusion injury by

coupling thrombolytic therapy with one or more cytoprotective agents.

Randomized therapeutic trials

Thrombolysis was first tested as a treatment for acute ischemic stroke nearly 40 years ago (Sussman and Fitch, 1958) and several experimental studies have demonstrated its efficacy and safety (Zivin *et al.*, 1985 ; Zivin *et al.*, 1988 ; Phillips *et al.*, 1988 ; Lyden *et al.*, 1989 ; Lyden *et al.*, 1990 ; Del Zoppo *et al.*, 1990 ; Saku *et al.*, 1990 ; Clark *et al.*, 1991 ; Carter *et al.*, 1992 ; Overgaard *et al.*, 1993b). The first clinical studies, performed before the eighties, reported an unacceptable high rate of hemorrhage, but they did not use brain CT to exclude pre-treatment hemorrhage, did not always rule out patients with severe hypertension, and they included patients up to 36 hours after stroke onset (Sloan, 1987 ; Overgaard *et al.*, 1993c).

The two Japanese alteplase studies (Mori *et al.*, 1992 ; Yamaguchi *et al.*, 1993) were negative but the number of patients was small and the doses were lower than those used in the ECASS and NINDS studies.

The Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS-A) (Clark *et al.*, 1999) trial randomized patients with any ischemic stroke within 6 hours. However, this study was early stopped on publication of the NINDS trial and thus included only a small number of patients treated within 3 hours (71 patients in each group), so that any conclusions can be drawn from this study.

The TTAIS Study (Clark *et al.*, 2000) included a total of 142 patients with acute (0 to 6 hours) ischemic stroke (part A), but enrollment was halted after 27 months because of Safety Committee concerns. The time window was changed to 0 to 5 hours and it was decided to restart enrollment as a separate study (part B).

The NINDS study (Marler *et al.*, 1995) included patients with ischemia in any territory and those with deficit in resolution were excluded. rtPA was given within 3 hours after stroke onset. In the ECASS-1 and ECASS-2 study (Hacke *et al.*, 1995 ; Hacke *et al.*, 1998), rtPA was given within 6 hours after stroke onset in patients with ischemia in the carotid territory. Only patients with hypodensity $\leq 1/3$ of the MCA territory on baseline brain CT scan were enrolled. In ECASS-1, a total of 109 patients (17.4%) were included in the trial despite major protocol violations and were excluded from the target population analysis. The percentage of asymptomatic patients or with a mild neurological deficit (modified Rankin score [mRS] ≤ 1) was significantly higher in the tPA group than in the placebo group in the NINDS and ECASS-1 study, but not in ECASS-2 (Fig. 1). The

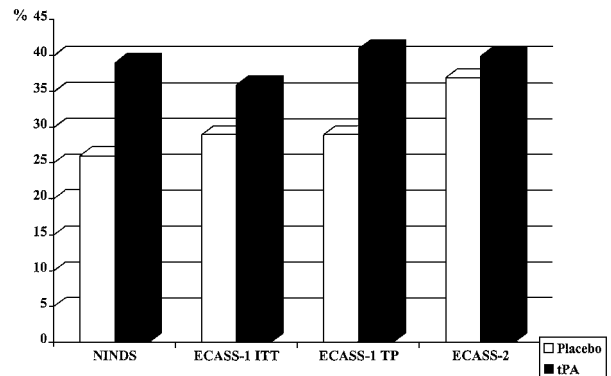


Fig. 1. — Favourable outcome (mRS ≤ 1).

ITT : intention-to-treat population ; TP : target population. Statistical significance - NINDS. O.R., 1.7 (95% C.I., 1.1-1.6 ; $p = 0.019$) ; ECASS-1 ITT : O.R., 1.15 (95% C.I., 0.98-1.35) ; ECASS-1 TP : O.R., 1.29 (95% C.I., 1.09-1.54) ; ECASS-2 : O.R., 1.17 (95% C.I., 0.9-1.16 ; $p = 0.277$).

number of independent patients per 1000 treated was 130 in the NINDS study, 70 in the intention-to-treat ECASS-1 population, 120 in the target ECASS-1 population, and only 37 in ECASS-2. However in ECASS-2, when the patients were dichotomized in terms of independence (mRS ≤ 2), 54.3% patients in the tPA group and 46% in the placebo group were independent at 3 months, with an absolute difference of 8.3% ($p = 0.024$). Moreover, the placebo group in ECASS-2 reached a high rate of improvement (36.6%) compared with that of the NINDS (26%) and ECASS-1 (29%) study, and this may explain the nonsignificant difference between the placebo and tPA groups in this study (Bath, 1998). The risk of early death (within 7 to 10 days) of any cause was higher, but without reaching significance, in the tPA group in ECASS-1 (O.R., 1.44 ; 95% C.I., 0.86-2.43) and ECASS-2 (O.R., 1.21 ; 95% C.I., 0.66-2.20) (Wardlaw *et al.*, 1999). In the NINDS trial, fewer deaths occurred at 30 days in the tPA-treated group (12.9%) than in the placebo group (15.8%). At 3 months, mortality was not significantly higher in the tPA group in the NINDS and ECASS-2 study. In the intention-to-treat population of ECASS-1, the rate of death was increased with tPA (Fig. 2). This may be due to the inclusion of patients with major protocol violations and the high level of performance of the placebo group in which the rate of death (16%) was lower than that found in the placebo group of the NINDS study (21%). The number of patients with CT-proven symptomatic hemorrhage was collected within the first 36 hours in the NINDS study and within 7 days in ECASS-1 and ECASS-2, but it may have been underestimated because some patients died without a CT scan or autopsy. In the three studies, there was a significantly higher rate of symptomatic (including fatal) cerebral hemorrhage in the tPA-treated group (Fig. 3). The risk of early (with-

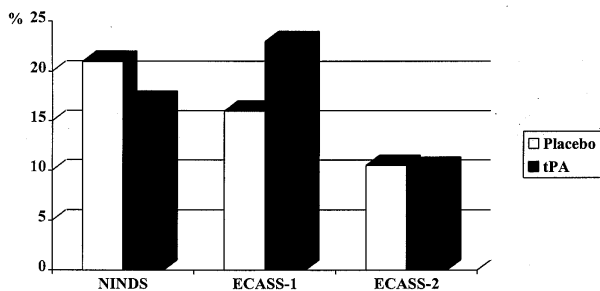


FIG. 2. — Death at 3 months.

Statistical significance - NINDS : O.R., 0,81 (95% C.I., 0,54-1,21) ; ECASS-1 : O.R., 1,52 (95% C.I., 1,02-2,27 ; p = 0,04) ; ECASS-2 : O.R., 0,98 (95% C.I., 0,62-1,53) .

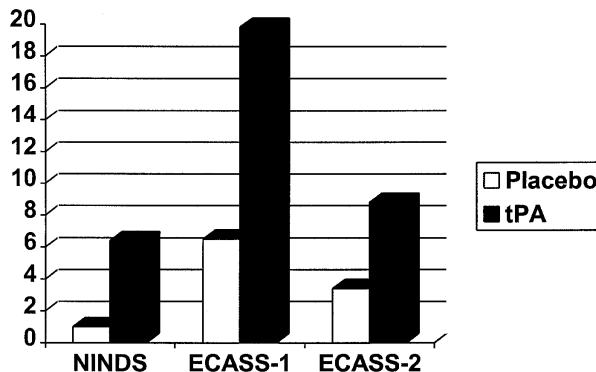


FIG. 3. — Symptomatic intracranial hemorrhage.

Statistical significance - NINDS : p<0,01 ; ECASS-1 : p<0,001 ; ECASS-2 : not reported.

in 7 to 10 days) fatal intracranial hemorrhage was also significantly higher with tPA in the NINDS study (O.R., 5.07 ; 95% C.I., 1.45- 17.67), ECASS-1 (O.R., 2.56 ; 95% C.I., 1.17-5.62) and ECASS-2 (O.R., 3.53 ; 95% C.I., 1.51-8.24) (Wardlaw *et al.*, 1999). In the ECASS study (Hacke *et al.*, 1995), the frequency of edema was not significantly different between the tPA (1.2%) and control group (0.6%).

Because angiographic procedures are time consuming and restricted to specialized centers, the issue is raised as to whether intravenous rTPA might be also effective in basilar occlusion. The open studies, which included a small number of patients (von Kummer *et al.*, 1991 ; Herderschee *et al.*, 1991 ; Huemer *et al.*, 1995 ; Grond *et al.*, 1998a), suggest that intravenous tPA is safe and effective but less than local intra-arterial infusion (Tyson *et al.*, 1982). However, randomized controlled trials are still needed to confirm a positive treatment effect, and a direct comparison between the two routes of administration should be performed.

What is the best therapeutic time window ?

Whereas the NINDS trial demonstrated efficacy and safety of tPA when given within 3 hours, the issue whether the time window can be expanded up to 6 hours remains controversial. In ECASS-1 and

ECASS-2, the patients were included within 6 hours, but the treatment effect observed in the target population of ECASS-1 might be due to the patients treated within 3 hours and the higher rate of intracranial hemorrhage to those treated between 3-6 hours. For this purpose, efficacy and safety of early thrombolysis (≤ 3 hours) was compared with late treatment (> 3 hours). In a post-hoc analysis, the data of ECASS-1 and ECASS-2 have been dichotomized according to the time window (≤ 3 hours and > 3 hours). Despite the too low number of patients treated within 3 hours to draw any definitive conclusion, the relative efficacy of the ECASS 0- to 3-hour cohort fit well with that of the NINDS study (Table I). In ECASS-2, treatment differences were similar whether patients were treated within 3 hours or within 3 to 6 hours. Compared with the patients treated between 3-6 hours, the ≤ 3 hour-time window was associated with a higher relative risk of death in ECASS-2 and a higher risk of parenchymal hemorrhage in ECASS-1. The conflicting results observed between the two studies may be due to the different level of performance of the placebo group for each time window.

A meta-analysis including the two ECASS studies (Wardlaw *et al.*, 1999) showed that the effect of treatment was similar whether given within 3 hours

Table I

Comparative relative efficacy and risk according to the time window

Trial	TPA n	Time	Good outcome	Death	Parenchymal hemorrhage Relative risk
NINDS	312	≤ 3 hours	+ 50%	- 23%	2.75
ECASS-1*	87	≤ 3 hours	+ 61%	+ 25%	5.0
	226	3 - 6 hours	+ 21%	+ 40%	2.7
ECASS-2	81	≤ 3 hours	+ 10%	+ 75%	1.6
	326	3 - 6 hours	+ 11%	- 19%	5.0

* Intention-to-treat population

(O.R., 0.70 ; 95% C.I., 0.4-1.2) or more than 3 hours after stroke (O.R., 0.76 ; 95% C.I., 0.6-0.96). Likewise, there was no treatment effect on death when the patients were treated within 3 hours (O.R., 1.56 ; 95% C.I., 0.77-3.15) or between 3 to 6 hours (O.R., 1.24 ; 95% C.I., 0.92-1.68). This does not mean that time is not important but rather that some third factor, such as age, hypertension or use of aspirin, interacts with the effect of thrombolytic treatment and with time. Moreover, the results of this meta-analysis must be interpreted with great caution since only the patients in the intention-to-treat population in ECASS-1 were analyzed and because there are imbalances in baseline variables between the thrombolysis and control patients as evidenced by the small and uneven number of patients (Wardlaw *et al.*, 1999).

With the same purpose, the ATLANTIS-B trial (Clark *et al.*, 1999) tested efficacy and safety of rt-PA when administered between 3 and 5 hours after symptom onset (tPA, 272 ; placebo, 275). The study failed to show any beneficial effect in terms of functional recovery. Treatment with rt-PA significantly increased the rate of symptomatic (1.1% vs. 7.0%, $p < 0.001$) and fatal intracerebral hemorrhage (0.3% vs. 3.0%, $p < 0.001$) within the first 10 days, and mortality at 3 months was 6.9% with placebo and 11.0% with rtPA ($p = 0.09$).

In summary, intravenous tPA is effective and safe within the first 3 hours in carotid ischemic stroke, but there is not enough evidence for a larger time window beyond 3 hours.

How to select the best candidates ?

Besides time of treatment, predictors of successful recanalization include *occlusion site* (up to 70% in MCA branch occlusion, mainly in the M2 and M3 segment ; less than 10% in intracranial ICA occlusion ; 9% for extracranial carotid occlusion), *embolic occlusion* (Yamaguchi *et al.*, 1987), and *good collateral circulation*, which allows through leptomeningeal anastomoses a retrograde blood flow into the distal part of occluded arteries so that the thrombolytic agent can reach the surface of the clot at both ends (Mori *et al.*, 1992 ; Ringelstein *et al.*, 1992 ; Wolpert *et al.*, 1993 ; Yamaguchi *et al.*, 1993 ; von Kummer *et al.*, 1995). The presence of early extended ischemia, which suggests ICA or MCA occlusion with poor collateral circulation (Bozzao *et al.*, 1989a ; Bozzao *et al.*, 1989b ; Bozzao *et al.*, 1991 ; von Kummer *et al.*, 1994 ; Toni *et al.*, 1995), is a predictive factor for late or no recanalisation (Ringelstein *et al.*, 1992 ; von Kummer *et al.*, 1994 ; Trouillas *et al.*, 1998) and higher risk of hemorrhagic transformation (Okada *et al.*, 1992 ; Turpie *et al.*, 1993 ; Hacke *et al.*, 1995 ; Toni *et al.*, 1996). As recognition of early CT infarct signs remains particularly difficult in the clinical setting, the best way of determining occlu-

sion site and type as well as the extent of ischemia related to the collateral supply is to perform MR-angiography and perfusion (PWI) / diffusion (DWI) MRI (Masaryk *et al.*, 1991 ; Ruggieri *et al.*, 1991 ; Warach *et al.*, 1992). Patients with a mismatch between the DWI- and PWI-MRI (PWI size > DWI size) are more likely to benefit because the territory delimited by the PWI and larger than the DWI territory is the brain tissue at risk for infarction which can be salvaged by an early recanalization (Warach *et al.*, 1996 ; Baird *et al.*, 1997 ; Rordorf *et al.*, 1998 ; Marks *et al.*, 1999).

Advanced age (Okada *et al.*, 1989 ; Sloan and Price, 1991 ; Ueda *et al.*, 1999), *severe clinical deficit* (von Kummer and Hacke, 1992 ; Trouillas *et al.*, 1998 ; Ueda *et al.*, 1999), *non controlled severe hypertension* (Matsumoto and Satoh, 1991 ; Brott *et al.*, 1992 ; Haley *et al.*, 1992 ; Levy *et al.*, 1994), *aspirin pretreatment* (Clark *et al.*, 1991 ; Zocchi *et al.*, 1995 ; Wardlaw *et al.*, 1999), and *post-treatment heparin* (Hommel *et al.*, 1996) are also predictive for poor outcome and increased risk of cerebral hemorrhage.

In summary, advanced age (> 80 years), mild or severe deficit, neurological signs in regression, non controlled hypertension, extended ischemia (> 1/3 MCA territory) on baseline CT or DWI-MRI, and associated anticoagulant therapy are exclusion criteria to add to the general contra-indications of thrombolysis. The best candidates for improved functional recovery are those treated within 3 hours, with a mismatch on DWI/PWI-MRI, and with a MCA occlusion on MR-angiography, especially in the distal branches.

Clinical experience in open studies

In the Copenhagen Stroke Study (COST) (Jorgensen *et al.*, 1999), a retrospective analysis showed that of 1197 patients, with a vast majority admitted beyond 3 hours, only 64 (5%) fulfilled the NINDS criteria. In our retrospective study (Osseman *et al.*, 2001), the median admission time was 04.10 hours in a cohort of 236 consecutive ischemic stroke patients. Ninety-three patients (38%) were admitted within 3 hours and 40 (17%) between 3 and 6 hours. Of the 93 patients with a < 3 hours admission time, 23 were excluded because the time of stroke onset was unknown. Of the remaining 70 patients, 26 had a transient ischemic attack, 5 followed anticoagulant therapy, 7 had a CT hypodensity covering more than 1/3 of the MCA territory, and 18 were > 80 years. When we discarded the patients with at least one of these exclusion criteria, we found 23 patients with ischemic stroke in the anterior and posterior circulation who fulfilled the NINDS criteria. However, we also excluded 8 patients admitted between 2 and 3 hours because the in-hospital time needed to perform neurological examination and brain CT

Table II
Comparison of the open studies with the NINDS trial

	NINDS (Marler, 1995)	Texas (Chiu, 1998)	Cologne (Grond, 1998b)	U.S. centers* (Tanne, 1999)	Calgary** (Buchan, 2000)
tPA Patients, n	312	30	100	189 (133)	68 (57)
Recovery, %					
mRS 0 - 1	39	30	40	34	–
mRS 0 - 2	43	–	–	–	57 (67)
I.C.H., %	3.5	7	5	6 (4)	9 (5)
Fatal I.C.H., %	2.8	3	1	2	5.7 (5)
Death, %	17	23	12	–	16 (10)
In hospital death	11	–	–	10	–

* protocol violation : 56 patients, follow-up restricted to the in-hospital period ; ** protocol violation 11 patients ; the data into brackets are those calculated after extracting the patients who strictly adhered to the tPA protocol ; I.C.H., symptomatic, excluding fatal, intracranial hemorrhage ; mRS, modified Rankin Scale.

usually is over 60 minutes. As a result, this simulation showed that the total number of potential candidates for intravenous rtPA thrombolysis was 15 of the 236 initial patients (6%). Since only 3-5% of our patients received each year intravenous tPA in our department, other factors may have played a role in the exclusion of some patients, such as cost of treatment, delayed call to neurologist, delayed arrival of neurologist, patient's refusal, and other contra-indications to thrombolysis.

Since the approval by the U.S. FDA of rt-PA for acute ischemic stroke within 3 hours of symptom onset, four open prospective studies at university and community hospitals have assessed effectiveness and safety of tPA by using the NINDS criteria (Chiu *et al.*, 1998 ; Grond *et al.*, 1998b ; Tanne *et al.*, 1999 ; Buchan *et al.*, 2000). The rates of independent patients, symptomatic intracranial hemorrhage, and death were in the range of those observed in the NINDS trial (Table II). In the Cologne Study (Grond *et al.*, 1998b), aspirin pre-treatment ($p = 0.01$), history of myocardial infarction ($p = 0.002$), and early infarct signs on CT ($p = 0.02$) were significantly associated with intracranial hemorrhage. In two studies, violation of the NINDS criteria was associated with an increased rate of symptomatic hemorrhage and death and a lower recovery rate (Tanne *et al.*, 1999 ; Buchan *et al.*, 2000). In the US study, the common deviations included use of heparin within the first 24 hours (15%), initiation of tPA beyond 3 hours (8%), excessively high blood pressure (3%), and abnormal baseline coagulation (4%). This suggests that strict adherence to protocol guidelines is prudent. At the present time, we have no prospective data on effectiveness and safety of tPA in Belgium.

Conclusions

There is now enough evidence that intravenous tPA is effective and safe if used within the first 3

hours in the right patients according to the NINDS criteria. The open studies performed after the publication of the NINDS and ECASS trials showed that the majority of symptomatic hemorrhages was due to protocol violation. MRI, including PWI/DWI-MR and MR-angiography, is a better technique than CT scan to select the best candidates. Given the risk of the therapy and the required selection of appropriate patients, thrombolysis should be restricted to specialized stroke centers with neurologists, neuroradiologists, and neurosurgeons available round the clock. With the support of the Belgian Stroke Council, the populations at risk for neurovascular disease must be advised on the need of very early admission after a stroke and new stroke units should be implemented in general hospitals across the country. A central data bank recording the patients treated in Belgium is also recommended to guarantee continued surveillance.

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