# Lessons Learned From 2 Years Experience in Intravenous Thrombolysis for Acute Ischemic Stroke in a Single Tertiary Medical Center

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**ABSTRACT:** **Background:** Intravenous tissue plasminogen activator has been approved treatment for acute (≤ 3 hours) ischemic stroke in Israel since late 2004. The Israeli experience with IV tPA is still limited. Several factors may influence the response to IV thrombolysis, including time-to-treatment parameters and tandem internal carotid artery/middle cerebral artery stenosis/occlusion.

**Objectives:** To compare our experience with IV tPA treatment of patients with acute ischemic stroke to the findings of the SITS-MOST (Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy, international data) and of the Sheba Medical Center (national data) and to compare the early outcome among patients with ischemic stroke in the MCA with and without severe ICA stenosis.

**Methods:** We obtained demographic data, timing details, stroke severity, hemorrhagic complications, mortality, and early outcome from the records of IV tPA-treated acute ischemic stroke patients.

**Results:** Fifty-eight patients (median age 69 years, 26 females) with acute ischemic stroke were treated by IV tPA at the Tel Aviv Sourasky Medical Center in 2006–2007. Median time between stroke onset and IV tPA administration was 148 minutes for the Sourasky center, 150 minutes for the Sheba center, and 140 minutes for SITS-MOST. The Sourasky mortality rate was 10.5%. Of the 31 patients who suffered MCA stroke, 8 had severe ipsilateral ICA stenosis. These 8 had significantly lower neurological improvement than the 23 without ipsilateral ICA stenosis (1/8 versus 15/23, $P < 0.001$).

**Conclusions:** Our data demonstrate fairly similar parameters of IV tPA treatment compared to other centers and suggest that patients with severe ICA stenosis might be less likely to benefit from IV tPA.

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**KEY WORDS:** stroke, thrombolysis, tissue plasminogen activator, carotid stenosis, outcome

tPA = tissue plasminogen activator
MCA = middle cerebral artery
ICA = internal carotid artery

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Intravenous thrombolytic therapy with tissue plasminogen activator is widely recommended as standard treatment for acute (≤ 3 hours) ischemic stroke in most clinical practice guidelines [1,2]. This therapy was approved by the United States Food and Drug Administration in 1996 and by European Union license in 2002 [3,4]. In Israel, IV tPA as a treatment for acute ischemic stroke was approved at the end of 2004. Based on the National Acute Stroke Israeli Survey, only 1.3% of all patients with ischemic stroke were treated with IV tPA in 2007 [5]. The results of the European Cooperative Acute Stroke Study III led to the extension of the therapeutic window for the use of IV tPA in acute ischemic stroke to 4.5 hours [6], thus potentially increasing the number of suitable candidates for IV tPA treatment among patients with acute ischemic stroke worldwide as well as in Israel.

The Tel Aviv Sourasky Medical Center is one of the largest hospitals in the country (1100 beds) whose catchment area includes the 400,000 inhabitants of metropolitan Tel Aviv in addition to the more than one million people who enter the city every day for any reason. From the start of our use of IV tPA at the Sourasky Center, we joined the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST) and the SITS International Stroke Thrombolysis Register (SITS-ISTR), the largest international database in stroke thrombolysis (6483 patients in 285 centers) [7,8]. We now present our initial 2 years of clinical experience with IV tPA in patients with acute ischemic stroke admitted to Sourasky in 2006–2007. We compare our demographic data, the most important timing details (from symptom onset to emergency room, ER to computed tomography scan, ER to IV tPA, symptom onset to IV tPA), stroke severity, hemorrhagic complications, mortality, and early outcome with the findings on the same parameters as recorded in the SITS-MOST Register (international database) and the records of Sheba Medical Center (national database), the largest hospital in Israel (1700 beds) [9]. Recent studies have shown contradictory results regarding the influence of

ER = emergency room

internal carotid artery occlusion on the clinical outcome of patients with acute ischemic stroke who were treated with IV tPA [10,11]. The impact of ICA severe stenosis (70–99%) ipsilateral to the stroke site on the thrombolytic response has not been investigated in depth. Therefore, we also included a comparison of early clinical outcome after IV tPA of patients with acute ischemic stroke in the middle cerebral artery with and without ipsilateral severe ICA stenosis.

## PATIENTS AND METHODS

The study group comprised all consecutive patients with acute ischemic stroke admitted to Sourasky in 2006–2007 who underwent thrombolysis by IV tPA. The main criteria for thrombolysis were adopted with some modification from the U.S. National Institute of Neurological Disorders and Stroke criteria [12]. The NINDS study criteria were combined with the CT exclusion criteria of the ECASS trials, i.e., exclusion of patients with major early infarct signs in more than one-third of MCA territory [13]. Clinical assessment was performed by means of the National Institutes of Health Stroke Scale and the modified Rankin Scale, which were conducted by a neurology resident or a senior neurologist who were video-trained and certified for application of the NIHSS and mRS [14]. NIHSS assessment was performed at baseline, 24 hours after stroke onset, and 7 days after IV tPA or at discharge. Neurological deterioration or improvement was defined as an increase or decrease of ≥ 4 points on the NIHSS score. The mRS was used to assess early clinical outcome at 7 days or at the time of discharge. We defined good early outcome as an mRS score ≤ 2. Pretreatment with aspirin or other antiplatelet agents was not an exclusion criterion. Special attention was paid to the control of elevated arterial blood pressure before, during, and for at least 24 hours after thrombolysis, according to the NINDS study criteria. Patients with rapidly improving symptoms before treatment were excluded. No upper age limit was stipulated; however, an mRS score of ≥ 3 before the acute event was an exclusion criterion. The tPA Alteplase® (Actilyse; Boehringer Ingelheim, Germany) was administered IV at a dose of 0.9 mg/kg body weight (maximum dose 90 mg), with 10% given as a bolus followed by delivery of the remaining 90% as a constant infusion over a period of 60 minutes. Patients' demographic data, clinical status, in-hospital course, hemorrhagic complications, and early outcome were recorded. All study patients underwent a CT scan within the first 3 hours after stroke onset, and the scan was repeated after 24 hours (or earlier/later when neurological deterioration occurred). The presence of hemorrhagic transformation was defined according to published criteria [15]. The performance of further CT or magnetic resonance imaging studies, as well as diagnostic studies to determine stroke etiology, were left to the discretion of the treating neurologist. Neither heparin nor aspirin or other antiplatelet agents were given for 24 hours after thrombolysis. Major logistic parameters – namely, time from symptom onset to arrival at the ER (onset-to-ER time), ER-to-CT time, ER-to-IV tPA time, onset-to-IV tPA time – were prospectively documented for all participants.

All the study patients underwent carotid artery ultrasound and/or CT angiography during hospitalization. The presence and severity of stenosis or occlusion was defined by peak systolic and end-diastolic velocity. A severe stenosis (≥ 70%) was defined by a peak systolic velocity of > 250 cm/sec and an end-diastolic velocity of ≥ 100 cm/sec, while a complete occlusion was defined by the absence of flow in the extracranial ICA [16].

### STATISTICAL ANALYSIS

ANOVA test was used to compare logistic parameters and clinical characteristics. NIHSS scores in patients with and without severe ICA stenosis were compared by the Fisher exact test. Significance was set at $P < 0.05$.

## RESULTS

A total of 58 patients with acute ischemic stroke were treated by IV tPA at the Sourasky Medical Center in 2006–2007, corresponding to 4% of all ischemic stroke patients (1450) admitted to Sourasky during the same period. These data are similar to the results of the Sheba Medical Center in 2005 [9]. Baseline characteristics of patients treated by IV tPA at Sourasky, Sheba and the SITS-MOST Register are shown in Table 1. There were significantly fewer females in Sheba than in both Sourasky and the SITS-MOST Register ($P = 0.001$). There were significantly fewer patients with diabetes mellitus and lacunar infarcts in the

**Table 1.** Baseline characteristics of patients with acute ischemic stroke treated with intravenous tissue plasminogen activator

| | Sourasky Medical Center (n=58) | Sheba Medical Center (n=37) | SITS-MOST (n=6,483) | *P* |
|---|---|---|---|---|
| Median age (yrs)<br>Range | 69<br>42–84 | 67<br>22–85 | 68<br>59–75 | 0.4 |
| Gender (% females) | 44 | 27 | 40 | 0.001* |
| Diabetes mellitus (%) | 31 | 43 | 16 | 0.001* |
| Atrial fibrillation (%) | 22 | 27 | 24 | 0.06 |
| Posterior circulation (%) | 8 | 5 | NA | 0.07 |
| Lacunar infarct (%) | 20 | 30 | 8 | <0.05* |
| Median NIHSS score<br>Baseline range | 12.7<br>2–22 | 14<br>10–18 | 12<br>8–17 | 0.09 |

* Significant difference (ANOVA test).

SITS-MOST = Safe Implementation of Thrombolysis in Stroke-MOnitoring ST Register, NA = data not available, NIHSS = National Institutes of Health Stroke Scale

NINDS = National Institute of Neurological Disorders and Stroke
ECASS = European Cooperative Acute Stroke Study
NIHSS = National Institutes of Health Stroke Scale
mRS = modified Rankin Scale

**Table 2.** Major logistic presentations and in-hospital course of patients with acute ischemic stroke treated with IV tPA

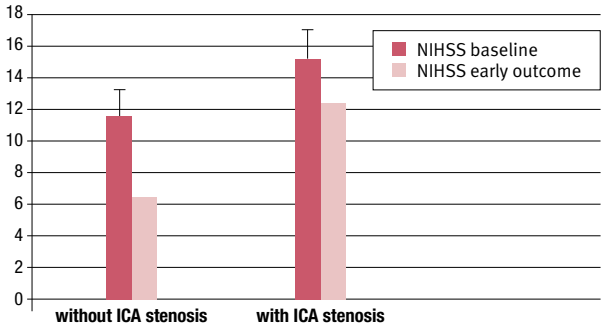
| | Sourasky Register | Sheba Register | SITS-MOST Register | *P* |
|---|---|---|---|---|
| Symptom onset → ER (min)<br>Median<br>Range | 52<br>15–105 | 49<br>NA | 72<br>NA | < 0.005* |
| ER → CT (min)<br>Median<br>Range | 50<br>18–120 | 40<br>17–62 | NA | < 0.05* |
| ER → IV tPA (min)<br>Median<br>Range | 96<br>68–140 | 101<br>72–150 | 68<br>NA | 0.002* |
| Symptom onset → IV tPA (min)<br>Median<br>Range | 148<br>60–180 | 150<br>120–178 | 140<br>115–165 | 0.4 |
| Significant early improvement (≥ 4 points in NIHSS) (%) | 54 | 54 | 55 | 0.2 |
| Favorable outcome at discharge (mRS 0-2) (%) | 37 | 38 | 39 | 0.4 |
| Hemorrhagic transformation per CT (%) | 14 | 2.7 | 17 | 0.001* |
| Mortality (%) | 10.5 | NA | 11.3 | 0.06 |

* Significant difference (ANOVA test).

SITS-MOST Register database than in the Sourasky and Sheba databases ($P < 0.05$). All other baseline parameters were similar for the three sources. Major logistic data and the in-hospital course of patients treated by IV tPA are presented in Table 2. The time of the transfer of patients to the ER after stroke onset was significantly shorter at Sourasky and Sheba than in the SITS-MOST Register (52, 49 and 72 min, respectively, $P < 0.05$ for the former two compared to the latter). The time that elapsed between arrival at the ER and the performance of CT was significantly shorter at Sheba than at Sourasky (median 40 and 50 min, respectively, $P < 0.05$) (SITS-MOST data on this parameter are not available). The time between arrival at the ER and IV tPA treatment (door-to-needle) was significantly shorter in the SITS-MOST Register but similar for Sourasky and Sheba (median 68, 96 and 101 min, respectively, $P = 0.002$ for the former compared to the latter two). The data on the in-hospital course for patients in Sourasky, Sheba and the SITS-MOST Register were similar, apart from a significantly very low frequency of hemorrhagic transformations in Sheba compared to Sourasky and the SITS-MOST Register (2.7%, 14% and 17%, respectively, $P = 0.001$).

We compared the early clinical outcome of our IV tPA-treated patients with an acute ischemic stroke in the MCA territory and concomitant severe ipsilateral ICA stenosis (n=8, mean age 64.4 ± 11.5 years, 5 males) with our IV tPA-treated patients who had an acute ischemic stroke in the MCA territory and no concomitant severe ipsilateral ICA stenosis (n=23, mean age 73.3 ± 15.5 years, 13 males). The two groups were comparable in their major vascular risk factors – arterial hypertension (6/8, 75%; 17/23, 74% respectively, $P = 0.4$) and diabetes mellitus (2/8, 25%; 7/23, 30% respectively, $P = 0.4$). There were significantly more patients with atrial fibrillation in the group without severe ICA stenosis (1/8, 12.5%; 5/23, 22% respectively, $P < 0.05$). The mean NIHSS scores at baseline in the patients with and without severe ICA stenosis were 15.2 ± 5.4 and 11.5 ± 8.5 points, respectively ($P = 0.4$). There was significantly less neurological improvement in the patients with severe ICA stenosis (1/8, 12.5%) than in patients without (15/23, 65.2%, $P = 0.001$) [Figure 1].

**Figure 1.** National Institutes of Health Stroke Scale (NIHSS) scores at baseline and after intravenous tissue plasminogen activator (IV tPA) treatment in patients with and without severe internal carotid artery (ICA) stenosis.




## DISCUSSION

The data that emerged from this descriptive observational study demonstrate fairly similar findings for the parameters of IV tPA treatment of patients with acute ischemic stroke in the Sourasky Medical center compared with the Sheba Medical Center on the national level and the results of the SITS-MOST Register on the international level. There were, however, some interesting differences. For example, there were significantly more patients with diabetes mellitus and lacunar infarcts among the patients treated in the Israeli hospitals than among those recorded in the SITS-MOST Register. These data are comparable with the 2007 NASIS database: 41.5% of ischemic stroke patients in Israel had diabetes mellitus and 33% had a lacunar stroke [5]. There was also a difference between time from stroke onset to ER arrival and from ER arrival to IV tPA treatment. Specifically, the time from stroke onset to ER arrival was approximately 20 minutes longer in the SITS-MOST Register than for Sourasky and Sheba, while the time needed to start IV tPA after stroke onset was similar. This "catching up" clearly stemmed from the fact that the interval from ER arrival to IV tPA in the SITS-MOST Register was 30 minutes less than in Sourasky and Sheba. Moreover, more time was required to perform CT scanning after ER arrival in Sourasky than in Sheba. There was a significantly lower rate of hemor-

NASIS = National Acute Stroke Israeli Survey

rhagic transformations (symptomatic and asymptomatic) in Sheba compared with that in Sourasky and the SITS-MOST Register, for which we have no explanation.

The lessons that can be learned from these data suggest that efforts should be made to shorten the time between ER arrival and beginning IV tPA, particularly the interval between ER arrival and CT performance. Shortening this interval will translate into a more beneficial outcome. An initial Israeli study of thrombolysis in acute ischemic stroke was conducted at Sheba in 2004 and expanded in 2006 [9,17]. At Sourasky we began to use IV tPA in acute ischemic stroke later, sporadically during 2005 and consecutively from 2006. Our results are comparable with those of another initial single center's 2 year experience with 75 acute ischemic stroke patients treated with IV tPA, namely, a German academic medical center serving 500,000 residents [18]. Although our data cannot compare directly with the one year experience of a Japanese neuro-unit with thrombolysis by IV tPA for ischemic stroke, due to a difference in the tPA dose, most of their reported in-hospital course features were also similar to ours [19].

The present study demonstrates that severe ipsilateral to MCA stroke carotid artery stenosis predicts a poor clinical outcome after IV tPA in acute ischemic stroke. Severe carotid disease was previously associated with a low rate recanalization and reocclusion [20,21]. Experimental studies observed that the presence of an extracranial carotid severe stenosis or occlusion leads to a regional decrease of cerebral perfusion pressure, which may favor blood stasis and hamper MCA clot dissolution [22,23]. This indicates that not only embolic but also hemodynamic factors may explain the poor outcome in these patients.

## CONCLUSIONS

The comparable national and international data in this report may be useful in the planning and optimization of thrombolytic therapy in patients with acute ischemic stroke in Israeli hospitals. We propose that an extracranial carotid evaluation should be performed in patients with acute ischemic stroke before deciding on more aggressive interventions, such as intraarterial thrombolysis or thrombectomy.

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