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# Efficacy and safety of intravenous thrombolysis for acute ischemic stroke within 3–4.5 hours in Lithuania

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**Background.** Intravenous thrombolysis has been shown as an appropriate treatment for stroke patients within 3–4.5 hours from the onset of stroke in randomized and observational studies, yet extended therapeutic window remains off-label in routine clinical setting. The aim of our study was to evaluate the efficacy and safety of intravenous thrombolysis within 3–4.5 hours for acute stroke patients in Lithuania.

**Methods.** In this pair-matched case control study stroke patients treated by intravenous thrombolysis during January 2002 – May 2010 were included. The patients were divided into two groups according to onset-to-needle time (0–180 min. (group I), and 181–270 min. (group II)), and were pair-matched 1 : 1 according to age and stroke severity. The primary end-point was good functional status after 3 months. Mortality and rates of life-threatening bleeding and symptomatic intracranial hemorrhage were used for analysis of safety profile.

**Results.** 28 pairs were included in the final analysis. The mean onset-to-needle time was significantly higher in group II. There was no difference between the groups according to baseline variables. 32.1% of patients in group I and 39.3% of patients in group II had good functional status (p = 0.58) after 3 months. No significant differences were found between the groups in the safety profile, however, the rate of symptomatic intracerebral hemorrhage was higher in group I.

**Conclusions.** Intravenous thrombolysis within 3–4.5 h after the onset of stroke is acceptable and effective treatment for acute ischemic stroke in our routine clinical setting. Further studies are needed to assess the reasons of higher rates of symptomatic intracerebral hemorrhage.

**Key words:** acute stroke therapy, thrombolysis, rtPA, efficacy, safety, time window

## INTRODUCTION

The efficacy and safety of intravenous thrombolysis (IVT) for acute stroke patients up to 3 hours from the onset of symptoms were established in the NINDS study in 1995 (1). Since this time, IVT

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is recommended as the first choice treatment for acute stroke patients in the USA in daily medical practice. In European countries, IVT is recommended for acute stroke patients since 2002. Other studies (ECASS II, ATLANTIS), in which the treatment window was prolonged up to 6 hours after the onset of symptoms, have not demonstrated the benefit of IVT due to increased rate of symptomatic intracranial hemorrhage (2, 3). On the other hand, meta-analysis of IVT studies showed a significantly higher efficacy of IVT compared with placebo up to 4.5 hours from the onset of stroke (4). The results of the ECASS3 study confirmed the suggestion that IVT is still an effective and safe treatment for patients with acute stroke within 3–4.5 hours after the onset of stroke (5). Another observational study, based on the SITS-ISTR database, showed comparable efficacy and safety of IVT applied within 3–4.5 hours and 0–3 hours after the onset of stroke (6). Consequently, European Stroke Organization recommended IVT as the first choice treatment for acute stroke patients up to 4.5 hours after the onset of stroke, although treatment between 3 and 4.5 h is not currently included in the European labeling (7).

According to national guidelines, IVT is recommended for the treatment of acute ischemic stroke within 3 hours after the onset in Lithuania. However, only a negligible part of acute stroke patients, mainly living in large cities, undergoes IVT. The substantial reason of IVT under-use in Lithuania is delayed admission of patients at appropriate hospitals. Extended time frame of IVT might alleviate the implementation of IVT for a greater number of acute stroke patients in our country. Nevertheless, the question about overall benefit of delayed IVT in less-experienced sites remains controversial.

The aim of our study was to estimate the efficacy and safety of IVT for the acute stroke patients within 3–4.5 hours after the onset in comparison with IVT within 0–3 hours after the onset of stroke in Lithuanian hospitals.

## MATERIALS AND METHODS

This pair-matched case control study included patients with acute ischemic stroke, who were admitted to Vilnius University Emergency Hospital and Vilnius University Hospital Santariskiu Clinics during January 2002 – 1 June 2010 and treated with IVT. Thrombolysed patients were divided into 2 groups according to onset-to-needle time (ONT): 0–180 min. – group I, and 181–270 min. – group II. Patients from group I and group II were pair-matched 1 : 1 according to age (±5 years) and stroke severity evaluated by National Institute of Health Stroke Scale (NIHSS) score (±1 point). After that, other baseline characteristics and outcomes of treatment were assessed and compared between the groups.

All patients received a full dose of rt-PA (Actilyse®) according to manufacturer's recommendations. The neurological status was estimated on admission, 2 hours and 24 hours after IVT, and on day 7. Brain CT was performed on admission and in 24 ± 6 hours after IVT. In case of deterioration of neurological status, brain CT was performed immediately. 3 months (± 1 week) after the stroke functional status of all patients was assessed during the visit in out-patient clinic or by phone contact using the modified Rankin Scale (mRS).

The primary end-point was good functional status (assessed as mRS score 0–1) after 3 months. Secondary end-points were: 1) significant early neurological improvement, and 2) independence in daily activity. Significant early neurological improvement was considered as a decrease of the neurological deficit ≥4 points by NIHSS in 24 hours and 7 days after IVT compared with the baseline neurological deficit. Independence in daily activity was considered as mRS score 0–2.

Mortality and rates of life-threatening bleeding and symptomatic intracranial hemorrhage (sICH) were used for analysis of the safety profile. The mortality rate was estimated in both groups on day 7 and after 3 months. In our study we used the SITS-MOST definition of sICH (local or remote parenchymal hemorrhage type 2 on 22–36 h post-treatment neuroimaging scan, combined with a neurologic deterioration of ≥4 points compared to baseline NIHSS or the lowest NIHSS value between baseline and 24 h after IVT).

Statistical analysis was performed using the SPSS (v. 16.0 for Windows) data analysis package. Parametric variables were reported as mean values and standard deviations, and nonparametric variables – as absolute values and percentages. Age, risk factors, neurological deficit on admission, rates of significant early neurological improvement, good functional outcome and independ-

ence in daily activity, as well as sICH, mortality and functional independence at 3 months were compared between the groups. The student's unpaired two-tailed *t* test was used to compare the means of normal distributed variables. The $\chi^2$ test and Fisher's exact test were performed to test the null hypothesis that the distribution of a discontinuous variable is the same in two groups. A p-value <0.05 was considered to prove a statistically significant difference.

## RESULTS

IVT was applied for 121 patients within 0–180 min. (group I), and 30 patients – within 181–270 min. (group II). Each patient from group II was paired with one patient from group I. 2 patients from group II were excluded from analysis due to missing baseline data (1 patient) or inability to match any patient from group I (1 case). Therefore, 56 patients (28 pairs) were included in final analysis. The mean ONT was 141 ± 25 min. in group I, and 208 ± 20 min. in group II (p < 0.0001). The main baseline characteristics are shown in Table. There was no difference between the groups according to baseline variables.

9 patients (32.1%) from group I and 11 patients (39.3%) from group II had good functional status (p = 0.58) after 3 months. The mRS score after 3 months was similar in both groups (Figure). After 24 hours, the significant early neurological improvement was documented for 13 patients in

**Table.** The baseline data of included patients

| | | Group I (0–180 min.) | Group II (181–270 min.) | P |
|---|---|---|---|---|
| Age, y | | 64.9 ± 10.7 | 64.0 ± 10.8 | 0.77 |
| PAH, % | | 64.3 | 71.4 | 0.57 |
| DM, % | | 17.9 | 7.1 | 0.32 |
| Previous stroke, % | Earlier than 3 months | 3.6 | 14.3 | 0.38 |
| | Within 3 months | 17.9 | 7.1 | |
| Smoker or previous smoker, % | | 3.6 | 10.7 | 0.23 |
| Sex (male), % | | 71.4 | 53.6 | 0.17 |
| AF, incl. paroxysmal, % | | 32.1 | 28.6 | 0.56 |
| CHF | | 3.6 | 10.7 | 0.48 |
| NIHSS | | 14.4 ± 3.9 | 14.1 ± 4.0 | 0.76 |

PAH – primary arterial hypertension; DM – diabetes mellitus; AF – atrial fibrillation; CHF – congestive heart failure
Data presented as means with standard deviations or absolute values and percentages.

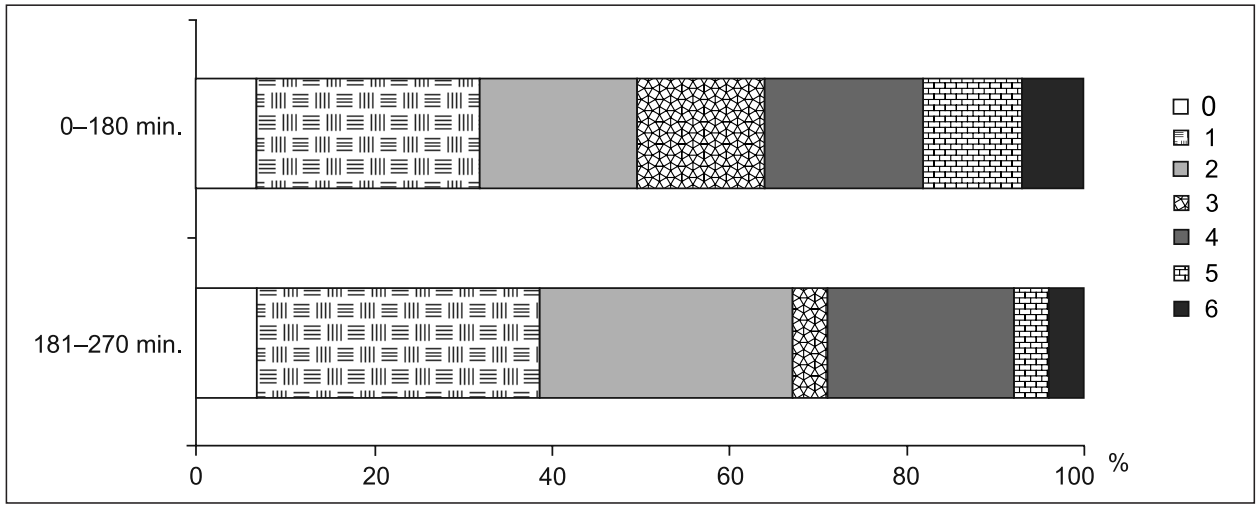


**Figure.** The functional status after 3 months, mRS

group I, and for 19 patients in group II (46.3% vs. 67.9%, p = 0.091, respectively). The significant early neurological improvement was noted in 14 patients from group I (50.0%) and 18 patients from group II (64.3%) after 7 days. No statistically significant difference was found between the groups. 15 patients (53.6%) were independent in daily activity after 3 months in group I, and 19 patients (67.9%) in group II (p = 0.27). The 3 month mortality rate was 2 fatal cases (7.1%) in group I, and 1 (3.6%) in group II, respectively (p = 0.56). All deaths during 1st week were due to malignant cerebral infarction and brain edema, and not related to rt-PA treatment. No life threatening bleeding was documented in both groups. The rate of sICH was 10.7% in group I, and 0% in group II (p = 0.075). No fatal intracranial hemorrhage was diagnosed. No other adverse effects related to rt-PA were observed in our patients.

## DISCUSSION

The results of IVT for acute stroke patients within 3–4.5 hours in Lithuania are analyzed for the first time. The IVT was started in Lithuania in 2002, but it was a relatively rare procedure in daily clinical practice up to 2006 (less than 10 cases per year). During recent few years the rate of IVT for the treatment of stroke in Lithuania increased, however, its accessibility still remains inadequate and available only in few main hospitals. Only once IVT was performed in 9 Lithuanian hospitals, and only in 5 hospitals IVT is a regular procedure (2 hospitals are in one city) (8). Our attempts to switch IVT from an exceptional therapeutical event to a standard care of acute ischemic stroke in our country (including educational activities for ambulance paramedics and doctors of emergency departments since 2007) are significantly limited by a narrow therapeutic window (0–3 h) for IVT, as in other countries. Therefore it is scarcely surprising that the positive results of ECASS3 and SITS-ISTR studies were met with enthusiasm giving more possibilities and encouragement to broader implementation of IVT in the clinical practice even in smaller countries and regional hospitals. On the other hand, there are reasonable doubts and uncertainty about safety and efficacy (even not considering the legal issues of labeling) of IVT within the extended time-window (3–4.5 h) outside of clinical trials, and especially in the setting of less experienced sites. Therefore our idea was to test if the results of large clinical trials performed in top-level highly educated institutions of Western countries could be translated and directly implemented into the clinical practice in such smaller countries as Lithuania.

In our study the excellent outcome (mRS score 0–1 after 3 months) was similar in both groups. In the observational SITS-ISTR study 41% of patients had an excellent outcome (6). It differs from our results, possibly because of the fact that our patients had higher neurological deficit on the baseline. It is known that a severe initial neurological deficit is one of the risk factors of poor outcome (9, 10). The mean severity of the neurological deficit on the baseline was 14 points by NIHSS. In SITS-ISTR study the mean neurological deficit was 12 points by NIHSS, and in ECASS3 study it was 10.6 (in target group) and 12.7 (in placebo group). 52.4% of patients in the target group had an excellent outcome in ECASS3 study; however, it is notable that 45.2% of patients had the same outcome in the placebo group.

We have got higher sICH rate in patients who received IVT within the first 3 hours, compared to the safety results of other studies. In the NINDS study occurrence of sICH in the target group was 7.2%, however, a different definition of sICH was used. In SITS-ISTR study the rate of sICH was 1.6% and 2.2% in 0–3 h and 3–4.5 h cohorts, respectively. In our opinion, higher rate of sICH in our study could be explained by a small group. This explanation is based on full analysis of all IVT, which have been performed in Vilnius. During 2002–2010 years, 121 patients received IVT within 3 hours, and just 4.1% of them had sICH. On the other hand, no sICH was diagnosed in patients within 3–4.5 h. We think that an additional analysis of patients is needed to clarify the cause of a high sICH rate.

The mortality in both groups was similar and lower than in other studies. It is an encouraging result; however, a small sample size should be kept in mind again. Mortality within 3 months after IVT among all patients was 15.2% in this our study. It should be noted that the mortality rate after IVT in Lithuania within 2002–2005 was 21.4%, and it decreased to 11.6% within next 2006–2008 (11). One of possible explanations might be the fact that IVT

in Lithuania was introduced in the clinical practice from 2002 and was performed in 2 hospitals only. During next 3 years, only 28 patients received IVT in both hospitals. Since 2006 about 15–20 acute stroke patients have been treated with IVT annually per center. Another study showed the mortality rate 11% in a single center where 450 patients were treated with IVT (12). These data are comparable with our data. Lack of experience also might have a negative influence on the mortality rate. It goes in line with observations in other countries from SITS registry that more frequent use of IVT in clinical practice decreases mortality rate (13).

## CONCLUSIONS

In summary, we believe that the results of our study confirm IVT as a safe and effective treatment for acute ischemic stroke patients not only within first 3 hours, but also within 3–4.5 h after the onset of stroke in the routine clinical setting. Extended time window will increase availability of IVT for treatment of acute stroke, especially in countries with limited facilities for IVT and non-optimized stroke center network. Nevertheless, every effort should be made to evaluate and treat patients as early as possible after the onset of stroke symptoms. The further studies are needed to assess the reasons of higher rates of sICH in our patients.

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## INTRAVENINĖS TROMBOLIZĖS EFEKTYVUMAS BEI SAUGUMAS LIGONIAMS LIETUVOJE, SUSIRGUSIEMS ŪMINIU IŠEMINIU INSULTU, PRAĖJUS 3–4,5 VAL. NUO LIGOS PRADŽIOS

*Santrauka*

**Įvadas.** Nors atsitiktinė atranka ir stebėjimai rodo, kad intraveninė trombolizė yra efektyvus ligonių ūminio išeminio insulto, praėjus 3–4,5 val. nuo ligos pradžios, gydymo būdas, tačiau iki šiol ji išlieka už protokolo ribų. Mūsų darbo tikslas – įvertinti intraveninės trombolizės efektyvumą bei saugumą ligoniams, susirgusiems ūminiu išeminiu insultu, praėjus 3–4,5 val. nuo ligos pradžios.

**Metodai.** Į tyrimą buvo įtraukti ūminiu išeminiu insultu susirgę asmenys, kurie buvo gydyti intravenine trombolize. Tyrimo laikotarpis – nuo 2010 m. sausio iki 2010 m. gegužės. Pagal laiką nuo simptomų atsiradimo iki gydymo pradžios ligoniai buvo suskirstyti į dvi grupes: I grupė – 0–180 min. ir II grupė – 181–270 min.; pagal amžių bei insulto sunkumą buvo suporuoti santykiu 1 : 1. Pirminis vertinimo kriterijus buvo gera funkcinė būklė praėjus trims mėnesiams. Vertinant saugumą buvo analizuojamas mirštamumas, gyvybei pavojingų kraujavimų ir simptominių intrasmegeninių kraujavimų dažnis.

**Rezultatai.** Į galutinį vertinimą buvo įtrauktos 28 poros ligonių. Laikas nuo simptomų atsiradimo iki gydymo pradžios buvo reikšmingesnis II grupei. Abiejų grupių pradiniai duomenys nesiskyrė. Praėjus trims mėnesiams gera funkcinė būklė buvo nustatyta 32,1 % ligonių I grupės ir 39,3 % ligonių II grupės ($p = 0,58$). Komplikacijų dažnis abiejose grupėse statistiškai nesiskyrė, nors intrasmegeninių kraujosruvų buvo daugiau I grupėje.

**Išvados.** Intraveninė trombolizė ligoniams, susirgusiems ūminiu išeminiu insultu, praėjus 3–4,5 val. nuo ligos pradžios yra efektyvus ir saugus klinikinės praktikos gydymo metodas. Reikalingi tolesni tyrimai, padėsiantys nustatyti dažnesnių intrasmegeninių kraujosruvų priežastis.

**Raktažodžiai:** ūminio insulto gydymas, trombolizė, rt-PA, efektyvumas, saugumas, terapinis langas