Southeast European Journal
of Emergency and Disaster Medicine
vol. II, godina 2016, br. 1

P a g e | 7

WHAT DETERMINES BETTER OUTCOME IN ACUTE ISCHEMIC STROKE PATIENTS TREATED WITH THROMBOLYSIS? - EXPERIENCES IN SLOVENIA

ŠTA ODREĐUJE BOLJI ISHOD U ISHEMIJSKOM MOŽDANOM UDARU U PACIJENATA LEČENIM TROMBOLIZOM? - ISKUSTVA U SLOVENIJI

Viktor Švigelj

University Medical Centre Ljubljana, Division of Neurology, Department of Vascular Neurology and Intensive Care, Neurocritical Care Unit, Zaloška 2, SI-1525 Ljubljana, Slovenia

Summary: *Aim of the work:* Ischaemic stroke is one of the leading causes of death and disability worldwide. Intravenous alteplase is, despite the recent promising results in mechanical revascularisation, the only proven effective and possible treatment option in many centres. The aim of our retrospective study was to analyse whether time to treatment, severity or territory of stroke, gender and age matter in acute ischemic stroke patients, treated with iv alteplase.

Materials and Methods: In retrospective study we analysed data of all patients from 2 university and 3 general hospitals treated with iv alteplase due to acute ischemic stroke between January 2003 and December 2015. Data were collected in Safe Implementation of Treatment in Stroke register. Results on onset-to-door time and door-to-needle time, stroke severity, sex and gender on admission, as well as outcome results after 3 months were statistically evaluated. We defined "golden hour" as group of patients, treated within 60 minutes after stroke onset, "classical" group, patients treated between 61 - 180 minutes, and "late" group, patients, treated between 181 – 270 minutes after stroke onset.

Results: Between January 1st, 2003 and December 31st, 2015 1228 acute ischemic stroke patients were treated with iv alteplase in 5 centres. However, due to lack of majority of important data (gender, age, NIHSS, time logistics, etc.), we analysed data from 1117 patients (91.0 %). Average age was 68.9 ± 12.5 years. There were more male than female patients (55.4 % vs. 44.6 %, respectively; p = 0.013), female patients were significantly older (71.3 ± 12.4 years; p < 0.001), had worse clinical presentation on stroke onset (NIHSS 13.8; p = 0.001) and worse outcome (p<0.0001).   The average NIHSS score in 1117 patients was 13.2 ± 6.7. Patients, older than 80 years (N=156), had statistically worse clinical picture on admission than younger group (N= 961) (13.8 ± 6.4; 13.0 ± 6.5, respectively; p = 0.003) and had worse outcome after 3 months (p < 0.0001). "Golden hour" patients were otherwise rare (N=24), however they have statistically worse clinical picture at presentation (NIHSS 13.7 ± 7.8), comparing to "classical" (N=893; NIHSS 13.6 ± 6.3) or "late" group (N= 200; NIHSS 11.1 ± 6.8)(p < 0.0001), but better outcome after 3 months (p < 0.0001). Patients with total anterior circulation infarct had worse NIHSS than patients with partial anterior circulation or lacunar infarct (p < 0.0001; p < 0.0001, respectively), as well as worse outcome (p < 0.0001).

Conclusion: Advances are being made in acute ischemic stroke reperfusion therapy, such as shortening of the exclusion criteria (e.g. elderly or severe stroke patients) or implementation of the ultra-early ("golden hour") thrombolytic treatment. In our retrospective study we were also able to show that patients benefit if they were presented within first 60 minutes. We also clearly showed that removing some exclusion criteria (extending time window, elderly patients) gave more patients chance to have a good outcome. However, according to the literature data, we should continuously encourage trends to improve onset to treatment time. This is a warrant for better outcome in this devastating disease.

Key words: stroke, ultra-early therapy, reperfusion, exclusion criteria, outcome

P a g e | 8

**Southeast European Journal
of Emergency and Disaster Medicine**
vol. II, year 2016, No. 1

INTRODUCTION

Ischaemic stroke is one of the leading causes of death and disability worldwide and intravenous alteplase is the only proven effective treatment in the acute setting worldwide [1, 2]. Recently, mechanical revascularisation showed promising results and as a method of an emergency stroke treatment, it is included in the guidelines [2]. Epidemiological data showed that stroke in the USA moved from its third position as a leading cause of death to the fifth [3]. This results are encouraging in developed countries, however, in most countries death rate due to stroke remains very high [4], and stroke is still the main cause of long-term disability in most industrialised countries [2,4]. Although new data show that rates of intravenous alteplase administration rose in last years [5, 6], and only a fraction of stroke patients are eligible for the drug because of its narrow treatment window. Another fact is that alteplase is completely effective only in a third of treated patients, recovering to the degree to be free from disability [1, 2]. Therefore, stroke societies implemented some concepts in stroke codes to accelerate treatment in stroke patients, such as FAST (Face Arm Speech Time) [7].

The effectiveness of intravenous thrombolysis in acute ischemic stroke is time dependent and the effect is highest if the time from symptom onset to treatment is as short as possible. A new concept, otherwise very well known in trauma and out-of-hospital cardiac arrest patients) [8, 9], termed the golden hour, should be implemented in the stroke code. The golden hour refers to a time lasting for one hour or less, during which there is the highest likelihood that prompt medical treatment will prevent disability or death [8]. Short good outcome is greatest if patients received care within a short period after a neurological emergency [10]. However, we should not generally conclude, that good outcome rates drop off after 60 minutes. Data on golden hour are primarily to show the core principle of rapid intervention in some neurological traumatic or non-traumatic conditions, rather than the narrow meaning of a critical one-hour time. In Republic of Slovenia, we started with thrombolytic treatment in our institution in 1997, and implemented as a routine treatment in other hospitals in 2003, when we joined Safe Implementation of Treatment in Stroke (SITS) register. The aim of our retrospective study was to analyse whether time to treatment, severity or territory of stroke, gender and age matter in acute ischemic stroke patients, treated with iv alteplase.

MATERIALS AND METHODS

The incidence of cerebrovascular diseases in Slovenia is around 200 patients/100.000 population, 85 % having ischemic stroke. We analysed all patients (2 university and 3 general hospitals; only University Medical Centre Ljubljana entered data regularly) included in SITS register, treated with i.v. thrombolysis with alteplase between January 1st, 2003 and December 31st, 2015. We presented results on onset-to-door time (prehospital evaluation) and door-to-needle time (hospital evaluation) logistics, stroke severity (according to National Institute of Health Stroke Scale) and age on admission, as well as outcome results (modified Rankin Scale (mRs) after 3 months. Results from a "golden hour" group of patients (defined as a group, treated within first 60 minutes) where compared to the group of patients treated between 61-180 minutes (defined as "classical" group) [11] and the group (defined as "late" group), where onset-to-treatment time was between 181-270 minutes.

We calculated and analysed some numerical results as the mean values, median and standard deviations. For statistical analysis, we used the Wilcoxon signed-rank test to compare groups, supposed to include non-normally distributed samples and univariate analysis of variance. Significance was set for p values < 0.05. For statistical analysis, we used IBM SPSS Statistics, ver. 22.

**Southeast European Journal
of Emergency and Disaster Medicine**
vol. II, godina 2016, br. 1

P a g e | **9**

RESULTS

In 2003, Republic of Slovenia joined international register (SITS register) in order to compare results between centres in the country and worldwide. At the begging, all data where entered immediately, since alteplase was not registered for treatment in acute ischemic stroke and as a rule for patient safety. Between January 1st, 2003 and December 31st, 2015 in 5 centres, entering data into SITS register, we treated with alteplase 1228 acute ischemic stroke patients. Due to lack of majority of important data (such as gender, age, NIHSS, time logistics, etc.), we analysed data from 1117 patients (91.0 %). Average age was 68.9 ± 12.5 years.

After better public awareness in 2010, when we implemented FAST (Face Arm Speech Time) system, called "GROM", we admitted and treated with thrombolysis a higher number of patients (Figure 1).

As seen in Table 1, there were more male than female patients (55.4 % vs. 44.6 %, respectively; p = 0.013). Female patients were significantly older (71.3 ± 12.4 years; p <0.001), as was the case also in a group of patients, adhering to an official guidelines concerning age eligibility (68.0 vs. 65.0, respectively; p < 0.0001).
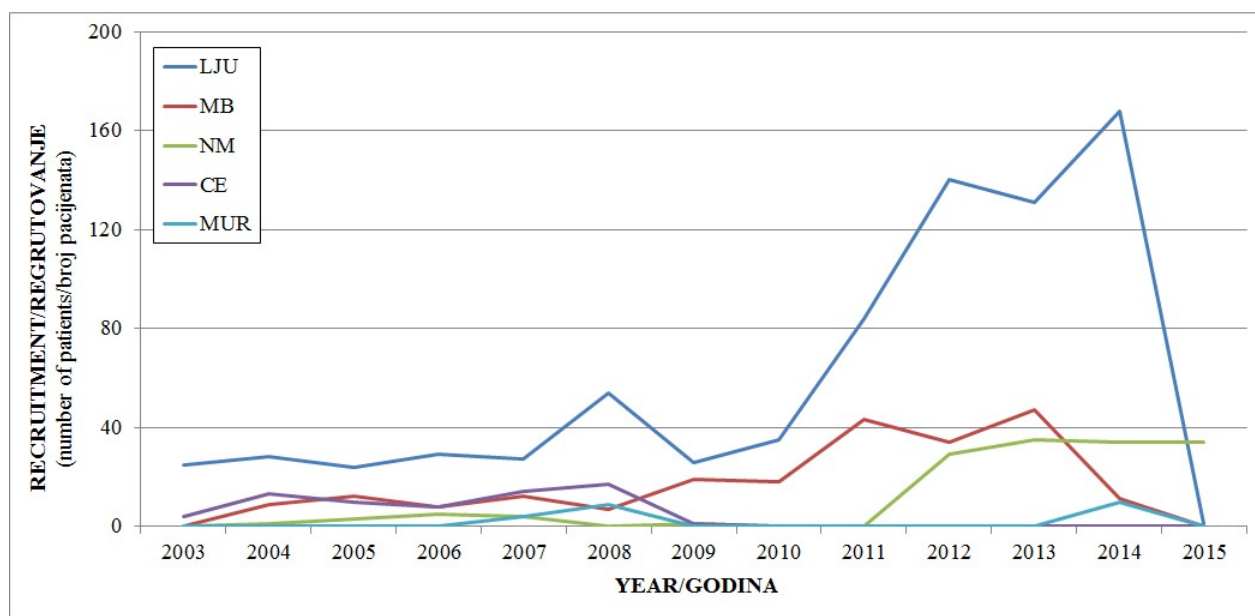

Figure 1. Number of patients recruited in Republic of Slovenia to Safe Implementation of Treatment in Stroke register between 2003 and 2015. Note higher recruitment number (year 2010), probably due to better public awareness.

Graf 1. Broj pacijenata, regrutovanih u Republici Sloveniji u registar "safe Implementation of Treatment in Stroke" između 2003 i 2015. Primetiti veči broj regrutovanih pacijenata (godina 2010) zbog bolje svesnosti javnosti.

LJU- University Medical Centre Ljubljana/ Univerzitetni klinički centar Ljubljana; MB - University Medical Centre Maribor/ Univerzitetni klinički centar Maribor; NM – General hospital Novo mesto/Opšta bolnica Novo mesto; CE - General hospital Celje/Opšđta bolnica Celje; MUR - General Hospital Murska Sobota/Opšta bolnica Murska Sobota

	All/Svi	Male/Muškarci	Female/Žene	P
Gender/Pol				
N (%)	1117 (100.0)			
N (%)		619 (55.4)	489 (44.6)	0.001
Age/starost: all/svi				
N / Average/Prosek; SE	1117 / 68.9; 12.5			
N / Average/Prosek; SE		619 / 67.0; 12.2	489 / 71.3 12.4	< 0.0001
Min		19	27	NA
Max		100	93	NA
Patients/Pacijenti: 18 - 80 years/godina				
N (%) / Average/Prosek; SE	961 (86.0); 66.3; 11.3			
N (%)		560 (58.3)	401 (41.7)	< 0.0001
Average age/Prosečna starost; SE		65.0; 11.1	68.0; 11.5	< 0.0001
Patients/Pacijenti: > 80 years/godina				
N (%) / Average age/Prosečna starost; SE	156 (14.0) 85.0; 3.4			
N (%)		59 (5.3)	97 (8.7)	< 0.0001
Average age/Prosečna starost; SE		85.3; 3.4	85.0; 3.1	ns

Table 1. Some demographic data, showing age and gender statistics in patients adhering to guidelines and those, older than 80 years at stroke onset.

Tabela 1. Demogafski podaci i statistika starosti i pola kod pacijenata, koji odgovaraju zvaničnim preporukama I kod onih, starijih od 80 godina u vreme nastanka moždang udara.

N – number/broj; P - p value/p vrednost; ns – not significant/nesignifikatno; NA - not applicable/nije primenljivo; SE - standard deviation/standardna devijacija, Min – minimum/minimum; Max – maximum/maksimum

Patients, older than 80 years are according to the guidelines [1, 2, 6] not eligible for thrombolytic treatment, except in experienced centres and with informed consent, if necessary, according to national rules. In Slovenia we treat such patients, when we have written consent (patients signed themselves or consent signed by the relatives). As seen from Table 1, we treated 156 (14.0 %) patients older than 80 years with alteplase (average age 85.0 ± 3.4 years).

In Table 2, we present NIHSS score in patients, adhering to guidelines [12] and in those, older than 80 years at stroke onset, as well as, according to time logistics (prehospital delay,

in-hospital delay). The average NIHSS score in 1117 patients was 13.2 ± 6.7. When results from the group, adhering to the guidelines (N = 961; 86.0 %) were compared to the results from the group, older than 80 years (N = 156; 14.0 %), we found that female patients had statistically weak, but significant worse clinical picture at admission than men (13.7 ± 6.4; vs. 12.5 ± 6.5; p = 0.049) in younger group. We did not find any statistical difference between male and female patients in the older group. However, comparing both groups, older group had worse clinical picture on admission (13.8 ± 6.4 vs. 13.0 ± 6.5) and the difference was statistically significant (p = 0.003).

Southeast European Journal
of Emergency and Disaster Medicine
vol. II, godina 2016, br. 1

P a g e | **11**

		All/Svi	Male/Muškarci	Female/Žene	P
NIHSS: All/Svi					
	N	1117			
	Average/Prosek; SE	13.2; 6.7			
	N		619	489	
	Average/Prosek; SE		12.7; 6.6	13.8; 6.2	0.001
	Min		1	1	NA
	Max		38	39	NA
NIHSS: age/starost 18 - 80 years/godina					
	N	961			
	Average/ Prosek; SE	13.0; 6.5			
	N		559	402	
	Average/Prosek; SE		12.5; 6.5	13.7; 6.4	0.049
	Min		2	1	NA
	Max		39	36	NA
NIHSS: age/starost > 80 years/godina					
	N	156			
	Average/Prosek; SE	13.8; 6.4			
	N		59	97	
	Average/Prosek; SE		13.9; 7.4	13.8; 5.7	ns
	Min		1	2	NA
	Max		34	25	NA
NIHSS in patients admitted within first 60 min after stroke onset/ NIHSS kod pacijenata primljenih u prvih 60 minuta nakon početka moždanog udara					
	N	24			
	Average/Prosek; SE	13.7; 7.8			
	N		13	11	
	Average/Prosek; SE		13.5; 6.6	14.6; 9.4	ns
	Min		2	4	NA
	Max		25	36	NA
NIHSS in patients admitted within 61-180 min after stroke onset/ NIHSS kod pacijenata primljenih između 61 i 180 minuta nakon početka moždanog udara					
	N	893			
	Average/Prosek; SE	13.6; 6.3			
	N		376	517	
	Average/Prosek; SE		13.0; 6.4	14.4; 6.1	0.001
	Min		1	1	NA
	Max		39	35	NA
NIHSS in patients admitted within 181-270 minutes after stroke onset/NIHSS kod pacijenata primljenih između 181 i 270 minuta nakom početka moždanog udara					
	N	200			
	Average/Prosek; SE	11.1; 6.8			
	N		89	111	
	Average/Prosek; SE		11.0; 7.8	11.3; 5.9	ns
	Min		2	2	NA
	Max		35	31	NA

Table 2. Stroke severity at admission according to National Institute of Health Stroke Scale in patients adhering to guidelines and those, older than 80 years at stroke onset and according to time logistics (prehospital delay, hospital delay).

Tabela 2. Ozbiljnost moždanog udara na prijemu u skladu sa Skalom za moždani udar Nacionalnog Instituta za Zdravlje kod pacijenata, koji odgovaraju zvaničnim uputstvima i onih, starijih od 80 godina kod nastanka moždanog udara i u skladu sa vremenskom logistikom (prehospitalno i bolničko kašnjenje).

N – number/broj; P - p value/p vrednost; ns – not significant/nesignifikatno; NA - not applicable/nije primenljivo; SE - standard deviation/standardna devijacija, Min – minimum/minimum; Max – maximum/maksimum; NIHSS - National Institute of Health Stroke Scale/Skala Moždanog Udara Nacionalnog Instituta za Zdravlje

P a g e | 12

**Southeast European Journal
of Emergency and Disaster Medicine**
vol. II, year 2016, No. 1

Patients, treated within first 60 minutes after stroke symptoms and signs onset, were otherwise rare (n=24; 2.1 %). Among them, 3 (12.5 %) patients were older than 80 years. The average NIHSS score was 13.7 ± 7.8. There was no significant difference between male and female patients. Patients, arriving according to the original study (n=893; 79.9 %) [12], within 60 to 180 minutes, had an average NIHSS before treatment of 13.6 ± 6.3. Between men and women we found statistically significant worse clinical picture on admission in woman (p = 0.001). As seen in Table 2, when we introduced new guidelines into a routine clinical practice, extending the time window up to 4.5 hours in 2009, we treated 200 patients with alteplase. The average NIHSS before treatment in this group (onset to needle time within 181 - 270 minutes) was 11.1 ± 6.8. We did not find any statistical difference between men and women.

We also compared NIHSS results before treatment in all three groups ("golden hour" group, "classical" group and "late" group). We found that "late" group had statistically better clinical picture than "classical" group (p < 0.0001) on admission; however, we did not find any differences between late and golden or classical and "golden hour" group. The reason was a low statistical power due to a low number of stroke patients in the "golden hour" group.

	TACI	PACI	LACI	POCI	No final diagnosis/ Bez konačne diagnoze	P
N	403	331	233	8	136	
Median age/Prosečna starost (years/godina)	73.0	71.0	69.0	74.5	71.5	ns
Male sex/Muški pol, N (%)	195 (48.4)	197 (59.5)	139 (59.7)	5 (62.5)	80 (58.8)	ns
Median/Prosečna NIHSS	18.0	12.0	7.0	2.5	14.0	< 0.001
Onset-to-needle time/ Vreme od početka do igle (median/prosečna) (min)	140	153	155	198	130	< 0.001
Door-to-needle time/Vreme od prijema do igle (median/prosečna) (min)	50	50	45	44	50	ns

Table 3. Stroke severity at admission (National Institute of Health Stroke Scale) in our cohort of patients according to stroke territory and time logistics.
Tabela 3. Ozbiljnost moždanog udara na prijemu (Skala za moždani udar Nacionalnog Instituta za Zdravlje) u našoj kohorti pacijenata procenjena prema teritoriji moždanog udara i vremenskoj logistici.

N – number/broj; P - p value/p vrednost; ns – not significant/nesignifikatno; NA - not applicable/nije primenljivo; SE - standard deviation/standardna devijacija, Min – minimum/minimum; Max – maximum/maksimum; NIHSS - National Institute of Health Stroke Scale/Skala Moždanog Udara Nacionalnog Instituta za Zdravlje; TACI - total anterior circulation infarct/Infarkt totalne prednje cirkulacije; PACI - partial anterior circulation infarct/Parcialni infarkt prednje cirkulacije; LACI - lacunar infarct/Lakunarni infarkt; POCI - posterior circulation infarct/infarkt stražne cirkulacije ; min – minutes/minute

Highest NIHSS score usually have patients with stroke in the posterior territory (mostly basilar artery occlusion). According to original study, published in 1995 [12], patients with NIHSS 4 or less and 25 or more, should not be treated with alteplase. All eligibility criteria from the National Institute of Neurological Disorders and Stroke recombinant tPA Stroke Study [12] were adopted within the alteplase package insert as contraindications/warnings.

We, clinicians have expressed the need for clarification and better definition of these treatment criteria. One of the exclusion criteria chosen was also rapidly improving stroke symptoms. None of our patients was treated with alteplase if has had rapidly improving symptoms, and this is not true for patients, that probably have had minor stroke, such as lacunar stroke. However, excluding patients with rapid improvement to non-mild deficits

Southeast European Journal
of Emergency and Disaster Medicine
vol. II, godina 2016, br. 1

P a g e | **13**

was not justified because these patients should and were treated according to latest literature data [13].

So, if patients or their relatives signed informed consent, than we treated these patients with alteplase (as an off-label treatment). There were 86 (7.2 %) patients with initial NIHSS 4 or less and 56 (4.7 %) with NIHSS score 25 or more.

In our cohort of patients, according to SITS registry data, posterior circulation infarct (POCI) was a rare final diagnosis (only in 8 patients). As seen in Table 3, most of the patients had stroke in either anterior circulation or lacunar stroke. In 142 patients (12.7 %), there was no final diagnosis

As expected, there was significantly worse clinical picture according to NIHSS on admission in patients with total anterior circulation infarct (TACI) than in partial anterior circulation infarct (PACI) ($p < 0.0001$) or lacunar infarct (LACI) ($p < 0.0001$) or when compared to a group with no final diagnosis ($p < 0.0001$).

We evaluated outcome after 3 months with mRs in all three groups as far as time logistic was concerned (Figure 2) and in groups younger and older than 80 years on admission (Figure 3). In Figure 4 we can see the outcome results (mRs) corresponding to the stroke territory.
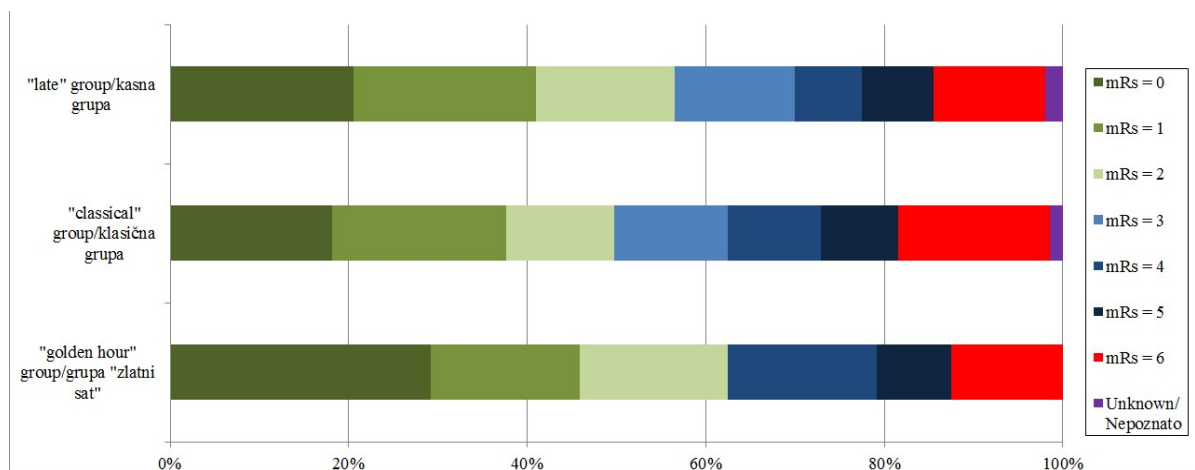

Figure 2. Outcome results in our cohort of patients, treated with alteplase, according to time logistic.
Graf 2. Ishod lečenja u našoj kohorti pacijenata, lečenim alteplazom, prema vremenskoj logistici.
– "Golden hour" group/ Grupa "Zlatni sat" - onset-needle < 60 minutes/ početak-igla < 60 minuta;
– "Classical" group/"klasična" grupa - onset-needle - 61 - 180 minutes/početak-igla - 61 - 180 minuta;
– "Late" group/"kasna" grupa - onset-needle - 181 - 270 minutes/početak-igla - 181 - 270 minuta;
– mRs - modified Rankin scale/modifikovana Rankinova skala

As seen from Figure 2, the best outcome (mRs 0 - 2) was in the "golden hour group". However, only 2.1 % of patients were in that group. Also, good clinical outcome after 3 months was also better in the "late" group, comparing to the "classical" group ($p < 0.0001$). However, as seen in Figure 3 and Table 4, older patients had worse outcome, then patients adhering to the official guidelines group ($p < 0.0001$). When presented to the

hospital, their clinical picture was also worse than in the younger group (Table 2).

Table 4 shows that women had statistically worse outcome than men ($p < 0.0001$), as well as patients with acute ischemic stroke in TACI territory ($p < 0.0001$), and, as expected, the best outcome was in patients with lacunar infarction (Figure 4).

P a g e | **14**

**Southeast European Journal
of Emergency and Disaster Medicine**
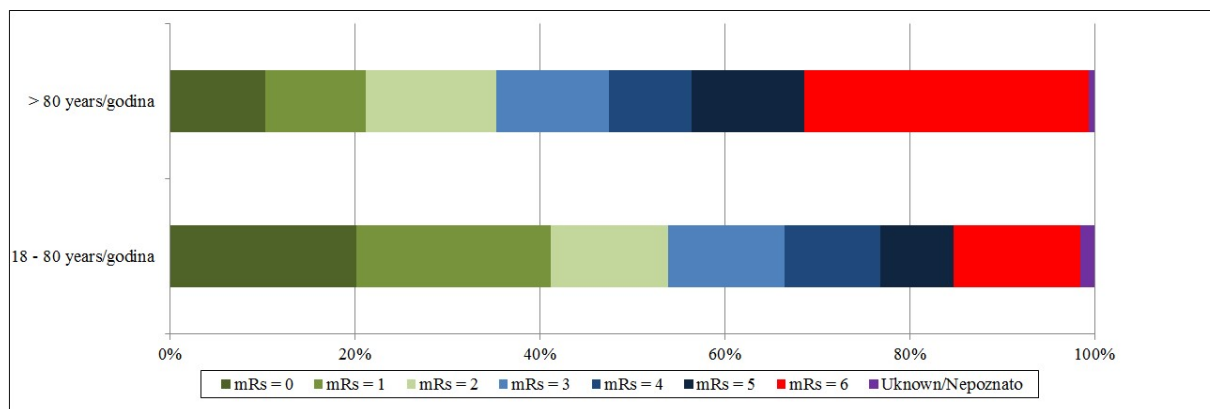vol. II, year 2016, No. 1

Figure 3. Outcome results in our cohort of patients, treated with alteplase, according to age on stroke onset.
Graf 3. Ishod lečenja u našoj kohorti pacijenata, tretiranih alteplazom, prema starosti kod moždanog udara.

	Outcome/Ishod (mRs)				
	Good/ Dobar (0-2)	Bad/ Loš (3-5)	Died/ Umrli (6)	Unknown/ Nepoznat (7)	P
Gender/Pol					
Male/Muškarci: N (%)	323 (52.2)	178 (28.8.)	104 (16.8)	14 (2.2)	< 0.0001
Female/Žene: N (%)	249 (50.0)	170 (34.1)	76 (15.3)	3 (0.6)	
Time logistic/Vremenska logistika					
"golden hour" group/Grupa "zlantni sat": N (%)	15 (62,5)	6 (25.0)	3 (12.5)	0	
"classical" group/"klasična" grupa: N (%)	445 (49.8)	284 (31.8)	152 (17.0)	13 (1.4)	< 0.0001
"late" group/"kasna" grupa: N (%)	113 (56.5)	58 (29.0)	25 (12.5)	4 (2.0)	
Age/Starost					
18-80 years/godine: N (%)	517 (53.8)	296 (30.8)	132 (13.7)	16 (1.7)	< 0.0001
> 80 years/godine: N (%)	55 (35.3)	52 (33.3)	48 (30.8)	1 (0.6)	
Stroke territory/Teritorij moždanog udara					
TACI: N (%)	145 (36.0)	163 (40.5)	93 (23.1)	2 (0.4)	
PACI: N (%)	185 (55.8)	87 (26.3)	54 (16.3)	5 (1.6)	< 0.0001
LACI: N (%)	170 (73.0)	48 (20.6)	11 (4.7)	4 (1.7)	
POCI: N (%)	6 (75.0)	2 (25.0)	0	0	NA
Undefined/Nedefinisano: N (%)	61 (44.9)	48 (35.2)	22 (16.2)	5 (3.7)	NA

Table 4. Stroke outcome after 3 months, evaluated with modified Rankin scale, according to gender, time logistic, age and stroke territory in our cohort of patients, treated with alteplase between 2003 and 2015.
Tabela 4. Ishod lečenja nakon 3 meseca, ocenjen sa modifikovanom Rankinovom skalom, prema polu, vremenskoj logistici, starosti i teritorije moždanog udara u našoj kohorti pacijenata, lečenih sa alteplazom između 2003. i 2015. godine.

mRs - modified Rankin scale/modifikovana Rankinova skala;

N – number/broj;

P - p value/p vrednost;

ns - not significant/nesignifikatno;

NA - not applicable/ nije primenljivo;

"golden hour" group/ Grupa "Zlatni sat" - onset-needle < 60 minutes/ početak-igla < 60 minuta;

"classical" group/"klasična" grupa - onset-needle - 61 - 180 minutes/početak-igla - 61 - 180 minuta;

"late" group/"kasna" grupa - onset-needle - 181 - 270 minutes/početak-igla - 181 - 270 minuta;

TACI - total anterior circulation infarct/infarkt totalne prednje cirkulacija;

PACI - partial anterior circulation infarct/parcialni infarkt prednje cirkulacije;

LACI - lacunar infarct/lakunarni infarkt;

POCI - posterior circulation infarct/infarkt stražne cirkulacije

Southeast European Journal
of Emergency and Disaster Medicine
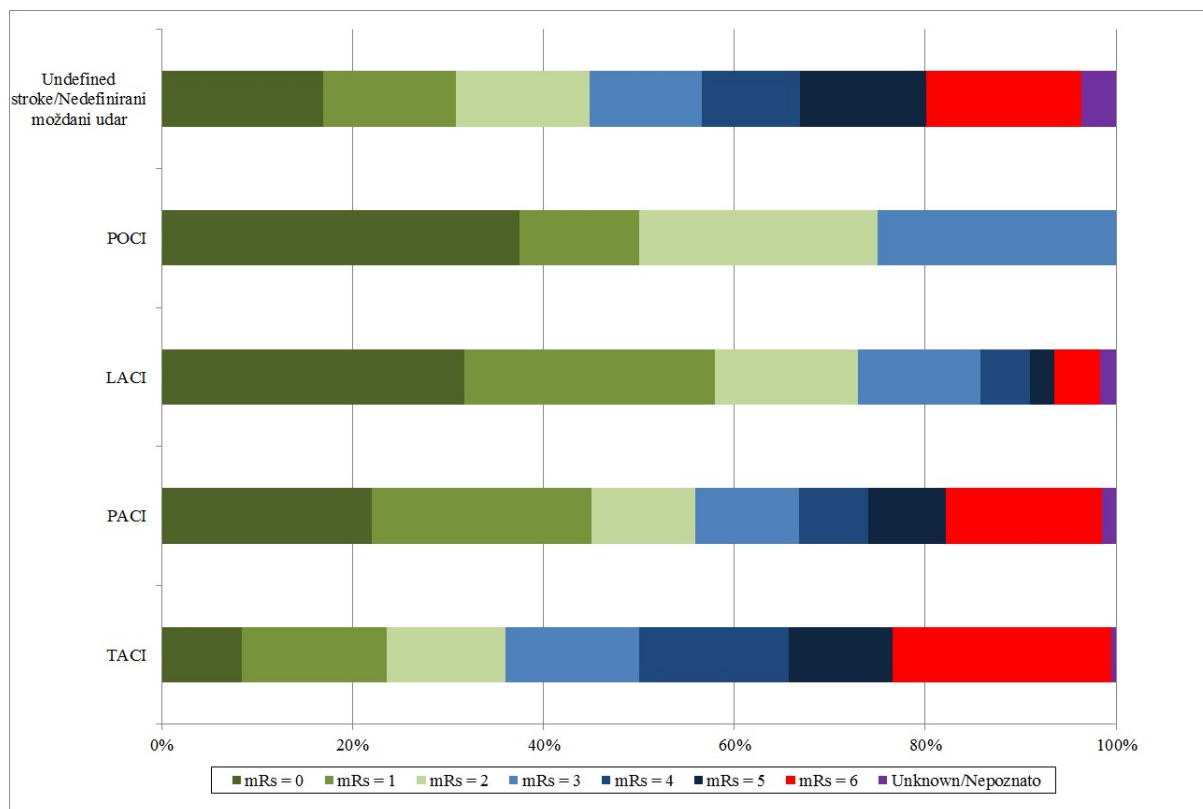vol. II, godina 2016, br. 1

P a g e | **15**

Figure 4. Outcome results in our cohort of patients according to the stroke territory.
Graf 4. Ishod lečenja s u našoj kohorti pacijenata prema teritoriji moždanog udara.
TACI - total anterior circulation infarct/infarkt totalne prednje cirkulacija; PACI - partial anterior circulation infarct/parcialni infarkt prednje cirkulacije; LACI - lacunar infarct/lakunarni infarkt; POCI - posterior circulation infarct/infarkt stražne cirkulacije; mRs - modified Rankin scale/modifikovana Rankinova skala

It is also important to analyse mortality rate and reason for death as a safety precaution. Between 2003 and 2015 180 (16.2 %) of all treated patients died, mostly due to stroke (52.2 %), stroke related therapy or hemorrhagic transformation (any intracranial haemorrhage) (24.4 %). Almost one quarter of patients died due to stroke complications, such as pneumonia, pulmonary embolism or due to concomitant myocardial infarction, or the reason was not declared or unknown. Detailed results are in Table 5.

Despite the fact, that time window is extended in eligible patients from 3 to 4.5 hours, it is important to shorten time from onset to the treatment as much as possible. This could be dome with "GROM" notification or any campaign for public awareness that stroke is a devastating disease. However, in the chain of survival, any lay public as well as medical professionals are equally important. In Figure 5 we show time delay in stroke management in our country, divided into pre and hospital delay.
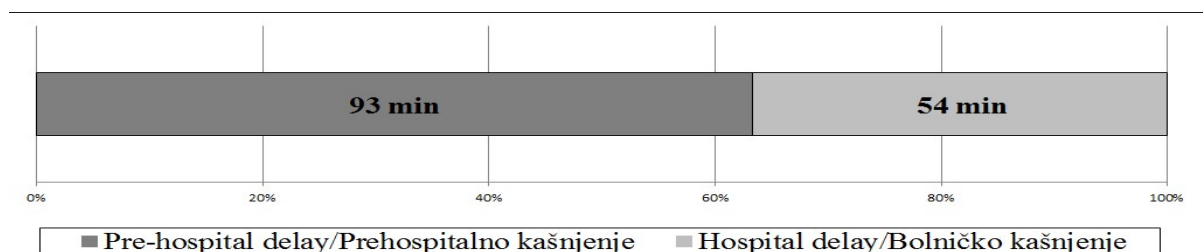
	Mortality rate/ Stopa mortalitete (N=1100)*	Death due to stroke/ Smrt zbog ishemijskog moždanog udara	Death due to ICH/ Smrt zbog intracerebralnog krvarenja	Death due to other reason (pulmonary embolism, pneumonia, myocardial infarction)/ Smrt zbog drugih razloga (pljućna embolija, upala pljuća, miokardni infarkt)
All/Svi N (%)	180 (16.2)	94 (52.2)	44 (24.4)	42 (23.4)
Gender/pol				
Male/Muškarci: N (%)	104 (57.8)	46 (44.3)	28 (26.9)	30 (28.8)
Female/Žene: N (%)	76 (42.2)	48 (63.1)	16 (21.1)	12 (15.8)
Time logistic/ Vremenska logistika				
"golden hour" group/ Grupa "zlatni sat": N (%)	3 (1.7)	1 (33.3)	2 (66.7)	0
"classical" group/ "klasična" grupa: N (%)	152 (84.4)	70 (46.1)	37 (24.3)	45 (29.6)
"late" group/ "kasna" grupa: N (%)	25 (13.9)	10 (40.0)	4 (16.0)	11 (44.0)
Age/Starost				
18-80 years/ godina: N (%)	132 (73.3)	68 (51.5)	31 (23.5)	33 (25.0)
> 80 years/godina: N (%)	48 (26.7)	13 (27.1)	13 (27.1)	22 (45.8)
Stroke territory/ Teritorij moždanog udara				
TACI: N (%)	93 (51.7)	46 (49.5)	23 (24.7)	24 (25.8)
PACI: N (%)	54 (30.0)	20 (37.0)	15 (27.8)	19 (35.2)
LACI: N (%)	11 (6.1)	2 (18.2)	2 (18.2)	7 (63.6)
POCI: N (%)	0	0	0	0
Undefined/ Nedefinisano: N (%)	22 (12.2)	13 (59.1)	4 (18.2)	5 (22.7)

Table 5. Mortality rate, reason for death and intracerebral hemorrhage due to alteplase treatment, according to gender, time logistic, age and stroke territory in our cohort of patients, treated with alteplase between 2003 and 2015.

Tabela 5. Stopa mortaliteta, razlog za smrt i intracerebralno krvarenje zbog tretmana alteplazom, prema polu, vremenskoj logistici, starosti i teritoriji moždanog udara u našoj kohorti pacijenata lečenih alteplazom između 2003. i 2015. godine.

*patients with unknown outcome were excluded/pacijenti sa nepoznatom ishodom lečenja su isključeni

mRs - modified Rankin scale/modifikovana Rankinova skala; N – number/broj; P - p value/p vrednost; ns - not significant/nesignifikantno; NA - not applicable/ nije primenljivo; ICH – intracerebral hemorrhage/intracerebralno krvarenje; "golden hour" group/ Grupa "Zlatni sat" - onset-needle < 60 minutes/ početak-igla < 60 minuta; "classical" group/"klasična" grupa - onset-needle - 61 - 180 minutes/početak-igla - 61 - 180 minuta; "late" group/"kasna" grupa - onset-needle - 181 - 270 minutes/početak-igla - 181 - 270 minuta; TACI - total anterior circulation infarct/infarkt totalne prednje cirkulacija; PACI - partial anterior circulation infarct/parcialni infarkt prednje cirkulacije; LACI - lacunar infarct/lakunarni infarkt; POCI - posterior circulation infarct/infarkt stražne cirkulacije

Southeast European Journal
of Emergency and Disaster Medicine
vol. II, godina 2016, br. 1

P a g e | **17**

min - minutes/minuta

Figure 5. Time delay in stroke management in patients, treated with alteplase in Republic of Slovenia between 2003 and 2015.

Graf 5. Kašnjenje u obradi pacijenata sa moždanom udarom, lečenih alteplazom u Republici Sloveniji između 2003. i 2015. godine.

DISCUSSION

Our study showed that iv alteplase delivered within the first 60 minutes after stroke symptoms and signs onset guarantee better outcome, when compared to the so called "classical" group, as well as to the "late" group. However, only 2.1 % of patients were treated within the "golden hour" (Table 2). This percentage is, however, higher than in the report from the Get With The Guidelines - Stroke Registry (< 1% of the total 58,353 acute stroke patients) [14]. The scarcity of such patients is not just the low absolute number, but probably also the severity of the clinical picture on stroke presentation, as shown further on. The NIHSS score was the worst in this group of patients (13.7), but not statistically significant, when compared to "classical" (13.6) or "late" (11.1) group. However, statistically better clinical picture was seen in the "late" group, when compared to the "classical" group (p < 0.0001). We can find the similar observation in the report from the Get With The Guidelines - Stroke Registry (12.0, 11.0, 9.0, respectively) [14].

Considering age, NIHSS pre-treatment in patients older than 80 years was compared to the results obtained from younger group, we found a statistically worse clinical picture in older group (p = 0.0003). Outcome, as seen in Figure 3, was also worse, than in younger group (p < 0.0001). Mishra KN et al. [15] showed similar results in a much bigger study of 29,500 patients, as well as in a meta-analysis of some smaller studies [16]. However, as concluded from those studies, our opinion is that there is scope for benefit from thrombolysis also for the older age group.

As seen from the literature, authors concluded, that women are more likely to have a worse outcome after an acute stroke than men, some others suggested that women benefit more from intravenous thrombolysis after an acute ischemic stroke and some found no sex differences in safety and efficacy [17-21]. Our study showed that

P a g e | 18

Southeast European Journal
of Emergency and Disaster Medicine
vol. II, year 2016, No. 1

there were less female patients (44.6 %, p = 0.001), they were older (71.3 years; p < 0.0001) had worse clinical presentation on stroke onset (NIHSS 13.8; p = 0.001) and worse outcome (p<0.0001) (Table 1 and 2). No statistical difference was found between men and women in group of patients, older than 80 years.

Classification of ischemic stroke, using the TOAST criteria, helps us to determine the pathophysiologic mechanism and stroke aetiology. According to literature data, patients with lacunar infarcts have higher probability of favourable outcome than patients with cardioembolism or large vessel disease [22, 23]. As seen in Figure 4, similar presentation was also seen in our cohort of patients.

Intracerebral haemorrhage still represents the most feared complication of thrombolysis. It is a complex and heterogeneous phenomenon, which involves multiple demographic, clinical, biological and hemodynamic parameters. The importance of a strict protocol for the control of elevated blood pressure is needed during the first 24 h following thrombolysis, as well as strict adherence to the eligibility for thrombolytic treatment. However, inclusion criteria, as were originally implemented with the first studies are probably obsolete, since we have now multimodal neuroradiological techniques [24]. However, since it was not the aim of our study to analyse and statistically evaluate in detail the mortality rate in our group of patients, we presented just some data on this topic. In our group of patients the mortality rate was relatively high (16.2 %) and most of the patients died due to ischemic stroke (52.2 %) or intracerebral haemorrhage (24.4 %).

Despite better organisation in late years, implementing a telestroke project, we did not shorten much the pre-hospital, as well as hospital delay. Similar observations are seen worldwide and telestroke is a promising effort to shorten time to stroke treatment, as well as repeating actions for public awareness.

CONCLUSION

Despite the increase in the global burden of stroke, advances are being made. Outcome in patients with acute ischaemic stroke, as shown in many studies, is significantly better in those who undergo thrombolysis compared with those who do not. It is also clearly evident that the levels of evidence supporting individual exclusion criteria for intravenous alteplase, such as treatment in elderly stroke patients or those with severe stroke vary widely.

Also, the term "golden hour" implies that morbidity and mortality are affected if care is not instituted within the first hour after insult. Earlier thrombolytic treatment of patients with acute ischemic stroke is associated with more frequent independent ambulation, reduced mortality and symptomatic intracranial haemorrhage. We were also able to show this in our study. However, we believe that this is still a

Southeast European Journal
of Emergency and Disaster Medicine
vol. II, godina 2016, br. 1

P a g e | 19

challenge of reperfusion therapy for acute ischemic stroke in the near future. The findings in studies support intensive efforts to accelerate patient presentation and to streamline local system to shorten onset to treatment time. Finally, we did not discuss coexistence of multiple exclusion factors in a single patient, and the variation in practice among treating clinicians. Probably this should also be a challenge in the future studies to improve stroke patient care. We should continuously encourage trends, the public and healthcare professionals, to remain vigilant and committed to improving overall stroke care.

Acknowledgment: None.

REFERENCES

1. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008; 25(5): 457-507.

2. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015; 46(10): 3020-3035.

3. Heron M. Deaths: preliminary data for 2013. Natl Vital Stat Rep 2016; 65 (2): 1–94.

4. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, et al. European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis; 2012.

5. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke 2011; 42(7): 1952-1955.

6. Demaerschak BM, Kleindorfer DO, Adeyoe OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke–a statement for healthcare professionals from the AHA/ASA. Stroke 2016; 47(2): 581-641.

7. Švigelj V, Žvan B, editors. Akutna možganska kap IV: učbenik za zdravnike in zdravstvene delavce. Ljubljana: Boehringer Ingelheim Pharma; 2009.

8. Lerner EB, Moscati RM. The golden hour: scientific fact or medical "urban legend"? Acad Emerg Med 2001; 8(7): 758-760.

9. De Maio VJ, Stiell IG, Wells GA, Spaite DW; Ontario Prehospital Advanced Life Support Study Group. Optimal defibrillation response intervals for maximum out-of-hospital cardiac arrest survival rates. Ann Emerg Med 2003; 42(2): 242-250.

10. Ebinger M, Kunz A, Wendt M, Rozanski M, Winter B, Waldschmidt C, et al. Effects of golden hour thrombolysis: a Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) substudy. JAMA Neurol 2015; 72(1): 25-30.

11. Zupan M, Švigelj V. Učinkovitost in varnost intravenske trombolize 3 do 4,5 ure po začetku akutne ishemične možganske kapi - rezultati raziskave ECASS III. In: Švigelj V, Žvan B, editors. Akutna možganska kap IV: učbenik za zdravnike in zdravstvene delavce. Ljubljana: Boehringer Ingelheim Pharma; 2009. p. 103-9

12. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. New Engl J Med 1995; 333(24): 1581-1587.

13. Levine SR, Khatri P, Broderick JP, Grotta JC, Kasner SE, Kim D, et al. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: Part 1: rapidly improving stroke symptoms. Stroke 2013; 44(9): 2500-2505.

14. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 2013; 309(23): 2480-2488.

15. Mishra KN, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, et al. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. BMJ 2010; 341:c6046 doi:10.1136/bmj.c6046

16. Engelter ST, Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of > or = 80 versus < 80 years of age--a systematic review across cohort studies. Age Ageing 2006; 35(6): 572-80.

17. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, et al; European BIOMED Study of Stroke Care Group. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital based registry. Stroke 2003; 34(5): 1114-1119.

18. Kapral MK, Fang J, Hill MD, Silver F, Richards J, Jaigobin C, et al. Sex differences in stroke care and outcomes: results from the registry of the Canadian Stroke Network. Stroke 2005; 36(4): 809-814.

P a g e | **20**

**Southeast European Journal
of Emergency and Disaster Medicine**
vol. II, year 2016, No. 1

19. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol 2008; 7(10): 915-926.

20. Lorenzano S1, Ahmed N, Falcou A, Mikulik R, Tatlisumak T, Roffe C, et al. Does sex influence the response to intravenous thrombolysis in ischemic stroke?: answers from safe implementation of treatments in Stroke-International Stroke Thrombolysis Register. Stroke 2013; 44(12): 3401-3406.

21. Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. Stroke 2005; 36(1): 62-65.

22. Mustanoja S, Meretoja A, Putaala J, Viitanen V, Curtze S, Atula S et al. Outcome by stroke etiology in patients receiving thrombolytic treatment: descriptive subtype analysis. Stroke 2011; 42(1): 102-106.

23. Patel A, Mahuwala Z, Limaye K, Bianchi N, Hinduja A, Patel R. Compare the functional outcome in ischemic strokes based on the TOAST classification. Neurology 2014; 82(10 Suppl): P1.117.

24. Derex L, Nighoghossian N. Intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: an update. J Neurol Neurosurg Psychiatry 2008; 79(10): 1093-1099.

Southeast European Journal
of Emergency and Disaster Medicine
vol. II, godina 2016, br. 1

P a g e | **21**

ŠTA ODREĐUJE BOLJI ISHOD U ISHEMIJSKOM MOŽDANOM UDARU U PACIJENATA LEČENIM TROMBOLIZOM? - ISKUSTVA U SLOVENIJI

Viktor Švigelj

University Medical Centre Ljubljana, Division of Neurology, Department of Vascular Neurology and Intensive Care, Neurocritical Care Unit

Sažetak: Cilj istraživanja: Ishemijski moždani udar je jedan od vodećih uzroka smrti i invaliditeta širom sveta. Intravenska alteplaza je, uprkos nedavnim obećavajućim rezultatima primene mehaničke revaskularizacije, jedini efikasni i u mnogim centrima i jedina opcija lečenja akutnog ishemijskog moždanog udara. Cilj naše retrospektivne studije bio je analizirati dali vreme, koje imamo za lečenje, težina kliničke slike ili teritorije moždanog udara, kako i pol te starost bolesnika u akutnih pacijenata sa ishemičnim moždanim udarom, tretiranim sa iv alteplazom, utječu na ishod lečenja.

Rezultati: Analizirali smo podatke 1117 bolesnika prosečne starost 68,9 ± 12,5 godine (55,4% muškaraca). Žene su bile značajno starije (71,3 ± 12,4 godina; p <0,001), imale su lošiju kliničku sliku (NIHSS 13,8) i lošiji ishod (p <0,0001). Prosečna ocena NIHSS u 1117 pacijenata bila je 13,2 ± 6,7. Pacijenti, stariji od 80 godina (N = 156), imali su statistički lošiju kliničku sliku u usporedi sa mlađim pacijentima (N = 961) (13,8 ± 6,4; 13,0 ± 6,5; p = 0,003), a također i lošiji ishod nakon 3 meseca (p <0,0001).U "zlatnom satu" bilo je tretirano 24 pacijenta, imali su statistički lošiju kliničku (NIHSS 13,7 ± 7,8), u odnosu na "klasičnu" grupu (N = 893; NIHSS 13,6 ± 6,3) ili "kasnu" grupu (N = 200; NIHSS 11,1 ± 6,8) (p <0,0001), ali je ishod lečenja bio bolji (p <0,0001). Infarkt kompletne prednje cirkulacije značio je lošiju NIHSS ocenu kao kod infarkta delimičnog teritorija prednje cirkulacije ili kod lakunarnog infarkta (p <0,0001; p <0,0001, respektivno), a također i lošiji rezultat ishoda lečenja (p <0,0001).

Zaključak: U zadnjih godina urađen je napredak reperfuzijske terapije. Takav rezultat je bio i u nšoj studiji, ali se može podrazumjeti, da postoje još mogučnosti za pobolšanje lečenja te katastrofalne bolesti.

Ključne reči: moždani udar, ultra-rana terapija, reperfuzija, isključivajuči kriteriji, ishod