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OUTCOME OF INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE
IN PATIENTS WITH AND WITHOUT ATRIAL FIBRILLATION

ISHOD NAKON AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA LEČENOG INTRAVENSKOM
TROMBOLIZOM KOD PACIJENATA SA ATRIJALNOM FIBRILACIJOM I BEZ NJE

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Summary
Introduction. Atrial fibrillation is associated with an increased risk of ischemic stroke. The benefit of intravenous thrombolysis in patients with acute ischemic stroke and atrial fibrillation is still unclear. The aim of the study was to assess and compare the effects of intravenous thrombolysis in stroke patients with and without atrial fibrillation.

Material and Methods. We analyzed stroke patients who were treated with intravenous thrombolysis. Patients were divided into two groups according to the presence of atrial fibrillation. Demographic, clinical and radiological characteristics of patients were compared between the two groups. The treatment efficacy was evaluated in relation to the improvement of neurological status after 24 hours, and functional recovery after three months. Binary logistic regression was used to evaluate predictors of outcome. Results. From a total of 188 patients, 39.4% presented with atrial fibrillation. Patients with atrial fibrillation were older (69.4 vs. 62.6 years; p < 0.0001), with female predominance (43.2% vs. 28.9%, p = 0.04) and had clinically more severe stroke (National Institutes of Health Stroke Scale, score on admission 15.4 vs. 12.1; p = 0.0001). Significantly more patients without atrial fibrillation (61.4% vs. 43.2%, p = 0.01) had a favorable clinical outcome at three months after stroke. Nevertheless, atrial fibrillation was not an independent predictor of poor outcome at three months after stroke (p = 0.66). Conclusion. Acute ischemic stroke patients, with atrial fibrillation, treated with intravenous thrombolysis, had worse outcomes than patients without atrial fibrillation did. However, it is mainly due to older age and a more severe stroke in patients with atrial fibrillation.

Key words: Stroke; Brain Ischemia; Thrombolytic Therapy; Atrial Fibrillation; Treatment Outcome; Neurologic Manifestations; Fibrinolytic Agents; Tissue Plasminogen Activator; Severity of Illness Index; Risk Factors

Sažetak

Materijal i metode. Analizirani su pacijenti koji su lečeni intravenskom trombolizom zbog akutnog ishemijskog moždanog udara. Pacijenti su podeljeni u dve grupe u odnosu na prisustvo atrijalne fibrilacije. Demografske, kliničke i radiološke karakteristike pacijenata poredene su između dve grupe. Efikasnost je procenjivana u odnosu na poboljšanje neurološkog nalaza nakon 24 sata i funkcionalni oporavak nakon tri mесеca od moždanog udara. Binarnom logističkom regresijom određeni su prediktori ishoda.

Rezultati. Od ukupno 188 pacijenata, njih 39.4% imalo je atrijalnu fibrilaciju. Ovi pacijenti su bili stariji (69,4 naspram 62,6 godina, p < 0,0001), češće ženskog pola (43,2% naspram 28,9%, p = 0,04) i imali su klinički teži moždani udar (Nacionalni vodič za skor kod akutnog ishemijskog moždanog udara na prijemu 15,4 naspram 12,1, p = 0,0001) u odnosu na pacijente bez atrijalne fibrilacije. Dobar klinički ishod nakon tri meseca imalo je značajno više pacijenata bez atrijalne fibrilacije (61,4% naspram 43,2%, p = 0,01). Ipak atrijalna fibrilacija nije bila nezavisni prediktor lošeg ishoda (p =0,66).

Zaključak. Pacijenti sa ishemijskim moždanim udarom i atrijalnom fibrilacijom lečeni intravenskom trombolizom imaju lošiji ishod u odnosu na one bez atrijalne fibrilacije, ali je to prevashodno posledica starijeg životnog doba i težeg moždanog udara ovih pacijenata.

Ključne reči: moždan udar; moždana ishemia; trombolitička terapija; atrijalna fibrilacija; ishod lečenja; neurološke manifestacije; fibrinolitički agensi; aktivator tkivnog plazminogena; indeks težine bolesti; faktori rizika

Introduction. Atrial fibrillation (AF) is the most common heart rhythm disorder, occurring in 2% of the general population, and in 20% of persons older than 80 years [1]. Its incidence increases with age, and doubles in each decade of life after the age of 55 years. Due to the extremely high embolic potential,
underwent brain computed tomography (CT) in or

with the size of cerebral infarction [10].

for assessment of severity of stroke and correlates

(NIHSS) score was determined. This score is used

their National Institute of Health Stroke Scale

all patients were examined by a neurologist and

Clinical Center of Vojvodina in Novi Sad, Serbia.

patients with AIS who were treated with IVT at the

compared to AIS patients without AF.

quite controversial.

and safety of IVT in AIS patients with AF are still

sults [9]. Even today, the attitudes on the efficacy

predictor of a poor outcome in AIS patients treated

stroke [7]. Some authors have shown that AF is a

ment efficacy in regard to the type and etiology of

hours after the onset of symptoms [7]. However,

[5, 6], improving the outcome if applied within 4.5

ment of patients with acute ischemic stroke (AIS)

with recombinant tissue plasminogen activator

AF was the only approved therapy for the treat

Embolic stroke clinically manifests as a severe neu

AF is the most important cardiac risk for the de

the development of cardio-embolic stroke [2–4]. The cardio

stroke clinically manifests as a severe neuro

go logical deficit, and radiologically as a territorial

non-lacunar) infarction.

Until recently, intravenous thrombolysis (IVT)

of these arrhythmias on at least one electrocardio

This cross-sectional study analyzed the data of

patients with AIS who were treated with IVT at the

Clinical Center of Vojvodina in Novi Sad, Serbia.

The data were prospectively collected in the period

from November 2008 to April 2015. On admission,

all patients were examined by a neurologist and

their National Institute of Health Stroke Scale

(NIHSS) score was determined. This score is used

for assessment of severity of stroke and correlates

with the size of cerebral infarction [10]. All patients

underwent brain computed tomography (CT) in or-

der to exclude intracranial hemorrhage (ICH). The Alberta Stroke Program Early CT (ASPECT) score, that reflects the size of the cerebral ischemia [11], presence of a hyperdense artery sign and leukoma-

tors, were assessed by a radiologist. The following

data were also recorded: age, gender, risk fac-
tors (arterial hypertension, diabetes mellitus, hy-

perlipidemia, and smoking), glucose level on admis-

sion, previous use of antiplatelet and statin therapy,

and the symptom onset-to-treatment time (OTT).

Twenty-four hours following the IVT treatment,

the NIHSS score was determined again and brain CT

was repeated. Neurological improvement showed a

reduction in the NIHSS score of ≥ 50% compared

with the NIHSS score on admission, or as NIHSS score ≤ 3. Based on repeated CT findings, we determined the

type of cerebral infarction, and possible presence of

hemorrhagic transformation (HT). Development of

symptomatic intracranial hemorrhage (sICH) in the early stages of AIS (within seven days) was assessed

according to the European Cooperative Acute Stroke

Study III (ECASS III) criteria [12]. The type of brain

infarction was determined in accordance with the Ox-

fordshire Community Stroke Project (OCSP) classifi-

cation [13]. According to OCSP classification, there

are four types of cerebral infarction: total anterior cir-

culation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction

(POCI) and lacunar infarction (LACI). All patients

underwent neurovascular status evaluation with ultra-

sound (carotid duplex ultrasound, transcranial Dop-

pler) and/or CT or magnetic resonance (MR) angiog-

raphy examinations. Functional outcome was assessed

after three months by the modified Rankin score

(mRS) and favorable outcome was defined as mRS 0

− 2 and unfavorable as mRS 3 − 6.

The presence of AF was defined as an evidence

of these arrhythmias on at least one electrocardio-

graphic (ECG) recording, obtained either from med-

ical history or during hospitalization. After admis-

sion, patients were monitored with ECG for at least

72 hours and, if necessary, had additional recordings.

Patient were divided into two groups, according to

the presence or absence of AF, and they were com-

pared with regard to demographic, clinical and

radiological characteristics, outcomes and adverse

events. The two-sample student t-test was used for

comparisons of parametric variables and chi-square

(χ²) test or Fisher’s exact test for categorical vari-

ables. A p value of less than 0.05 (p < 0.05) was re-

garded statistically significant. Binary logistic re-

gression analysis was used to evaluate predictors of

neurological improvement, favorable outcome and

HT. The variables which were analyzed included age,

gender, baseline NIHSS score, OTT, glucose level on admission, presence of AF and other risk factors (arterial hypertension, diabetes mellitus, hyperlipidemia, smoking). Odds ratio (OR) was cal-

culated with 95% confidence interval (95% CI).

Data were analyzed with the SPSS/PC Win package

version 20.0. The study was approved by the Ethical

Board of the Clinical Center of Vojvodina.

Material and Methods

This cross-sectional study analyzed the data of

patients with AIS who were treated with IVT at the

Clinical Center of Vojvodina in Novi Sad, Serbia.

The data were prospectively collected in the period

from November 2008 to April 2015. On admission,

all patients were examined by a neurologist and

their National Institute of Health Stroke Scale

(NIHSS) score was determined. This score is used

for assessment of severity of stroke and correlates

with the size of cerebral infarction [10]. All patients

underwent brain computed tomography (CT) in or-

Abbreviations

AF – atrial fibrillation
IVT – intravenous thrombolysis
rtPA – recombinant tissue plasminogen activator
AIS – acute ischemic stroke
NIHSS – national institutes of health stroke scale
ICH – intracranial hemorrhage
CT – computed tomography
ASPECT – Alberta stroke program early computed tomography
OTT – onset-to-treatment time
HT – hemorrhagic transformation
sICH – symptomatic intracranial hemorrhage
ECASS III – European cooperative acute stroke study III
OCS – Oxfordshire community stroke project
TACI – total anterior circulation infarction
PACI – partial anterior circulation infarction
POCI – posterior circulation infarction
LACI – lacunar infarction
MR – magnetic resonance
mRS – modified Rankin score
ECG – electrocardiography
OR – odds ratio
CI – confidence interval
The study included a total of 188 patients. Among them, 74 patients (39.4%) had AF and 114 patients (60.6%) were without AF. Demographic, clinical and radiological characteristics, as well as stroke subtypes of the two groups are shown in Table 1. Patients with AF were older (69.4 vs. 62.6, p<0.0001) and there were more female patients (43.2% vs. 28.9%, p=0.04). In regard to risk factors, only smoking was significantly more frequent among patients without AF (35.09% vs. 17.57%; p=0.009). Time from symptom onset to thrombolytic treatment (OTT) did not differ significantly between the two groups of patients. Regarding other clinically significant characteristics, only previous use of antiplatelet therapy was significantly more frequent in patients with AF (48.65% vs. 28.07%, p=0.004). On average, patients with AF had a more severe stroke, i.e., a higher NIHSS score on admission (15.0 vs. 12.1, p=0.0001). The average baseline ASPECT score on brain CT did not differ significantly between the two groups of patients. In patients with AF, the most frequent were total and partial anterior circulation infarctions (TACI 47.3%; PACI 45.9%), whereas lacunar infarctions were significantly more frequent in patients without AF (LACI type 21.9% vs. 2.7%).

The outcome at 90 days post treatment is shown in Graph 1. Approximately half of the patients without AF had a mRS score of 0 or 1 (mRS 0 – 23.1 %, mRS 1 – 25.4%), whereas majority of patients with AF had mRS 6 (29.7%).

Comparison of outcomes and complications after application of IVT is shown in Table 2. Neurological improvement at 24 hours was more frequent in patients without AF (42.1% vs. 31.1%), although without a statistical significance. A good outcome at three months (mRS 0 - 2) was significantly more frequent in patients without AF (61.4% vs. 43.2%; p=0.01). Furthermore, patients with AF commonly had a significant hemorrhagic transformation (29.7% vs. 10.5%; p=0.0008), as well as symptomatic intra-cerebral hemorrhage (9.5% vs. 0%);

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Group with AF (n = 74)/Grupa sa AF (n = 74)</th>
<th>Group without AF (n = 114)/Grupa bez AF (n = 114)</th>
<th>p (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic características</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years/Starost, godine</td>
<td>69.4±9.2</td>
<td>62.6±10.2</td>
</tr>
<tr>
<td>Gender, male/Pol, muški</td>
<td>42 (56.8%)</td>
<td>81 (71.1%)</td>
</tr>
<tr>
<td>Risk factors/Faktori rizika</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension/Arterijska hipertenzija</td>
<td>68 (91.9%)</td>
<td>100 (87.7%)</td>
</tr>
<tr>
<td>Diabetes/Dijabetes</td>
<td>10 (13.5%)</td>
<td>23 (20.2%)</td>
</tr>
<tr>
<td>Hyperlipoproteinemia/Hiperlipoproteinemija</td>
<td>38 (51.4%)</td>
<td>64 (56.1%)</td>
</tr>
<tr>
<td>Smoking/Pušenje</td>
<td>13 (17.6%)</td>
<td>40 (35.1%)</td>
</tr>
<tr>
<td>Current stroke/Aktuelno stanje</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score on admission/NIHSS skor na prijemu</td>
<td>15.0±4.1</td>
<td>12.1±4.5</td>
</tr>
<tr>
<td>Glycemia on admission/Glikemija na prijemu, mmol/l</td>
<td>7.7±2.8</td>
<td>8.1±3.7</td>
</tr>
<tr>
<td>Previous antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prethodna antiagregaciona terapija</td>
<td>36 (48.7%)</td>
<td>32 (28.1%)</td>
</tr>
<tr>
<td>Previous statin therapy/Prethodna terapija statinima</td>
<td>8 (10.8%)</td>
<td>8 (7.0%)</td>
</tr>
<tr>
<td>ASPECT score/ASPECT skor</td>
<td>9.2±1.1</td>
<td>9.2±1.1</td>
</tr>
<tr>
<td>Leukoaraiosis/Leukoarajoza</td>
<td>12 (16.2%)</td>
<td>17 (14.9%)</td>
</tr>
<tr>
<td>OTT on admission, min./OTT na prijemu, min.</td>
<td>164.9±72.9</td>
<td>167.5±52.7</td>
</tr>
<tr>
<td>Stroke subtype/Tip infarkta mozga</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>35 (47.3%)</td>
<td>22 (19.3%)</td>
</tr>
<tr>
<td>PACI</td>
<td>34 (45.9%)</td>
<td>51 (44.5%)</td>
</tr>
<tr>
<td>LACI</td>
<td>2 (2.7%)</td>
<td>25 (21.9%)</td>
</tr>
<tr>
<td>POCI</td>
<td>3 (4.1%)</td>
<td>15 (13.2%)</td>
</tr>
</tbody>
</table>

Legend: AF – Atrial fibrillation; NIHSS score - The National Institutes of Health Stroke Scale; MAP-Mean Arterial Pressure; ASPECT score - Alberta Stroke Program Early CT score; OTT-Onset to-treatment time; TACI - total anterior circulation infarction; PACI - partial anterior circulation infarction; LACI – lacunar infarction; POCI - posterior circulation infarction

Legenda: AF – atrijalna fibrilacija; NIHSS skor – Nacionalni vodič za skor kod akutnog ishemijskog moždanog udara; MAP – srednji arterijski pritisak; ASPECT skor – Alberta program moždanog udara – rani rezultat kompjuterizovane tomografije; OTT – vreme početka tretmana; TACI – totalni anteriorni cirkulatorni infarkt; PACI – delimični anteriorni cirkulatorni infarkt; LACI – lakunarni infarkt; POCI – infarkt posteriorne cirkulacije
Lethal outcome (mRS 6) within 90 days post treatment was also more frequent in patients with AF (31.08% vs. 7.89%; p<0.0001). The binary logistic regression analysis did not show AF to be an independent predictor of poor (p=0.66) or lethal outcome (p=0.17) at three months post IVT for AIS. In our study, predictors of an unfavorable outcome (mRS 3 - 6) at three months were: older age (p<0.0001; OR 1.08, 95% CI 1.03-1.13), a higher NIHSS score on admission (p<0.0001; OR 1.31, 95% CI 1.19-1.45), a lower ASPECT score on admission (p=0.013; OR 0.64, 95% CI 0.45-0.91) and higher glucose levels on admission (p<0.0001; OR 1.28, 95% CI 1.13-1.45). Predictors of lethal outcome (mRS 6) at three months were older age (p<0.0001; OR 1.15, 95% CI 1.08-1.23), a higher NIHSS score on admission (p<0.0001; OR 1.35, 95% CI 1.18-1.54) and presence of diabetes (p=0.003; OR 5.95, 95% CI 1.86-18.97). In addition, AF was not independently associated with neurological improvements at 24 hours (p=0.38). Predictors of neurological improvement at 24 hours were a lower NIHSS score on admission (p=0.003; OR 0.89, 95% CI 0.83-0.96), a higher ASPECT score (p=0.027; OR 1.44, 95% CI 1.04-1.99) and absence of diabetes (p=0.008; OR 0.27, 95% CI 0.1-0.7). However, AF was independently associated with development of hemorrhagic transformation (p<0.0001; OR 4.44, 95% CI 1.92 - 10.27).

Discussion

Our study showed that AIS patients with AF treated with IVT had a worse outcome than patients without AF. Patients with AF were older (7 years, on average) and clinically had a more severe stroke (NIHSS score higher by around 3 points) compared to patients without AF. Higher NIHSS score in patients with AF was a result of larger cerebral infarction in patients with AF. Lacunar infarction was found only in 2.7% of patients (two patients) with AF, versus 21.9% of patients without AF. Development of HT and sICH was significantly more frequent in patients with AF. Similar results have been reported in some other studies [8, 14, 15]. In a Japanese study of 85 patients, including 51.8% of patients with AF, neurological improvement at seven days post IVT was considerably lower in patients with AF (31.8% vs. 60%; p = 0.007) [8]. In addition, a favorable outcome (mRS 0 - 2) at three months was also recorded in significantly fewer patients with AF compared to those without AF (15.9% vs. 46.3%, p = 0.002). Another study included 734 patients, of whom 21.1% had AF, a poor outcome (mRS 3-6) was reported in 52.3% of patients with AF and in 35.2% of patients without AF (p < 0.001) [14]. The mortality at 3 months following stroke was 21.9% in the group with AF and 9% in the group without AF. Correspondingly, we found a higher percentage of poor outcome and a higher mortality rate in the group of patients with AF within three months following IVT. In a recent study which examined predictors of early neurological improvement, AF was independently associated with the absence of the major neurological improvement 24 h after IVT [15]. In our study, early neurological im-

### Table 2. Outcome of intravenous thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Group with AF</th>
<th>Group without AF</th>
<th>p (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological improvement at 24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurološko poboljšanje nakon 24 h</td>
<td>23 (31.1%)</td>
<td>48 (42.1%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Good outcome (mRS 0-2)/Povoljan ishod (mRS 0-2)</td>
<td>32 (43.2%)</td>
<td>70 (61.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemorrhagic transformation/Hemoragijska transformacija</td>
<td>22 (29.7%)</td>
<td>12 (10.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICH/Simptomatska intracerebralna hemoragija</td>
<td>7 (9.5%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS 6/Modifikovana Rankinova skala</td>
<td>23 (31.1%)</td>
<td>9 (7.9%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Legend: AF – atrial fibrillation, mRS – modified Rankin Scale; sICH – symptomatic intracerebral hemorrhage.

Legenda: AF – atrijalna fibrilacija, mRS – modifikovana Rankinova skala; sICH – simptomatska intracerebralna hemoragija.
provement was more common in patients without AF, but it was not significant.

In the above-mentioned studies [8, 14], patients with AF were also older and had a higher NIHSS score and more frequent HT, compared to patients without AF, which is consistent with our findings. All of these characteristics (older age, higher NIHSS score, common HT) are typical of ischemic stroke caused by AF. As numerous studies have shown that age and the NIHSS score on admission are the most important predictors of outcome, independent of risk factors and the type of ischemic stroke, it is expected that patients with AF would have a worse outcome because of these characteristics [8, 14]. Thus, AF was not an independent predictor of poor outcome, unlike older age and a higher NIHSS score. Similarly, in our study, AF was also not an independent predictor of poor outcome, as opposed to older age, higher NIHSS score and lower ASPECT score on admission, as well as higher blood glucose levels on admission. Moreover, some studies have shown that among patients with severe clinical ischemic stroke (NIHSS score ≥ 10) AF was associated with a better outcome [9]. A study by Shang Feng et al. analyzed the outcomes in subgroups of patients, depending on their NIHSS scores (scores above and below 10). In the group of patients with a NIHSS score over 10, a favorable outcome after three months was seen in 31% of patients with AF, and 8% of patients without AF (p = 0.005), and mortality rates were 8% among cases with AF and 17% among patients without AF (p = 0.168). This study concluded that, if NIHSS score on admission was above 10, patients with AF had a better outcome after IVT than those without AF. However, the most reliable results on the efficacy of IVT in AIS patients with AF were obtained from studies that included only patients with AF and compared those who were treated with IVT and those not treated with IVT [16]. The conclusion of those studies was that patients treated with IVT had a much better outcome compared to those who were not treated with IVT. Similar results were obtained in a multicenter study in China [17]. In this study, administration of IVT was an independent predictor of a favorable outcome (OR 5.73, 95% CI 2.4 - 13.7; p < 0.001) in patients with AIS and AF.

From the pathophysiological point of view, the success of IVT treatment in ischemic stroke caused by AF should be the most conclusive. In most cases, cardio-embolic stroke is caused by the red thrombus, which essentially consists of erythrocytes and fibrin [18, 19]. In cases with red thrombus, IVT is much more effective, as demonstrated by animal studies [20]. This finding is supported by clinical studies that have demonstrated successful recanalization after the IVT therapy in ischemic stroke caused by AF [21, 22]. The controversial results about the efficacy of IVT in patients with AIS and AF can be explained by additional factors that are often not considered when assessing the outcome at three months after IVT. Namely, AF is associated mainly with chronic heart failure [23, 24], which often causes reduced premorbid functionality (premorbid mRS ≥ 1) and a reduced ability for maximum mobility during rehabilitation treatment. Given that patients with AF are older and have a clinically more severe ischemic stroke, they often, even after successful recanalization and initial neurological improvement, have persisting neurological deficits requiring extended hospitalization [24], which itself carries the risk of further complications and after three months, patients do not reach mRS ≤ 2, i.e., a favorable outcome.

Limitations of our study were the small number of patients with AF. Secondly, the lack of a control group of AIS patients with AF who were not treated with IVT, whose outcome would be compared with thrombolysis patients. Also, the study included only patients with the same type of cerebral infarction (TACI, PACI or POCI), and if it included patients with different types, it would have given more reliable and perhaps different results. However, this would require more patients, and it should be a topic for future researches.

Conclusion

Patients with acute ischemic stroke and atrial fibrillation, treated with intravenous thrombolysis, had a worse outcome compared with patients without atrial fibrillation. However, patients with atrial fibrillation were older, had more severe neurological deficits, larger cerebral infarction and more commonly developed hemorrhagic transformation, which were likely the main reasons for their poorer treatment outcome.

References


