Patients with Acute Lacunar Infarction Have Benefit from Intravenous Thrombolysis

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Introduction: Usefulness of intravenous thrombolysis in patients with acute lacunar cerebral infarction is questionable. The aim of this study was to evaluate the efficacy and safety of intravenous thrombolysis in patients with lacunar infarction in comparison with patients with nonlacunar infarction as well as with patients with lacunar infarction who were not treated with intravenous thrombolysis. *Materials and methods*: In the first part of the study, among patients with acute ischemic stroke treated with intravenous thrombolysis, characteristics and outcomes of 46 patients with lacunar and 221 patients with nonlacunar infarction were compared. In the second part, 46 patients with lacunar infarction treated with intravenous thrombolysis were compared with 45 lacunar infarction patients who were not treated with intravenous thrombolysis. *Results*: Patients with lacunar infarction had a lower National Institutes of Health Stroke Scale score (9.2 versus 13.9, $P < .001$), a greater Alberta Stroke Program Early computed tomography (CT) score (9.7 versus 9.2, $P = .002$), a lower prevalence of atrial fibrillation (6.5% versus 41.2%, $P < .001$), and significantly more frequently an excellent outcome after 3 months (76.1% versus 36.2%, $P < .001$) compared with patients with nonlacunar infarction. Among patients with lacunar infarction, an excellent outcome at discharge was significantly more frequent in the intravenous thrombolysis group (41.3% versus 15.6%, $P = .01$), and the length of hospitalization was significantly shorter (9.5 days versus 14.3 days, $P = .002$). There was no hemorrhagic transformation among patients with lacunar infarction treated with intravenous thrombolysis. *Conclusion*: Intravenous thrombolysis has proven to be effective and safe in patients with lacunar infarction and should always be applied if there are no absolute contraindications.

Key Words: Acute ischemic stroke—lacunar infarction—intravenous thrombolysis—outcome—complications

Introduction

In the previous several years, the expert's discussions in the field of the treatment of acute ischemic stroke (AIS) is mainly about mechanical thrombectomy in patients with a large vessel occlusion. Moreover, serious expert debates were conducted as to whether the intravenous thrombolysis (IVT) is "dead." In the shadow of this, the dilemmas about the treatment of acute lacunar infarction have somehow remained neglected. Lacunar cerebral infarction (LACI) accounts for about 25% of all AIS.[1] These are small

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infarctions (3-15 mm), which occur due to small vessel disease.[2,3] Most patients have a good recovery, which is why LACI are considered benign vascular lesion. However, the long-term prognosis is unfavorable, with an increased risk of recurrent stroke, other cardiovascular events, death, as well as of developing cognitive decline and dementia.[4] A key step in the treatment of all types of AIS continues to be the intravenous administration of the recombinant tissue plasminogen activator.[5] The effectiveness of the treatment depends mainly on the rate and grade of recanalization of the previously occluded blood vessel.[6] However, in some patients with AIS, such as patients with LACI, standard radiological methods (computed tomography or magnetic resonance angiography) cannot prove vascular occlusion and the presence of thrombus at the time of the onset of symptoms. In the absence of a substrate which thrombolytic therapy may potentially affect, there is the question of the efficacy of the treatment in patients with LACI.[7] On the other hand, IVT can potentially be harmful, and since most patients with LACI have a mild clinical picture and a good recovery, also the question about safety of this therapy is raised.[8] The final dilemma is related to the economic justification of giving this still expensive treatment for developing countries to patients with a small neurological deficit, who generally recover well and fully.[7]

The aim of this paper was to assess effectiveness and safety of IVT in patients with LACI, by comparing them with patients treated with IVT for nonlacunar infarction (non-LACI) and with patients with LACI who were not treated with IVT.

Materials and Methods

The research was conducted as an observational study of patients who were treated for AIS in the Clinical Center (CC) of Vojvodina in Novi Sad in the period from January 2009 to December 2016 and whose data were collected prospectively. In the first part of the study, 267 AIS patients who were treated with IVT in the CC Vojvodina in the mentioned period were included, and their data were collected within the national Serbian Experience with Thrombolysis in Ischemic Stroke registry.[9] In the second part of the study, additional 45 consecutive patients with LACI who were hospitalized during 2016, but were not treated with IVT, were included. All patients were treated according to the guideline's recommendations for the treatment of AIS.[5] Patients with incomplete data or those with unavailable data about outcome at 3 months were not included. The study was approved by the Ethics Committee of the CC Vojvodina.

On admission, all patients were examined by a neurology specialist. Data on risk factors (arterial hypertension, diabetes, hypercholesterolemia, atrial fibrillation, smoking, and chronic cardiomyopathy) and prior use of antiplatelet therapy and/or statins were obtained from medical history. Clinical severity of stroke was assessed by neurological examination on admission and the use of National Institutes of Health Stroke Scale (NIHSS). Based on the findings of the initial head CT, the Alberta Stroke Program Early CT (ASPECT) score,[10] the hyperdense middle cerebral artery sign and the presence of leukoaraiosis were determined. In patients treated with IVT, the onset to treatment time was recorded. Laboratory blood analysis was performed on admission and/or within the first 24 hours after admission to hospital treatment. After 24 hours of intravenous thrombolytic therapy, the severity of neurological symptomatology was again evaluated using the NIHSS scale. Early neurological improvement was defined as a NIHSS score of 0-3 or a reduction in a NIHSS score by 40% in relation to the admission score after 24 hours.[11] Repeat head CT was performed in the period from 24 to 48 hours after admission. Based on the findings, the type of brain infarction was determined according to recommendations of the OCSP classification,[12] and the occurrence of hemorrhagic transformation (HT) or intracerebral hemorrhage (ICH) was registered. Symptomatic ICH was defined according to the European Cooperative Acute Stroke Study III criteria.[13] At discharge, the duration of hospitalization, the NIHSS score, and the degree of functional disability were recorded, and functional disability was determined on the basis of the modified Rankin scale (mRS). Treatment outcome was evaluated at 3 months using the mRS. An excellent functional outcome was defined as mRS 0-1 (representing the absence of a deficit or minimum disability), a good functional outcome as mRS 0-2 (representing functional independence), while mRS 6 represented lethal outcome.

In the first part of the study, patients treated with IVT were analyzed. Patients were divided into 2 groups: a group of patients with LACI and a group of patients with non-LACI. Demographic, clinical and radiological characteristics, outcome at 3 months, and occurrence of complications were compared between the 2 groups of patients. Then, binary logistic regression was employed to analyze the effect of the type of brain infarction on the outcome after IVT. The statistical models included: demographic characteristics (age and sex) of patients, risk factors (hypertension, diabetes, hypercholesterolemia, smoking, and atrial fibrillation), clinical characteristics (NIHSS score and glycaemia), radiological characteristics (ASPECT and leukoaraiosis) on admission, the onset to treatment time, and the type of ischemic stroke (IS) (LACI and non-LACI).

In the second part of the study, the group of patients with LACI treated with IVT (LACI IVT) was compared with another group of patients with LACI who were not treated with IVT (LACI no-IVT). In this part of the study, comparison was performed with regard to demographic and clinical characteristics, occurrence of complications, the outcome at discharge, and the length of hospitalization. Finally, the binary logistic regression was used to analyze the effect of IVT in these patients on the outcome

(mRS 0-1). The statistical model included: demographic characteristics of patients (age and sex), risk factors (hypertension, diabetes, smoking, and atrial fibrillation), clinical (NIHSS score and glycaemia) and radiological characteristics (leukoaraiosis) on admission, and the application of IVT.

Statistical data analysis included methods of descriptive statistics. To describe the distributions of measurement variables, the arithmetic mean and standard deviation were used, while the distributions of nominal (categorical) variables were described using tables of frequency. To determine the difference in the arithmetic means between the 2 groups, the *t* test was used, while the difference in the distributions of the 2 groups with nominal variables was determined using the Pearson's chi-square (χ^2) test and the Fisher's exact test.

Test values with probability of $P < .05$ were considered statistically significant, while $P < .001$ was considered statistically highly significant. The binary logistic regression was used to determine the association between the set of predictors and the outcome as the defined criterion, and the obtained results were presented as odds ratio (OR) with 95% confidence interval (CI) and *P* value. Statistical data processing was done using the statistical software Statistical Package for the Social Sciences, version 23.

Results

In the period from 2009 to 2016, a total of 8109 patients were treated at the CC Vojvodina due to AIS, of whom 1706 were with LACI (21.04%). Only 3.4% (274 patients) of them were treated with IVT.

Evaluation of Efficacy and Safety of IVT in LACI Patients Compared with Non-LACI Patients

In the first part of the study, out of a total of 274 patients with AIS treated with IVT, 267 were included (7 patients were excluded due to incomplete data). The patients were divided into 2 groups: a group with LACI (n = 46) and a group of patients with non-LACI (n = 221). Differences in demographic, clinical and radiological characteristics are shown in Table 1. Among the risk factors, diabetes was significantly more prevalent in the LACI group (32.6% versus 17.2%, $P = .03$), while atrial fibrillation was significantly more frequent in the non-LACI group (6.5% versus 41.2%, $P < .001$). Patients with LACI had significantly milder neurological deficit on admission (admission NIHSS 9.2 ± 2.7 versus 13.9 ± 4.7, $P < .001$) and a higher ASPECT score (9.7 ± .7 versus 9.2 ± 1.2, $P = .002$). The outcome and occurrence of complications in patients are shown in Table 2. Neurological improvement after 24 hours was recorded in 58.7% of patients with LACI versus 35.7% of non-LACI patients. There were no cases of HT in the LACI group, while lethal outcome (mRS 6) within the 3-month follow-up period was observed in only 1 patient with LACI (2.2%).

Predictors of neurological improvement 24 hours after IVT administration were a lower NIHSS score on admission ($P = .04$, OR = .88, 95% CI = .83-.93), a higher ASPECT score ($P = .01$, OR = 1.43, 95% CI = 1.08-1.90), and the absence of leukoaraiosis on CT ($P = .04$, OR = .43, 95% CI .20-.96), but not the lacunar type of infarction ($P = .41$). The observed predictors of favorable outcome (mRS 0-2) at 3 months were a younger age ($P < .001$, OR = .94, 95% CI = .91-.97), a lower NIHSS score on admission ($P < .001$, OR = .77, 95% CI = .72-.83), and lower glucose levels on admission ($P < .001$, OR = .85, 95% CI = .79-.93), but not the LACI ($P = .11$). Predictors of HT were a higher NIHSS score on admission ($P = .03$, OR = 1.10, 95% CI = 1.01-1.19) and the presence of atrial fibrillation ($P = .02$, OR = 2.34, 95% CI = 1.16-4.71).

Evaluation of Efficacy and Safety of IVT in LACI Patients in Comparison with LACI Patients not Treated with IVT

In the second part of the study, a group of LACI patients treated with IVT (LACI IVT, n = 46) were compared with a group of LACI patients who were not treated with IVT (LACI no-IVT, n = 45). Demographic, clinical and radiological characteristics of patients are shown in Table 3. Patients treated with IVT more frequently had a more severe neurological deficit on admission (NIHSS 9.2 ± 2.7 versus 5.8 ± 2.9, $P < .001$), while leukoaraiosis was more prevalent in the LACI no-IVT group (19.6% versus 40.0%, $P = .04$). The differences in the outcome at discharge between LACI IVT and LACI no-IVT are shown in Table 4. An excellent outcome at discharge (mRS 0-1) was recorded in 41.3% of patients treated with IVT and in 15.6% of patients not treated with IVT ($P = .01$). The length of hospitalization was shorter in patients treated with IVT (9.5 days versus 14.3 days, $P = .002$).

Predictors of an excellent outcome were the absence of leukoaraiosis ($P = .01$, OR .07, 95% CI 0.01-0.54), the absence of diabetes as a risk factor ($P = .02$, OR = .23, 95% CI= 0.06-0.82), and administration of IVT ($P = .03$, OR = 3.47, 95% CI = 1.15-10.44).

Discussion

The results of the first part of our study showed that patients with LACI had significantly more frequently a favorable outcome after IVT, compared with patients with non-LACI, and that there were no hemorrhagic complications among them. In the second part of our results, it was shown that patients with LACI had a better outcome if they were treated with IVT than if they were not.

The efficacy of IVT in AIS has been clearly proven and it has been demonstrated that all subtypes of stroke benefit from thrombolysis, including LACI.[14] However, several studies examined differences in outcomes after IVT in relation to subtype of AIS.[15-18] The studies showed that patients with LACI more frequently had a favorable

Table 1. *Differences in baseline characteristics between LACI and non-LACI patients*

	LACI (n = 46)	Non-LACI (n = 221)	*P*
Demographic characteristics			
Age (years)	63.2 ± 10.3	66.0 ± 11.0	.11
Sex (male)	34 (73.9%)	147 (66.5%)	.39
Risk factors			
Arterial hypertension	43 (93.5%)	195 (88.2%)	.44
Diabetes	15 (32.6%)	38 (17.2%)	**.03**
Hypercholesterolemia	28 (60.9%)	114 (51.6%)	.26
Atrial fibrillation	3 (6.5%)	91 (41.2%)	<**.001**
Smoking	21 (45.7%)	66 (29.9%)	.06
Chronic cardiomyopathy	3 (6.5%)	36 (16.3%)	.11
Current stroke			
NIHSS score on admission	9.2 ± 2.7	13.9 ± 4.7	<**.001**
Glycemia on admission (mmol/l)	8.5 ± 4.1	8.1 ± 3.4	.53
MAP on admission (mmHg)	112.2 ± 14.0	110.0 ± 21.6	.50
ASPECT score	9.7 ± 0.7	9.2 ± 1.2	**.002**
Leukoaraiosis	9 (19.6%)	32 (14.5%)	.37
Other clinical characteristics			
OTT (min.)	186.4 ± 47.2	162.4 ± 59.5	**.01**
Prior use of antiplatelet therapy	13 (28.3%)	78 (35.3%)	.40
Prior use of statins	4 (8.7%)	21 (9.5%)	1.00

Abbreviations: ASPECT, Alberta Stroke Program Early CT; LACI, lacunar stroke; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; OTT, onset to treatment time.

outcome and less frequently hemorrhagic complications or lethal outcome at 3 months, compared to other stroke subtypes.[15-19] However after correction for other factors (age, sex, and NIHSS score on admission), this association with a favorable outcome in some studies was not significant.[17,19] In our study, it was shown that patients with LACI more frequently had both a better neurological recovery after 24 hours and a better outcome at 3 months compared to patients with non-LACI. This finding is not surprising having in mind the definition of this stroke subtype. However, LACI did not prove to be an independent predictor of a favorable outcome. The stronger predictors of a good outcome were a lower NIHSS score and a higher ASPECT score on admission. These results should not be confusing because the patients with the LACI stroke subtype have the ASPECT score 10 and mainly a mild neurological deficit, i.e., a low NIHSS score. It was also expected that LACI patients would have a better outcome compared to patients with non-LACI, given the size of the threatening brain infarction, i.e., the size of potentially occluded blood vessel.[2,4] These are the real causes of the results of generally better outcomes in LACI patients compared with non-LACI patients, and not a better efficacy of IVT in these patients.[2]

A more reliable estimate of IVT efficacy in patients with LACI can be obtained by comparison with patients with this subtype of brain infarction who were not treated with IVT. In the second part of our study, it was shown that patients with LACI had a better outcome if they were treated with IVT and that administration of IVT in patients with LACI increased the odds that a patient would have no or minimal neurological deficit at discharge (mRS 0-1) for approximately 3.5 times (OR = 3.47, $P = .03$).

Table 2. *Differences in outcomes between LACI and non-LACI patients*

	LACI (n = 46)	Non-LACI (n = 221)	*P*
Favorable outcome			
Neurological improvement after 24 h	27 (58.7%)	79 (35.7%)	**.005**
Good outcome (mRS 0-2)	38 (82.6%)	106 (48.0%)	<**.001**
Excellent outcome (mRS 0-1)	35 (76.1%)	80 (36.2%)	<**.001**
mRS	1.2 ± 1.4	2.8 ± 2.1	<**.001**
Complications			
Hemorrhagic transformation	0 (0.0%)	44 (19.9%)	<**.001**
sICH	0 (0.0%)	10 (3.7%)	.22
Lethal outcome (mRS 6)	1 (2.2%)	43 (19.5%)	**.002**

Abbreviations: LACI, lacunar stroke; mRS, modified Rankin scale; sICH, symptomatic intracerebral hemorrhage.

Table 3. *Differences in baseline characteristics between LACI and non-LACI patients*

	LACI (n = 46)	LACI no-IVT (n = 45)	*P*
Demographic characteristics			
Age (years)	63.2 ± 10.3	65.3 ± 9.5	.30
Sex (male)	34 (73.9%)	24 (53.3%)	**.05**
Risk factors			
Arterial hypertension	43 (93.5%)	32 (71.1%)	**01**
Diabetes	15 (32.6%)	15 (33.3%)	1.00
Hypercholesterolemia	28 (60.9%)	9 (20.0%)	**<.001**
Atrial fibrillation	3 (6.5%)	1 (2.2%)	**<.001**
Smoking	21 (45.7%)	16 (35.6%)	.39
Current stroke			
NIHSS score on admission	9.2 ± 2.7	5.8 ± 2.9	**<.001**
Glycemia on admission (mmol/l)	8.5 ± 4.1	7.6 ± 2.8	.24
Leukoaraiosis	9 (19.6%)	18 (40.0%)	**.04**
Other clinical characteristics			
Prior use of antiplatelet therapy	13 (28.3%)	78 (35.3%)	.40
Prior use of statins	4 (11.1%)	9 (20.0%)	.37

Abbreviations: LACI, lacunar stroke; NIHSS, National Institutes of Health Stroke Scale.

Several similar studies also showed that patients with LACI had a better outcome if they received IVT than if they were not.[18,20,21] According to the results of the Canadian Stroke Network Registry,[18] the application of IVT was associated with an improved outcome in LACI patients and increased the odds of a favorable outcome (mRS 0-2) at discharge for about 25% (risk ratio = 1.25; 95% CI = 1.08-1.44). In a study by Austrian Stroke Unit Registry Collaborators,[20] it was demonstrated that among patients with LACI, those who were treated with IVT had a more significant neurological improvement than those who were not (improvement of NIHSS score by 3 points versus 2 in non−IVT-treated patients, $P < .001$), and that LACI patients treated with IVT significantly more frequently showed functional independence (mRS 0-1) at 3 months. Lahoti et al in their study[21] reported that patients with LACI significantly more frequently did not have any neurological deficit at discharge if they were treated with IVT (37% versus 15%, $P = .01$) and that application of IVT in LACI patients increased the chance of full recovery for approximately 8 times (OR = 8.25, 95% CI = 2.37-28.66, $P \leq .001$). The results of the mentioned studies, as well as our results, suggest that IVT is effective in patients with LACI. Moreover, our results also showed that hospitalization in patients with LACI was significantly shorter if they were treated with IVT, which justifies the cost-benefit ratio of this treatment.

Bearing in mind that most patients with LACI have a mild clinical picture, in addition to the efficacy of IVT, safety assessment is also important in the treatment decisions. Among our 46 LACI patients treated with IVT, none of them had intracranial hemorrhagic complications. In contrast, every fifth patient with non-LACI had HT, and 3.7% had a symptomatic ICH after administration of IVT. In other studies, as well, HT occurred significantly more frequently in patients with non-LACI than in patients with LACI.[18,22] HT is most frequently present in patients with non-LACI of anterior circulation,[22] and ICH following treatment with IVT is the least common in patients with LACI.[18] Among LACI patients in the aforementioned study by Eggers,[20] hemorrhagic complications were more frequent in IVT than in non-IVT patients with LACI, but this difference was not statistically significant, and the frequency was very low (1.0% versus 0.2%, NS). In other similar studies that compared patients with LACI treated and not treated with IVT, there were either no significant hemorrhagic complications or they were very rare.[21,23] Such results certainly support the fact that the use of IVT in patients with LACI is safe.

Table 4. *Differences in outcomes between LACI IVT and LACI no-IVT*

	LACI IVT (n = 46)	LACI no-IVT (n = 45)	*P*
Outcome			
NIHSS score at discharge	3.4 ± 3.3	3.6 ± 2.7	.74
mRS at discharge	2.0 ± 1.5	2.9 ± 1.3	**.004**
Excellent outcome at discharge (mRS 0-1)	19 (41.3%)	7 (15.6%)	**.01**
Length of hospitalization (days)	9.5 ± 5.8	14.3 ± 7.9	**.002**
Discharged at home	23 (50.0%)	18 (40.0%)	.40

Abbreviations: LACI, lacunar stroke; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

The main limitation of our study is the small number of LACI IVT patients. In addition, in the second part patients were not randomized in relation to whether they were treated with IVT, but they represented a cohort of consecutive hospitalized patients with LACI during 1 calendar year. The reasons why these patients did not receive IVT were not considered in this study. The time from onset of symptoms to arrival to hospital in most cases exceeded 4.5 hours. However, in this group of patients (LACI no-IVT) there were significantly more patients with leukoaraiosis, which may lead to the conclusion that this could have been a reason for not applying IVT. Lastly, the study could be stronger if all non-IVT patients with LACI who were seen during the observation period could have been included.

In conclusion, we could say that the results of our study have confirmed that the use of IVT is effective and safe in patients with lacunar infarction. If there are no absolute contraindications, IVT should always be applied in patients with lacunar infarction.

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