Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 81 (2018) 865−870

www.jcma-online.com

Original Article

Early neurological deterioration in acute ischemic stroke: A propensity score analysis

Zhi-Xin Huang [a], Qi-Zhang Wang [b], Ying-Yi Dai [a], Hai-Ke Lu [a], Xiao-Yu Liang [a], Huan Hu [a], Xin-Tong Liu [a,*]

[a] *Department of Neurology, Guangdong Second Provincial General Hospital, Guangzhou, Guangdong, China*
[b] *Department of Neurology, Shenzhen Shajing Affiliated Hospital of Guangzhou Medical University, Shenzhen, Guangdong, China*

Received March 31, 2017; accepted March 1, 2018

Abstract

Background: To investigate whether endovascular therapy (EVT) was one of the factors influencing the incidence of early neurological deterioration (END) in patients with acute ischemic stroke (AIS) as compared with intravenous thrombolysis alone.
Methods: This study was based on our single-center's database that included information on stroke patients hospitalised between January 2012 and September 2015. A total of 220 patients who underwent EVT after IV rt-PA, EVT or IV rt-PA alone. To reduce the lack of randomization, we conducted a propensity score analysis using the SPSS custom dialog. After matching was completed, the 2 groups (with END versus non-END) were compared between matched groups. Variables with a p value ≤ 0.1 by univariate analysis were candidates for inclusion in logistic regression analysis.
Results: Of 220 acute ischemic strokes attended, 213 patients were included (62.0%, 23.0% and 15.0% with circulation occlusion in the anterior, posterior and both branches, respectively). END was detected in 68 patients (31.9%). Multivariable analysis showed that END was positively associated with glucose level (OR, 1.40; 95%CI, 1.10−1.79; $p = 0.007$), uric acid level (OR, 1.01; 95% CI, 1.00−1.02; $p = 0.026$) and treatment methods (EVT: OR, 3.87; 95% CI, 1.32−11.35; $p = 0.014$). However, there was significant difference in baseline data (NIHSS and INR) between EVT group and non-EVT group.
Conclusion: Our findings suggest that hyperglycemia, hyperuricemia and EVT may be independently associated with END in AIS, even after controlling for possible confound factors. Further studies are warranted to confirm these results.

Keywords: Acute ischemic stroke; Early neurological deterioration; Endovascular therapy

1. Introduction

Ischemic stroke (IS) takes no prisoners, which was the first leading cause of death and a major cause of long-term disability in many developing countries, especially China.[1] Intravenous thrombolysis (IVT) for patients presenting up to 4.5 h after symptom onset has been considered as the key step to reduce the risk of severe disability and mortality.[2] Unfortunately, <5% of acute ischemic stroke (AIS) patients received intravenous recombinant tissue-type plasminogen activator (rt-PA) in China mainly because most of stroke patients missed the proper time of treatment.[3] Furthermore, recanalization rates following intravenous rt-PA are low especially for occlusions of acute intracranial large vessels or large clots (≥8 mm).[4] With the adventure of new treatment strategy in AIS, Endovascular therapy (EVT) has been proven to be an advantage of a higher recanalization and better functional

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Xin-Tong Liu, Department of Neurology, Guangdong Second Provincial General Hospital, 466, Middle Xingang Road, Guangzhou, 510317, Guangdong, China.
E-mail address: xintongliu@163.com (X.-T. Liu).

https://doi.org/10.1016/j.jcma.2018.03.011

outcome in anterior circulation stroke patients treated up to 6 h after symptom onset,[5] whose benefits were further confirmed by four other randomized clinical trials, such as ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT.[6−9]

Early neurological deterioration (END) in the acute phase of IS usually leads to a marked increase in disability and mortality rates, after reperfusion treatment due to diverse mechanisms.[10] Previous studies have shown that the predictors of END were as follows: diabetes,[11] hyperglycemia, neurological functional deficits at admission,[12] systolic BP,[13] fibrinogen,[14] and a delay until treatment.[15] Nevertheless, studies on the influence of different treatments in END have been quite rare. Therefore, the aim of this retrospective study was to evaluate whether EVT was one of the factors influencing the incidence of END in patients with AIS as compared with intravenous thrombolysis alone.

2. Methods

2.1. Study subjects

This retrospective single center case study was designed to analyze the risk factors of END in patients with AIS in our stroke center, which provides neurological care to the population of Southeast China. Exclusion criteria comprised (1) renal or hepatic disease, unstable angina, ventricular aneurysm, myocardial infarction, heart failure, malignant disease, vascular malformations, aneurysm, hemorrhagic stroke and brain surgery; (2) patients with a previous history of carotid endarterectomy or carotid artery stenting; (3) patients with other causes & undetermined causes. All eligible patients within 4.5 h after symptom onset were intravenously administered with rt-PA (0.9 mg/kg) and then immediately transferred to the digital subtraction angiography (DSA) room for repeating imaging. Additional EVT was performed in the patients according to the following criteria: catheter-accessible persistent occlusion of internal carotid artery (ICA), M1 of the middle cerebral artery (MCA) on follow-up DSA after rt-PA therapy. EVT alone was carried out in patients with an occlusion in the proximal anterior or posterior circulation that could be treated between 4.5 and 8 h or 4.5−24 h, respectively, after symptom onset.

A total of 220 subjects were enrolled from the consecutive patients who underwent EVT after IV rt-PA, EVT or IV rt-PA alone in our center between January 2012 and September 2015. According to the different treatment methods, patients were divided into two groups: EVT group (EVT plus IV rt-PA, or EVT alone) and rt-PA group (IV rt-PA alone). They were thoroughly investigated for demographics and baseline clinical characteristics. The prevalence of certain cardiovascular risk factors identified at the baseline has been previously described.[16] Neurological deficits were estimated using the National Institutes of Health Stroke Scale (NIHSS) score by two neurologists, who were blind of DSA images and baseline clinical characteristics. In the presence of inconsistent scores, a consensus was reached via discussion. The study protocol was approved by the Ethical Committee of our center. The authors of this study did not interact with the participants in any way. Moreover, authors had no access to information that could identify individual participants during or after data collection.

2.2. Definition of END

In this study, We defined END as an increment of NIHSS score $\geq$2 points within 72 h 1−3 times a day after admission according to a previous recommended definition; this was a restrictive criterion less influenced by subjective observation, enabling differentiation from the late deterioration mostly due to systemic complications such as aspiration pneumonia or to stroke recurrence.[17]

2.3. Statistical analysis

Statistical analysis was performed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL). To reduce the lack of randomization, we conducted a propensity score analysis using the SPSS custom dialog. Before matching, comparisons were performed using independent sample t tests, Kruskal−Wallis tests, Mann−Whitney U tests, or analysis of variance for normal distributed continuous variables, and the chi−square test or fisher's exact test for categorical variables, as appropriate. Then, the propensity score was developed by using a logistic regression model in which the following variables were entered: Total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), homocysteine, uric acid. After estimation of the propensity score, we matched participants using a simple 1:4 nearest neighbor matching. After matching is completed, the 2 groups (with END versus non-END) were compared between matched groups. Variables with a p value ≤ 0.1 by univariate analysis were candidates for inclusion in logistic regression analysis. A selection process was used to develop the final multivariable model, and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as estimates of relative risk. Moreover, baseline patient characteristics between IV rt-PA group and EVT group were assessed with logistic regression. A two-tailed p value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between January 1 2012 and September 31 2015, among 220 patients with AIS, 7 patients with incomplete clinical data were excluded from this study, 189 patients underwent IV rt-PA for AIS, and other 24 (11.3%) were treated with EVT. Finally, a total of 213 patients were enrolled into the study: 132 (62.0%), 49 (23.0%) and 32 (15.0%) with circulation occlusion in the anterior, posterior and both branches, respectively. The median time from symptom onset to treatment was 3.3 h (interquartile range [IQR] 1.9). 68 of 213 subjects (31.9%) had END, 145 of which served as non-END

controls. The baseline characteristics of the patients with END versus non-END before and after propensity score matching were shown in Table 1. Before matching, presence of diabetes mellitus was more prevalent in the END group than in the non-END group. TC, HDL, LDL, glucose levels, and the number of female were higher, and neurologic impairment was worse, in the END group than in the non-END group. After matching, there were no statistically differences between the two groups in TC, HDL, LDL levels, diabetes mellitus, time from symptom onset to treatment, and the proportion of female except for glucose, uric acid and NIHSS score. Notably, NIHSS score was not included in the propensity score matching because it is inherently expected to be higher in the END group (Table 1).

Binary regression analysis for predicting factors associated with END was shown in Table 2. The analysis showed the significant predictors of END in the study were glucose level (OR, 1.40; 95% confidential interval [CI], 1.10–1.79; $p = 0.007$), uric acid level (OR, 1.01; 95% CI, 1.00–1.02; $p = 0.026$) and treatment methods (EVT: OR, 3.87; 95% CI, 1.32–11.35; $p = 0.014$). In addition, we compared baseline patient characteristics between IV rt-PA group (n = 189) and EVT group (n = 24), and there was significant difference in NIHSS scores at admission [10.0 (7.0–13.0) vs 12.0 (11.0–17.5), $p = 0.002$], time to treatment [3.0 (2.5–4.5) vs 4.3 (3–5.4), $p = 0.024$], and international normalized ratio (INR) [1.1 ± 0.1 vs 1.0 ± 0.1, $p = 0.004$] between 2 groups. In binary regression analysis these two variables (INR and NIHSS) remained significantly associated with and correlated conversely to EVT by controlling for alcohol habit, and time from symptom onset to treatment (results shown in Table 3).

Table 1
Comparison of demographic and therapeutic characteristics of END and non-END.

	Prematched			Postmatched		
	END	non-END	*p*	END	non-END	*p*
No.	68	145	–	39	81	–
Age, year	62.9 ± 12.9	60.0 ± 10.6	0.080	61.9 ± 14.0	58.5 ± 10.2	0.175
ST, h, median (IQR)	4.0 (3.0–5.0)	3.0 (2.5–4.5)	0.003	4.0 (3.0–5.0)	3.5 (3.0–4.8)	0.531
NIHSS, median (IQR)	12.0 (10.0–18.0)	10.0 (7.0–12.0)	0.000	12.0 (9.0–18.0)	9.0 (6.0–12.0)	0.004
HCY, umol/L	13.6 ± 3.9	15.3 ± 10.1	0.172	13.2 ± 3.6	15.6 ± 11.3	0.201
SBP, mm Hg	153.4 ± 27.4	150.1 ± 21.6	0.348	151.7 ± 23.4	152.6 ± 23.0	0.847
DBP, mm Hg	92.1 ± 20.8	91.4 ± 13.8	0.822	89.5 ± 17.2	93.3 ± 14.4	0.205
BMI, kg/m^2	25.2 ± 4.3	24.1 ± 4.2	0.077	25.4 ± 4.5	24.2 ± 3.9	0.176
Uric acid, umol/L	305.2 ± 91.2	293.5 ± 70.0	0.302	336.4 ± 85.2	300.6 ± 77.6	0.024
TC, mmol/L	5.5 ± 1.6	4.9 ± 1.0	0.008	5.3 ± 1.5	5.1 ± 1.1	0.424
TG, mmol/L	1.5 ± 0.8	1.4 ± 0.8	0.666	1.2 ± 0.5	1.4 ± 0.8	0.289
LDL, mmol/L	3.7 ± 1.3	3.1 ± 0.9	0.003	3.6 ± 1.3	3.3 ± 1.0	0.281
HDL, mmol/L	1.4 ± 0.7	1.2 ± 0.3	0.005	1.3 ± 0.2	1.2 ± 0.2	0.242
Glu, mmol/L	9.7 ± 5.4	6.7 ± 1.7	0.000	7.8 ± 2.2	6.6 ± 1.5	0.001
HbA1c, %	7.3 ± 0.8	7.3 ± 0.5	0.518	7.1 ± 0.3	7.2 ± 0.4	0.476
Fibrinogen, g/L	3.2 ± 1.1	3.2 ± 0.8	0.580	3.2 ± 1.1	3.3 ± 0.9	0.497
INR	1.1 ± 0.1	1.0 ± 0.1	0.877	1.1 ± 0.1	1.0 ± 0.1	0.381
Male, n (%)	44 (64.7)	68 (46.9)	0.015	25 (64.1)	39 (48.1)	0.102
Treatment methods			0.003			0.003
IV rt-PA	54 (79.4)	135 (93.1)		25 (64.1)	71 (87.7)	
EVT	14 (20.6)	10 (6.9)		14 (35.9)	10 (12.3)	
Hypertension, n (%)	44 (64.7)	80 (55.2)	0.190	25 (64.1)	45 (55.6)	0.376
Diabetes mellitus, n (%)	20 (29.4)	14 (9.7)	0.000	7 (17.9)	9 (11.1)	0.304
Dyslipidemia, n (%)	20 (29.4)	48 (33.1)	0.591	11 (28.2)	27 (33.3)	0.573
TIA, n (%)	0 (0.0)	2 (1.4)	0.332	0 (0.0)	2 (2.5)	0.324
Smoking, n (%)	8 (11.8)	28 (19.3)	0.172	4 (10.3)	12 (14.8)	0.493
Alcohol habit, n (%)	6 (8.8)	10 (6.9)	0.620	4 (10.3)	6 (7.4)	0.598
IHD, n (%)	22 (32.4)	33 (22.8)	0.137	8 (20.5)	16 (19.8)	0.923
ischemic stroke, n (%)	10 (14.7)	19 (13.1)	0.689	8 (20.5)	10 (12.3)	0.243
Offending vessel			0.145			0.190
Anterior circulation, n (%)	38 (55.9)	94 (64.8)		21 (53.8)	49 (60.5)	
Posterior circulation, n (%)	16 (23.5)	33 (22.8)		6 (15.4)	22 (27.2)	
Both, n (%)	14 (20.6)	18 (12.4)		12 (30.8)	10 (12.3)	
Toast subtype			0.678			0.748
Large artery atherosclerosis	66 (94.1)	137 (94.5)		36 (92.3)	77 (95.1)	
Cardiogenic embolism	2 (2.9)	2 (1.4)		2 (5.1)	2 (2.5)	
Small artery occlusion	2 (2.9)	6 (4.1)		1 (2.6)	2 (2.5)	
AF	2 (2.9)	2 (1.4)	0.594	2 (5.1)	2 (2.5)	0.595
Hemorrhagic transformation	2 (2.9)	3 (2.1)	0.696	2 (5.1)	1 (1.2)	0.203

ST = time from symptom onset to treatment (onset-to-puncture); IQR = interquartile range; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; HCY = homocysteine; TC = total cholesterol; TG = triacylglycerol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; INR = International Sensitivity Index; IHD = ischemic heart disease; Both = involvement of the anterior and posterior circulation; AF = atrial fibrillation.

Table 2
Binary regression analysis for predicting factors associated with END following matching by PSM.

Variable	OR	95% CI	p
Glu, mmol/L	1.40	1.10–1.79	0.007
NIHSS	1.09	0.99–1.18	0.053
Uric acid, umol/L	1.01	1.00–1.02	0.026
Treatment methods[a]	3.87	1.32–11.35	0.014

END = early neurological deterioration; PSM = propensity score matching; OR = odds ratio; CI = confidence interval.
[a] Treatment methods: EVT group (EVT plus IV rt-PA, or EVT alone) and rt-PA group (IV rt-PA alone).

4. Discussion

IS is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding neurological functional deficit. AIS is caused by thrombotic or embolic occlusion of a cerebral artery and is more common than hemorrhagic stroke. With the increasing elderly population, AIS is a kind of common and frequently-occurring disease among the middle-aged and elderly groups with severe disability rate and high mortality rate. END after AIS has been found to be associated with more severe fatality and worse functional outcome, which seriously affects the quality of life of patients and their partners.[18] Consistent with our findings (31.9%), 10–40% of patients with AIS suffer an END,[19] which can be explained by the diverse criteria used to evaluate the neurological deficits.

In our study, the most important finding was that EVT was related with a higher risk of developing subsequent END development when compared to those patients with IV rt-PA (adjusted OR 3.87). Generally, there are several possible reasons accounting for his phenomenon. Firstly, EVT is an excellent alternative as a less invasive procedure to treat AIS because of recent advances in the devices and techniques. Especially, recent robust evidence from randomized clinical trials suggests that EVT is beneficial for selected patients with AIS due to large vessel occlusions in the anterior circulation but not posterior circulation.[5–9] EVT in vertebrobasilar territory is still not supported by any randomized trial. Therefore proper patient selection is crucial for achieving a good clinical outcome. Moreover, several studies indicated that the presence of large vessel occlusion has been recognized as an independent risk factor for END.[19] Secondly, vascular occlusion leads to distal hypoperfusion and potential reperfusion injury unless effective collateral circulation develops. The other possible mechanisms of END after EVT include recanalization failure, distal migration of the thrombus, and reocclusion after initially successful arterial revascularization. It is necessary to investigate effective preventive strategies for vessel reocclusion after successful reperfusion therapy in AIS. Also, operator's experience affected the outcome of EVT. Thirdly, hemorrhagic transformation is also one of the most clinically significant risk factors for END. Previous studies found that the incidence of symptomatic transformation was higher in patients treated with EVT than with IV rt-PA.[20,21] Fourthly, basic imaging data was routinely done in recent trials to evaluate the location of the arterial occlusion and the extent of the penumbra, collateral blood flow status, and core infarct areas and thereby to improve patient selection for endovascular therapy. In particular, EXTEND-IA trial regarding perfusion imaging data may be prudent to improve the science before changing clinical practice. In this study, the large vessels occlusion was evaluated visually by the neurointerventionalist on call, collateral perfusion and core/penumbra volumes were not assessed as potential predictors, but need to be investigated in future studies. Fifth, perhaps because of the low proportion of EVT in this study, however, EVT was administered in the most assigned participants—from 73% in the REVASCAT trial to 100% in the EXTEND-IA. Finally, baseline NIHSS between the EVT and IV rt-PA groups (OR 1.20, $p = 0.000$) can result in differences in outcome not based on the therapeutic effect, but due to dissimilarities in inclusion criteria. The NIHSS was highly correlated with the occurrence of major vessel pathology,[22] and major vessel occlusions were more likely to perform EVT.

Hyperglycemia was significantly positively associated with END which might lead to poor short-term outcome in this study. A possible explanation is that the post-ischemic inflammatory responses and neuroprotective heat-shock chaperone gene attenuation have been shown to significantly higher in the diabetic mice than in that the nondiabetic mice.[23] In addition, based on previous research findings, hyperglycemia on admission was associated with SICH after EVT in AIS patients with anterior circulation occlusions, and that SICH leads to significantly poor prognosis. In experimental stroke models, acute hyperglycemia leads to increased brain lactate production, the development of brain edema, breakdown of the blood–brain barrier, increased risk of hemorrhagic transformation and enlarged infarct size, which may contribute to the risk of END development.[24]

In agreement with previous studies,[25] higher uric acid levels at stroke admission are associated with a worse clinical outcome, but to date results from several studies have been inconsistent.[26] Uric acid is the end product of purine catabolism in humans, the main constituents of DNA and RNA. For one thing, Uric acid uptake in adipocytes activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increase production of reactive oxygen species (ROS) through the activation of multiple intracellular signaling pathways, which can exert pro-inflammatory and pro-oxidant effects.[27] Our findings give further support to this adverse effect of uric acid and spread its effects to the setting of AIS, suggesting that increased uric acid concentration led to further neurological deterioration following

Table 3
Binary regression analysis for the factors associated with EVT.

Variable	OR	95% CI	p
NIHSS	1.20	1.09–1.32	0.000
time to treatment, hours	1.13	0.96–1.33	0.149
INR	0.00	0.00–0.01	0.001
Alcohol habit	5.67	1.28–24.26	0.022

ischemic stroke. For another, hyperuricemia may stimulate vascular smooth muscle cell proliferation, inhibit endothelial cell proliferation, attenuate vascular nitric oxide production, reduce vascular nitric oxide activity, and lead to endothelial dysfunction,[28,29] thus resulting in increased risk of hemorrhagic transformation and infarct volume expansion after thrombolysis in AIS.[30]

There are several limitations in the present study. First, it is a single-center retrospective observational study and has small sample size, which may lead to selection bias and weak conclusion. Data on some potential predictive variables are lacked; however, propensity matching helped to overcome variations in patient and clinical characteristics between the END and non-END groups. Second, it represents a hospital−based study and is not population based. Selection bias is a possibility, it is likely that patients with more severe strokes received EVT. In other words, patients with EVT indicated more severe neurological function impairment. Third, there is a lack of data on the long-term post-hospitalization neurological outcome. In addition, higher prevalence of large artery atherosclerosis stroke in the hospital-based study might be attributed to a genetic trait, and designing a treatment study, for example, with a limited age range might lead to a bias in what subtypes will be included in the study. Finally, we have no data on recanalization and time to reperfusion therapy.

In conclusion, after the propensity score matching analysis, this study provides further evidence that hyperglycemia, hyperuricemia and inappropriate choice for EVT may increase the risk of END events and short-term poor prognosis, thus need to be managed after AIS. Future studies, preferably randomized controlled studies should explore whether recognition and appropriate management of hyperglycemia and hyperuricemia may prevent END and improve patient outcome. In addition, EVT is a promising therapeutic alternative for large vessel occlusion in patients with an AIS, and identification of appropriate patients for EVT may improve reperfusion, early neurologic recovery, and functional outcome.

Acknowledgments

This work was partially supported by the Science and Technology Planning Project of Guangdong Province, China (2017A020215051 to XL), Guangdong Second Provincial General Hospital Medical Scientific Research Projects (YY2016-005 to ZH) and Administration of Traditional Chinese Medicine of Guangdong Province, China (20173024 to XL; 20181012 to ZH). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the global burden of disease study 2010. *Lancet* 2013;**381**:1987−2015.
2. Kim YD, Nam HS, Kim SH, Kim EY, Song D, Kwon I, et al. Time-Dependent thrombus resolution after Tissue-Type plasminogen activator in patients with stroke and mice. *Stroke* 2015;**46**:1877−82.
3. Jin H, Zhu S, Wei JW, Wang J, Liu M, Wu Y, et al. Factors associated with prehospital delays in the presentation of acute stroke in urban China. *Stroke* 2012;**43**:362−70.
4. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013;**368**:893−903.
5. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;**372**:11−20.
6. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;**372**:1019−30.
7. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;**372**:1009−18.
8. Saver JL, Goyal M, Diener HC. Stent-Retriever thrombectomy for stroke. *N Engl J Med* 2015;**373**:1077.
9. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;**372**:2296−306.
10. Alawneh JA, Moustafa RR, Baron JC. Hemodynamic factors and perfusion abnormalities in early neurological deterioration. *Stroke* 2009;**40**:e443−50.
11. Tanaka R, Ueno Y, Miyamoto N, Yamashiro K, Tanaka Y, Shimura H, et al. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. *J Neurol Sci* 2013;**332**:45−50.
12. Seners P, Turc G, Tisserand M, Legrand L, Labeyrie MA, Calvet D, et al. Unexplained early neurological deterioration after intravenous thrombolysis: incidence, predictors, and associated factors. *Stroke* 2014;**45**:2004−9.
13. Chung JW, Kim N, Kang J, Park SH, Kim WJ, Ko Y, et al. Blood pressure variability and the development of early neurological deterioration following acute ischemic stroke. *J Hypertens* 2015;**33**:2099−106.
14. Dziedzic T. Clinical significance of acute phase reaction in stroke patients. *Front Biosci* 2008;**13**:2922−7.
15. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke* 2015;**17**:38−53.
16. Huang Z, Yin Q, Sun W, Zhu W, Li Y, Liu W, et al. Microbleeds in ischemic stroke are associated with lower serum adiponectin and higher soluble E-selectin levels. *J Neurol Sci* 2013;**334**:83−7.
17. Rocco A, Fam G, Sykora M, Diedler J, Nagel S, Ringleb P. Poststroke infections are an independent risk factor for poor functional outcome after three-months in thrombolysed stroke patients. *Int J Stroke* 2013;**8**:639−44.
18. Seners P, Turc G, Oppenheim C, Baron JC. Incidence, causes and predictors of neurological deterioration occurring within 24 h following acute ischaemic stroke: a systematic review with pathophysiological implications. *J Neurol Neurosurg Psychiatry* 2015;**86**:87−94.
19. Nacu A, Bringeland GH, Khanevski A, Thomassen L, Waje-Andreassen U, Naess H. Early neurological worsening in acute ischaemic stroke patients. *Acta Neurol Scand* 2016;**133**:25−9.
20. Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J Neurointerventional Surg* 2015;**7**:170−5.
21. Ginsberg MD, Hill MD. Symptomatic intracranial hemorrhage in the ALIAS Multicenter Trial: relationship to endovascular thrombolytic therapy. *Int J Stroke* 2015;**10**:494−500.
22. Hansen CK, Christensen A, Ovesen C, Havsteen I, Christensen H. Stroke severity and incidence of acute large vessel occlusions in patients with hyper-acute cerebral ischemia: results from a prospective cohort study based on CT-angiography (CTA). *Int J Stroke* 2015;**10**:336−42.

23. Tureyen K, Bowen K, Liang J, Dempsey RJ, Vemuganti R. Exacerbated brain damage, edema and inflammation in type-2 diabetic mice subjected to focal ischemia. *J Neurochem* 2011;**116**:499−507.
24. McBride DW, Legrand J, Krafft PR, Flores J, Klebe D, Tang J, et al. Acute hyperglycemia is associated with immediate brain swelling and hemorrhagic transformation after middle cerebral artery occlusion in rats. *Acta Neurochir Suppl* 2016;**121**:237−41.
25. Wu H, Jia Q, Liu G, Liu L, Pu Y, Zhao X, et al. Decreased uric acid levels correlate with poor outcomes in acute ischemic stroke patients, but not in cerebral hemorrhage patients. *J Stroke Cerebrovasc Dis* 2014;**23**:469−75.
26. Llull L, Amaro S, Chamorro A. Administration of uric acid in the emergency treatment of acute ischemic stroke. *Curr Neurol Neurosci Rep* 2016;**16**:4.
27. Madlala HP, Maarman GJ, Ojuka E. Uric acid and transforming growth factor in fructose-induced production of reactive oxygen species in skeletal muscle. *Nutr Rev* 2016;**74**:259−66.
28. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005;**67**:1739−42.
29. Valle M, Martos R, Canete MD, Valle R, van Donkelaar EL, Bermudo F, et al. Association of serum uric acid levels to inflammation biomarkers and endothelial dysfunction in obese prepubertal children. *Pediatr Diabetes* 2015;**16**:441−7.
30. Lakhan SE, Kirchgessner A, Tepper D, Leonard A. Matrix metalloproteinases and blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 2013;**4**:32.