MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 4427-4432
DOI: 10.12659/MSM.909015

Received: 2018.01.17
Accepted: 2018.03.01
Published: 2018.06.27

Pentraxin-3 in Thrombolytic Therapy for Acute Ischemic Stroke: No Relation with Curative Effect and Prognosis

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Source of support: This study was supported by the Medical Guiding Project of Shanghai Science and Technology Committee (124119a8900)

Background: Pentraxin-3 (PTX3) is considered a high quality inflammatory marker of the severity and prognosis of several diseases, however, the value of PTX3 in thrombolytic therapy for acute ischemic stroke remains unclear and PTX3 is still controversial in evaluating the prognosis of stroke patients. In this study, we investigated the association of PTX3 with thrombolytic therapy in patients with acute ischemic stroke.

Material/Methods: Forty-seven stroke patients who received thrombolytic therapy within 4.5 hours after symptom onset were enrolled consecutively between July 2016 and June 2017. All the patients underwent multiphase CTA (computerized tomography angiography) or CT perfusion before thrombolysis with no indication for endovascular treatment. Initial and 24 hours of National Institute of Health Stroke Scale (NIHSS) scores and serum PTX3 level, stroke risk factors and predictors, and mRS (modified Rankin scale) at 3 months were collected prospectively. Predictors of thrombolytic therapy effect and long-term prognosis were investigated by univariate and multivariate logistic regression.

Results: The 24 hour NIHSS score and the treatment time was associated with symptom improvement, while the PTX3 level had no association with neurological improvement and prognosis in stroke patients receiving thrombolytic therapy.

Conclusions: PTX3 is not suitable to serve as an indicator of thrombolytic efficacy and had no association with long-term prognosis in stroke patients receiving thrombolytic therapy.

MeSH Keywords: Prognosis • Stroke • Thrombolytic Therapy

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/909015

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Background

Stroke is one of the most common causes of death and permanent disability worldwide. Recombinant tissue plasminogen activator (rt-PA) is the only available treatment for acute ischemic stroke (AIS). But due to the narrow therapeutic time-window of 4.5 hours and the risk of intracranial hemorrhage, less than 5% of stroke patients would benefit from it [1]. Recently, endovascular treatment of AIS was proved effective for vessel occlusion and computerized tomography angiography (CTA) played a vital role in the process [2]. However, for those patients who are not suitable for endovascular treatment, it is still difficult to improve most patients' symptoms with rt-PA. This suggests that new adjuvant therapies are needed for AIS patients. Early biomarkers in AIS might serve as a useful tool and a therapeutic target for clinicians.

Pentraxin-3 (PTX3) is a prototypical member of the long pentraxin family and its expression level significantly increases in several cardiovascular and cerebrovascular diseases, especially in atherosclerotic lesions [3–5]. Research has shown that PTX3 is a strong and independent prognostic marker of long-term mortality in AIS patients [6]. Therefore, we aimed to investigate the correlation between PTX3 level and effectiveness of thrombolytic treatment as well as the prognosis of AIS patients receiving thrombolysis.

Material and Methods

Informed consent was obtained from all the individual participants included in the study.

Study population

Between July 2016 and June 2017, there were 118 consecutive AIS patients with symptom onset within 4.5 hours who received thrombolytic therapy in the Stroke Center of Changhai Hospital, Second Military Medical University (Shanghai, China). All the patients received rt-PA (Actilyse, Boehringer-Ingelheim) intravenously at a dose of 0.9 mg/kg (10.0% as a bolus in 1 min, with the rest being infused during a 1-hour period). All the patients underwent multiphase CTA or CT perfusion (iCT, PHILIPS, Netherlands) before thrombolysis and had no indication of endovascular treatment. Exclusion criteria were as follows: nonconformity with the thrombolytic treatment standard [7], infection, TIA or stroke history, acute or chronic cor pulmonale or heart failure, drug addiction/abuse, mortality within 24 hours after admission, and peripheral arterial disease. The diseases in the exclusion criteria were clearly diagnosed by clinicians.

Data collection

Clinical data including demographic characteristics (age and sex) and risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, smoking or alcohol habit, and medical history of statin use) were collected prospectively. In addition, whether the patient received rt-PA within 3 hours was also recorded. National Institute of Health Stroke Scale (NIHSS) scores were recorded to assess neurological status at admission and at 24 hours. All NIHSS scores were performed by certified stroke neurologists. Neurological improvement was defined retrospectively as a ≥40% decrease in NIHSS score at 24 hours in comparison to the baseline pretreatment score after the initiation of therapy [8,9]. Since none of NIHSS scores of the patients increased, the standard of neurological deterioration was not adopted. The 3-month modified Rankin scale (mRS) score was assessed according to the follow-up visits or telephone interviews, with a score of more than 2 meaning dependency [10].

Immunoassay methods

Blood samples were drawn from each patient at admission and at 24 hours after thrombolytic therapy. Plasma was extracted in EDTA tubes, separated by centrifugation at 3000 rpm for 10 min and stored at –80°C until analysis. Serum PTX3 level was measured by a commercial ELISA kit (ab214570; Abcam, Cambridge, UK). The analytic coefficient of variation was 3.7%.

Statistical analyses

Continuous variables were presented as median (interquartile range [IQR]) or mean ± standard deviation (SD). PTX3 was described with median and extrema particularly. Categorical variables were summarized as percentage. Independent samples *t*-test or analysis of variance or Mann-Whitney U test were used for comparison of continuous variables, and χ^2 test or Fisher exact test was used for comparison of categorical variables on the base of data characteristics. Univariate and multivariate logistic regression were used to explore predictors of the effect of thrombolytic therapy and the long-term prognosis. Variables were professionally selected into the multivariate regression models based on previous publications. To investigate the effect of different levels of PTX3 on neurological improvement and prognosis, the patients were divided into 3 groups (T1, T2, T3) according to the tertiles of initial or 24-hour PTX3 levels respectively. And the T1 group was used as the control group (OR=1). Statistical analyses of the data were performed with SAS© 9.4 (SAS Institute Inc., Cary, NC, USA) and all statistical tests were done with a 2-tailed level of significance of 0.05.

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Table 1. Baseline characteristics of study population.

Variable	Neurological improvement				*P*
	Y (n=22)		N (n=25)		
Age (Mean, SD)	63.32	(11.22)	62.92	(9.20)	0.89
Male (%)	14	(63.64)	16	(64.00)	0.98
Hypertension (%)	14	(63.64)	20	(80.00)	0.21
Diabetes mellitus (%)	9	(40.91)	9	(36.00)	0.73
Hyperlipidaemia (%)	10	(45.45)	17	(68.00)	0.12
Smoking (%)	11	(50.00)	8	(32.00)	0.21
Alcohol (%)	5	(22.73)	4	(16.00)	0.56
Statin use (%)	4	(18.18)	1	(4.00)	0.17
CHD (%)	2	(9.09)	2	(8.00)	1.00
Initial NIHSS*	4	(2–9)	4	(3–6)	0.54
24 h-NIHSS*	1	(1–3)	4	(2–6)	<0.001
Treatment within 3 hours (%)	18	(81.82)	13	(52.00)	0.03
Initial PTX3 (pg/mL)**	539	(291–956)	560	(184–944)	0.72
24 h-PTX3 (pg/mL) **	499	(213–893)	547	(156–938)	0.36

CHD – coronary heart disease; NIHSS – National Institute of Health stroke scale; * These data are represented by 'Median(IQR)'; ** these data are represented by 'Median (min–max)'.

Results

A total of 47 AIS patients met the criteria and were recruited in our study. The mean age was 63.11±10.08 years, and 63.8% of the patients were male. There were 34 cases (72.3%) of hypertension, 18 cases (38.3%) of diabetes, 27 cases (57.4%) of hyperlipidemia, and 4 cases (8.5%) of coronary heart disease. In addition, 31 patients received thrombolytic therapy within 3 hours.

Patients with indication of neurological improvement at 24 hours were classified into the effective thrombolytic group, and the others were assigned to the ineffective thrombolytic group. Clinical variables and serum PTX3 level of the study population are shown in Table 1. In the 2 groups, the initial PTX3 levels were 539 pg/mL (291–956) and 560 pg/mL (184–944), respectively. And, the 24 hour PTX3 levels were 499 pg/mL (213–893) and 547 pg/mL (156-938), respectively. No significant difference was found in initial and 24 hour PTX3 levels between the 2 groups, although the level of PTX3 in the effective thrombolytic group was lower than that of the ineffective thrombolytic group at both the time points. In addition, no differences were found in common risk factors for AIS. However, there were significant differences between the 2 groups in the treatment within 3 hours and the 24 hours for NIHSS score ($P<0.001$).

We further compared the characteristics of the patients according to the tertiles of initial PTX3 levels (Table 2). The 24 hour NIHSS score in the T1 group was lower than T2 and T3 group, meaning the 24 hour NIHSS score would be lower if the PTX3 levels were low. However, there was no differences across tertiles of initial PTX3 ($P=0.16$). Also, the proportion of treatment within 3 hours in T1 group was insignificantly higher than the other groups ($P=0.59$). In addition, no statistical difference was found among the risk factors associated with stroke. The univariate analysis showed that the 24 hour NIHSS score ($P<0.01$) and treatment time ($P=0.04$) were associated with neurological improvement, while initial and 24 hour PTX3 levels had no association with 24 hour neurological improvement. Based on the multivariable analysis by logistic regression, no difference between PTX3 levels and the neurological improvement was found (Table 3).

The factors associated with the long-term prognosis (mRS) were evaluated by univariate analysis, and the association between prognosis and 24 hour NIHSS score remained significant ($P=0.01$). However, initial and 24 hour PTX3 in the groups revealed no significant differences. Finally, we carried out the multivariable regression. The adjusted odds ratio (OR) of prognosis for T2 relative to T1 was 0.74 (95% CI, 0.04–13.05) and the adjusted OR of prognosis for T3 relative to T1 was 0.81 (95% CI, 0.05–14.02), the connection between initial PTX3 levels and long-term prognosis still remained a negative result (Table 4).

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Table 2. Characteristics of patients according to tertiles of Initial PTX3.

Variable	Tertiles of initial PTX3 (pg/mL)						*P*
	T1 (<555)		T2 (555–687)		T3 (>687)		
Age (mean, SD)	65.06	(10.55)	59.24	(9.01)	65.57	(10.02)	0.14
Male (%)	11	(68.75)	12	(70.59)	7	(50.00)	0.44
Hypertension (%)	11	(68.75)	13	(76.47)	10	(71.43)	0.88
Diabetes mellitus (%)	6	(37.50)	7	(41.18)	5	(35.71)	0.95
Hyperlipidaemia (%)	8	(50.00)	11	(64.71)	8	(57.14)	0.70
Smoking (%)	6	(37.50)	9	(52.94)	4	(28.57)	0.38
Alcohol (%)	1	(6.25)	3	(17.65)	5	(35.71)	0.13
Statin use (%)	2	(12.50)	3	(17.65)	0	(0)	0.28
CHD (%)	2	(12.50)	2	(11.76)	0	(0)	0.40
Initial NIHSS*	4	(2–5.5)	5	(4–7)	4	(2–7)	0.28
24 h-NIHSS*	1.5	(1–4)	3	(2–5)	3	(2–5)	0.16
Treatment within 3 hours (%)	12	(75.00)	11	(64.71)	8	(57.14)	0.59

CHD – coronary heart disease; NIHSS – National Institute of Health stroke scale. * These data are represented by 'Median (IQR)'.

Table 3. Univariate and multivariable analysis of variables for Neurological improvement*.

Variable	Univariate analysis			Multivariable analysis		
	Crude OR and 95% CI		P	Adjusted OR and 95% CI		P
Age	1.00	(0.95,1.06)	0.89	1.01	(0.95, 1.09)	0.72
Male	0.98	(0.30,3.24)	0.98	1.24	(0.27, 5.58)	0.78
Hypertension	0.44	(0.12,1.62)	0.22	0.41	(0.10, 1.73)	0.22
Diabetes mellitus	1.23	(0.38,4.00)	0.73	1.52	(0.38, 6.09)	0.56
Hyperlipidaemia	0.39	(0.12,1.29)	0.12	0.32	(0.08, 1.30)	0.11
Smoking	2.13	(0.65,6.95)	0.21			
Alcohol	1.54	(0.36,6.66)	0.56			
Statin use	5.33	(0.55,51.88)	0.15			
CHD	1.15	(0.15,8.93)	0.89	0.69	(0.06, 7.69)	0.76
Initial NIHSS	1.10	(0.93,1.31)	0.28			
24h-NIHSS	0.56	(0.38,0.83)	<0.01			
Treatment within 3 hours	4.15	(1.09,15.83)	0.04			
24 h-PTX3 T2**	1.13	(0.29,4.41)	0.87	1.47	(0.30, 7.29)	0.64
24 h-PTX3 T3	0.56	(0.13,2.41)	0.43	1.04	(0.18, 5.92)	0.97
Initial PTX3 T2***	1.14	(0.28,4.68)	0.85	1.49	(0.32, 6.81)	0.61
Initial PTX3 T3	0.60	(0.15,2.46)	0.47	0.63	(0.11, 3.47)	0.59

CHD – coronary heart disease; NIHSS – National Institute of Health stroke scale. * The first tertile (T1) as the reference group OR=1; ** The tertiles of 24h-PTX3 levels: T1 (<527 pg/ml), T2 (527–642 pg/ml), T2 (>642 pg/ml); *** The tertiles of initial PTX3 levels: T1 (<555pg/ml), T2 (555–687 pg/ml), T2 (>687 pg/ml).

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Table 4. Univariate and multivariable analysis of variables for prognosis*.

Variable	Univariate analysis		Multivariable analysis	
	Crude OR and 95% CI	*P*	Adjusted OR and 95% CI	*P*
Male	0.83 (0.13, 5.56)	0.85	2.67 (0.16, 44.61)	0.49
Age	1.06 (0.95, 1.17)	0.30	1.10 (0.95, 1.27)	0.20
Hypertension	1.60 (0.16, 15.82)	0.69	1.87 (0.12, 28.85)	0.65
Hyperlipidaemia	1.13 (0.17, 7.45)	0.90	0.73 (0.08, 6.89)	0.78
Diabetes mellitus	0.37 (0.04, 3.58)	0.39	0.29 (0.02, 3.79)	0.35
Initial PTX3 T2**	0.44 (0.04, 5.36)	0.52	0.74 (0.04, 13.05)	0.84
Initial PTX3 T3	1.17 (0.14, 9.59)	0.89	0.81 (0.05, 14.02)	0.88
24 h-PTX3 T2***	2.31 (0.19, 28.47)	0.51		
24 h-PTX3 T3	2.14 (0.17, 26.33)	0.55		
Smoking	0.33 (0.03, 3.24)	0.34		
Treatment within 3 hours	0.75 (0.11, 5.02)	0.77		
Initial NIHSS	1.24 (0.98, 1.55)	0.07		
24 h-NIHSS	1.95 (1.17, 3.24)	0.01		

NIHSS – National Institute of Health stroke scale. * The first tertile (T1) as the reference group OR=1; ** the tertiles of initial PTX3 levels: T1 (<555 pg/ml), T2 (555–687 pg/ml), T2 (>687 pg/ml); *** the tertiles of 24 h-PTX3 levels: T1 (<527pg/ml), T2 (527–642 pg/ml), T2 (>642 pg/ml).

Discussion

AIS is one of the leading causes of mortality in most countries in the world. A number of studies have demonstrated the effectiveness of thrombolytic therapy [11–13]. However, due to considerably varied definitions of early neurological changes used in the studies, the efficiency varies widely as well. In our study, we showed that 8.5% AIS patients showed complete recovery (NIHSS score=0) and 46.8% patients had achieved clinical improvement at 24 hours.

It is generally accepted that inflammation is critically implicated in the pathogenesis and progression of ischemic stroke [14]. PTX3 is a 45 kDa protein that assembles to form high molecular weight multimers linked by interchain disulfide bounds and the sequence and regulation of PTX3 gene is highly conserved in evolution [15]. Different from C-reactive protein (CRP), which is mainly produced in the liver, PTX3 is abundantly produced in various cells including monocytes, macrophages, adipocytes, fibroblasts, endothelial cells, dendritic cells, and vascular smooth muscle cells [5]. PTX3 reflects local inflammatory reactions because it is produced by cells involved in atherosclerotic lesions in response to toll-like receptor agonists, TNF-α, IL-1β, and other inflammatory mediators, and PTX3 has been detected in human carotid atherosclerotic lesions and coronary arterial lesions [16]. PTX3 is rapidly induced in the heart after unstable angina or acute myocardial infarction and could predict 3-month mortality in patients with myocardial infarction, which is superior to hsCRP in predicting prevalent cardiovascular diseases [17]. PTX3 might represent baseline atherosclerotic burden more accurately in acute stroke [6] and is related with severity of stroke [18].

Researchers found that PTX3 is associated with mortality at 3 months after acute myocardial infarction and is connected with heart disease and hypoxic respiratory failure [14]. In the field of cerebrovascular diseases, PTX3 has been identified as a novel and independent prognostic marker in ischemic stroke [6]. However, due to different inclusion criteria, a study by Ceylan et al. led to an opposite result, that serum PTX3 level was not associated with stroke prognosis in the patients without cardiovascular, cardiopulmonary or infectious diseases [19].

In our study, we found that in patients with no necessity for interventional therapy, PTX3 was irrelevant to both symptomatic nerve function changes in 24 hours and long-term prognosis. It is worth noting that the concentration of PTX3 was slightly elevated in the 2 groups after thrombolytic therapy, which suggested that PTX3 may increase at 24 hours, but it requires multi-time interval measurement within 24 hours for further confirmation. Different from other research, we adopted a "≥40% improvement" in NIHSS score as an effective standard because

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the majority of the patients in our study had low NIHSS scores. Patients with large-vessel occlusions may receive a poor mRS score without endovascular therapy. However, in our study, all patients had confirmation by iCT that they were the best candidates for rt-PA and needed no further treatment. This led to lower NIHSS scores and better mRS scores in our cohort. Besides, we used mRS instead of the Barthel Index (BI) to assess patient outcomes, because mRS is more sensitive for distinguishing between mild and moderate disability and more suitable for evaluating acute stroke treatment effects [10].

In the study by Ceylan et al. [19], infectious diseases were not excluded from the inclusion criteria, which might significantly affect the concentration of inflammatory factors and have a close correlation with mortality [20]. They evaluated functional changes of the nervous system on the first and seventh days of a stroke event. However, short-term functional assessment could not represent long-term prognosis. Therefore, we chose mRS score to assess patient prognosis at 3 months later.

There were some limitations to our study. First, the population capacity was limited. Because of the limitation of therapeutic time-window and rigorous inclusion criteria, the number of patients enrolled in the research was considerably reduced. Second, patients with cerebral vascular stenosis and atrial fibrillation [21] were included in our study, which might act as confounders in our study. Third, infarct volume was not included in this study. Due to technical limitation, the CTP of multiphase CT could not accurately calculate the infarct volume if the infarct was not caused by significant stenosis or occlusion. Therefore, it was difficult to investigate the correlation between infarct volume and PTX3 level.

Conclusions

In patients who receive thrombolytic therapy with no indications of endovascular treatment, neurological improvement at 24 hours was associated with the treatment time. However, PTX3 level has no association with the neurological improvement or long-term prognosis.

Acknowledgements

We thank the Central Laboratory of Changhai Hospital for technical assistance. We wish to thank the patients for their sincere and generous contribution to the research protocol.

Conflict of interests

None.

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