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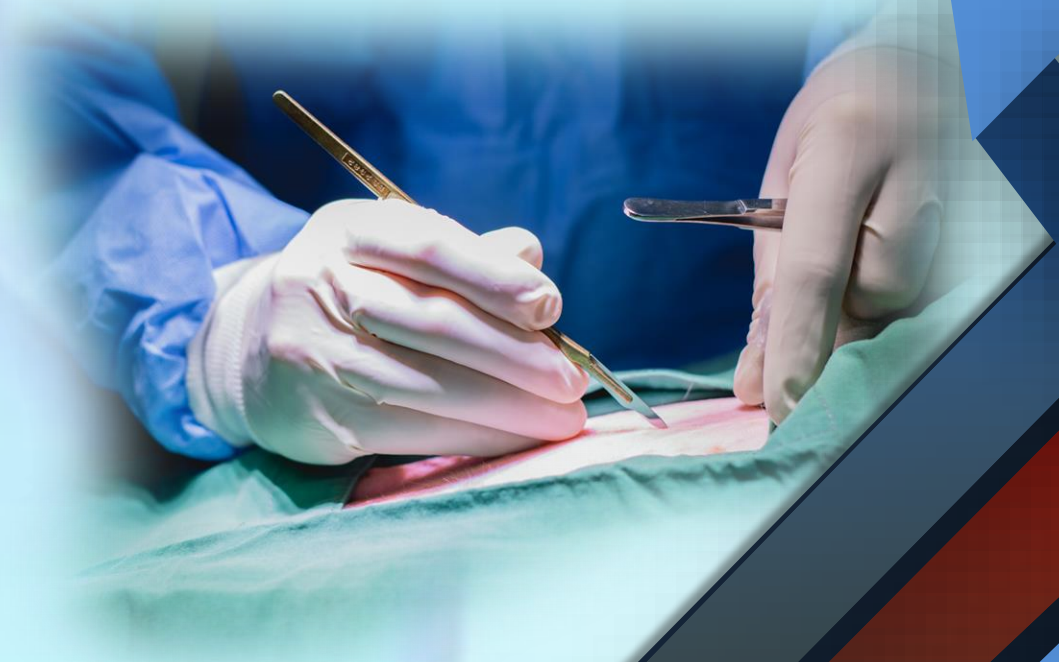

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Original article

Effect of Tissue Plasminogen Activator on Treatment Outcome and Neuronal Degeneration in Acute Ischemic Stroke

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ABSTRACT

Background: Acute ischemic stroke [AIS] is a leading worldwide neurological morbidity with significant disability. Recombinant tissue plasminogen activator [r-TPA] is approved for the treatment of AIS. Neuron-specific enolase [NSE] is a marker of brain damage in patients with traumatic brain injury, stroke, and hypoxic encephalopathy.

Aim of the work: The present study assessed the prognostic value of serum NSE in r-TPA treatment of patients with AIS.

Patients and methods: The present prospective study included 53 patients with AIS. They comprised 25 patients who didn't receive r-TPA and 28 patients who received r-TPA. The clinical severity of the stroke was assessed using National Institute of Health Stroke Scale [NIHSS]. A modified Rankin score was used to evaluate the degree of disability in the affected patients. Radiological imaging included echocardiography, brain computed tomography, and carotid and vertebrobasilar duplex. NSE was assessed at 24 h after r-TPA infusion.

Results: Patients subjected to r-TPA treatment had significantly lower NSE one day of stroke when compared with another group [23.7 ±14.3 versus 11.9 ± 8.9; p=0.001]. Also, patients with r-TPA treatment had a significantly higher frequency of favorable outcome at day 90 [67.8 % versus 44.0 %; p=0.001]. Interestingly, NSE levels one day after stroke were significantly lower in patients with favorable outcome [14.39 ±9.6 versus 19.83 ±14.9; p=0.048] and showed significant correlation with infarct size [r=0.63;p=0.001] and NIHSS after 24h [r=0.67;p=0.001].

Conclusion: r-TPA treatment resulted in a significant decrease in NSE levels. These levels were significantly correlated with infarct size, NIHSS at 24 hours, and MRS at 90 days.

Keywords: Acute ischemic stroke; Recombinant tissue plasminogen activator; Neuron-specific enolase; Modified Rankin score.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Acute ischemic stroke [AIS] is one of the most common and most disabling neurological conditions affecting a wide range of populations worldwide [1]. Considering the long-term disability related to AIS, appropriate management of the condition is amongst the top clinical priorities in current neurological practice [2].

In 1996, recombinant tissue plasminogen activator [r-TPA] was released as the only FDA approved therapy for ischemic stroke patients. About 32 patients from every 100 patients improved clinically after receiving r-TPA [3].

r-TPA is a thrombolytic drug that activates plasminogen conversion into plasmin that binds to the fibrin part of the formed clot and dissolves it. Also, r-TPA was found to improve neuroplasticity, which participates in the recovery after stroke in rats [4]. According to the European Cooperative Acute Stroke Study III [ECASS III], patients must receive r-TPA treatment within 4.5 hours to save brain tissues before ischemia-induced necrosis [5].

Neuron-specific enolase [NSE] is a 78-kD gamma-homodimer representing the dominant enolase-isoenzyme found in neuronal tissues and is an important and well-known biomarker for demonstrating neuronal damage in neurological disorders[6].

It has been studied as a marker of brain damage in patients with traumatic brain injury, stroke, and hypoxic encephalopathy[7].

Clinical studies reported increased serum NSE levels in ischemic stroke patients. They concluded that increased NSE concentrations are significantly correlated with volumes of infarcted brain areas, the severity of an acute ischemic stroke, and poor functional outcome[8].

The present study tried to assess the prognostic value of NSE in AIS patients treated with r-TPA. We describe our experience with r-TPA treatment in a cohort of Egyptian patients and its effect on neuronal degeneration in those patients. To our knowledge, this relation wasn't previously reported in Egyptian patients.

AIM OF STUDY

The present study aimed to assess the prognostic value of NSE in AIS patients treated with r-TPA.

PATIENTS AND METHODS

The present prospective interventional study was conducted at Stroke Unit, Beni-Suef University Hospital in the period from July 2019 through January 2020. The local ethical committee approved the study protocol, and the included patients or their legal guardians gave written informed consent before participation in the study.

The study included 53 patients with acute ischemic stroke. The sample size was calculated using G Power 3.1 with an estimated study power of 80.0 % and an alpha error rate of 20.0 %. Patients were excluded if they had impaired daily living before stroke onset with a pre-stroke modified Rankin scale > 4, associated neurodegenerative diseases, e.g., Parkinson's disease, Alzheimer's disease or any other dementia, psychiatric disorders, e.g., psychosis or major depressive disorder, other associated comorbidities, e.g., severe heart failure, hepatic or renal failure, hemorrhagic blood diseases or malignancy.

Upon admission, all patients were submitted to careful history taking, thorough clinical and neurological examination. The clinical severity of the stroke was assessed using the National Institute of Health Stroke Scale [NIHSS][9]**.** It was assessed at baseline, one day of the stroke, and seven days after the stroke. A modified Rankin score[10] was used to evaluate the degree of disability in the affected patients at 90 days after stroke.

Patients were also subjected to laboratory investigations, including complete blood count [CBC], lipid profile, uric acid, and coagulation profile using the automated chemical analyzer. NSE was assessed 24 hours after r-TPA infusion using commercially available quantitative enzyme-linked immunosorbent assay kits. Radiological imaging included echocardiography [Vivid 5 GE, USA], brain computed tomography [Philips, Netherlands], and carotid and vertebrobasilar duplex [Philips duplex ultrasound machine, Netherlands].

Eligible patients [n=28] received intravenous rt-PA [0.9 mg/kg, Actilyse, Boehringer Ingelheim] in the therapeutic window [first 4.5 hours]. Other patients [n=25] with contraindications to

intravenous rt-PA weren't given rt-PA.

The present study's data were presented as number and percent or mean ± standard deviation [SD]. Categorical data were compared using Fisher's exact test or chi-square test, while numerical data were compared using *t*-test. Correlations were achieved using Pearson's correlation coefficient. All statistical operations were computed using SPSS 25 [IBM, USA] with p values less than 0.05 considered statistically significant.

RESULTS

The present study was conducted on 53 patients with acute ischemic stroke. They comprised 25 patients who didn't receive r-TPA and 28 patients who received r-TPA. Comparison between the studied groups regarding the baseline clinical, laboratory, echocardiographic and radiological data revealed no statistically significant differences [Table 1].

Comparison between the studied groups revealed no statistically significant differences between the studied groups regarding NIHSS at baseline, after one day, and after seven days of treatment. However, patients subjected to r-TPA therapy had significantly lower NSE one day of stroke than another group [23.7 ±14.3 versus 11.9 ± 8.9; p=0.001]. It was also found that patients with r-TPA treatment had a significantly higher frequency of cases with favorable outcomes according to modified Rankin scale at day 90 [67.8 % versus 44.0 %; p=0.001] [Table-2].

Interestingly, NSE levels one day after stroke were significantly lower in patients with favorable outcome [14.39 ±9.6 versus 19.83 ±14.9; p=0.048] [Figure 1] and showed significant correlation with infarct size [r=0.63;p=0.001] and [Figure 2] and NIHSS after 24h [r=0.67;p=0.001] in the studied patients [Figure 3]. No significant correlations were found between NSE levels and other clinical, laboratory, or imaging data.

Table [1]: Comparison between the studied groups regarding baseline data

		Receiving rTPA N= 28	Not-Receiving rTPA N= 25	P value
Age [years] mean ± SD		59.1 ±13.8	60.5 ±13.6	0.72#
Male/female [n]		16/12	12/13	0.59
BMI [Kg/m^2]		27.3 ± 5.2	29.6 ± 4.9	0.11#
Risk factors n [%]	Diabetes	5 [17.9]	5 [20.0]	0.56
	Hypertension	17 [60.7]	17 [68.0]	0.78
	Atrial fibrillation	14 [50.0]	10 [40.0]	0.58
	Smoking	11 [39.3]	8 [32.0]	0.78
	Previous stroke	6 [21.4]	5 [20.0]	0.99
	Family history of stroke	3 [10.7]	3 [12.0]	0.99
Laboratory findings [mean ± SD]	Uric Acid [mg/dl]	6.2 ±1.9	6.6 ±1.7	0.47#
	Triglycerides [mg/dl]	147.3 ± 85.5	120.6 ± 58.9	0.2#
	Cholesterol [mg/dl]	208.0 ± 57.8	189.1 ± 58.8	0.24#
	LDL [mg/dl]	103.6 ± 43.1	104.5 ± 34.7	0.94#
	HDL [mg/dl]	40.2 ±10.9	39.8 ± 9.2	0.9#
Echocardiographic findings [n [%]]	Valvular heart disease	8 [28.6]	11 [44.0]	0.24
	Pulmonary hypertension	7 [25.0]	15 [60.0]	0.01*
	Ejection fraction <45%	2 [7.2]	3 [12.0]	0.098
	Dilated left atrium	14 [50.0]	15 [60.0]	0.33
Carotid artery duplex [n [%]]	Abnormal right carotid artery	1 [3.6]	-	0.34
	Abnormal left carotid artery	2 [7.1]	2 [8.0]	0.91
Infarction site [n [%]]	Middle cerebral artery	10 [35.7]	6 [24.0]	0.064
	Basal ganglia or thalamus	9 [32.1]	9 [36.0]	
	Parietal	8 [28.6]	7 [28.0]	
	Fronto-temporo-parietal	1 [3.6]	1 [4.00]	
	Brain stem & cerebellar	0 [0.00]	2 [8.00]	
Infarction size [cm] mean ± SD		6.1 ± 8.2	8.7 ± 10.1	0.31#

BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Comparison were made using t test [#] or Fisher exact test; * Significant results

Table [2]: Comparison between the studied groups regarding the outcome parameters

	Receiving rTPA N= 28	**Not-Receiving rTPA N= 25**	**P value**
NIHSS			
At the onset of stroke	13.0 ± 4.7	10.6 ± 6.2	0.12#
After one day of stroke	9.7 ± 6.5	9.2 ± 5.8	0.75#
After 7 days of stroke	5.8 ± 5.3	8.2 ± 6.5	0.17#
NSE one day of stroke	11.9 ± 8.9	23.7 ±14.3	0.001#*
Modified Rankin scale at day 90 n [%]			
Favorable	19 [67.8]	11 [44.0]	0.001*
Unfavorable	9 [32.2]	14 [56.0]	

NIHSS: National Institutes of Health Stroke Scale; NSE: Neuron-specific enolase. The comparison was made using t-test [#] or Fisher exact test. * Significant results

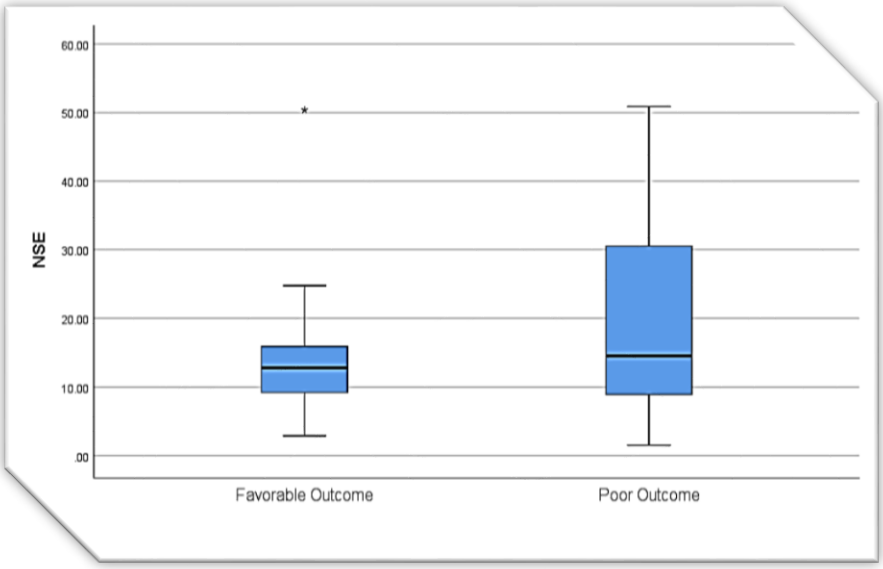

Figure [1]: Effect of NSE marker on patients' outcome by MRS

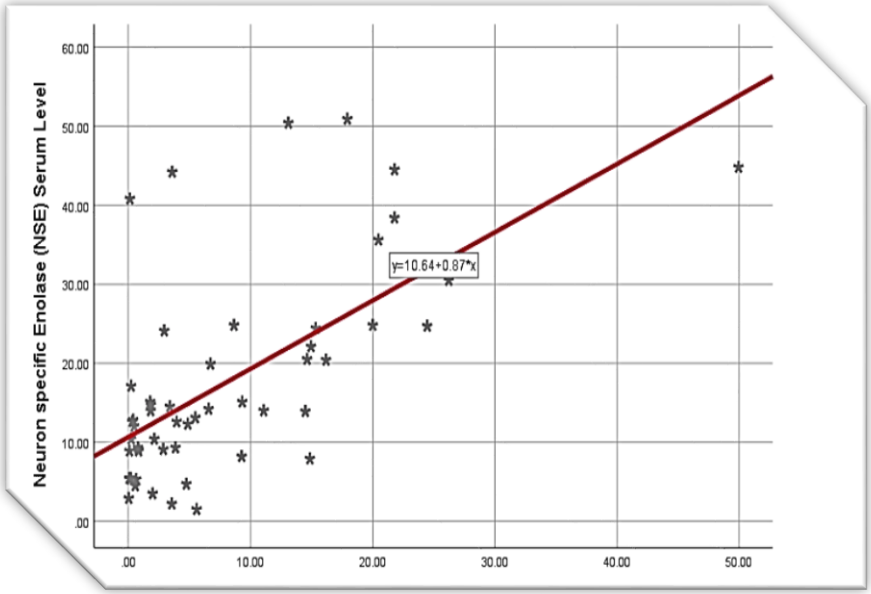

Figure [2] Correlation between Neuron specific Enolase [NSE] and infarction size

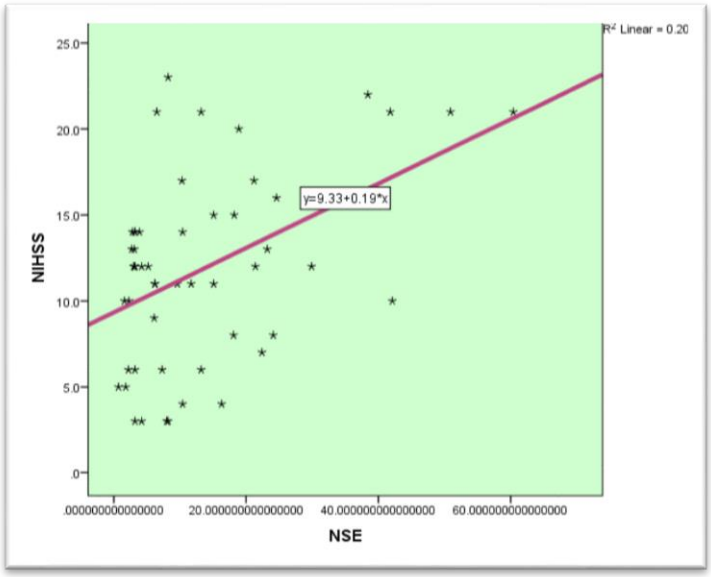

Figure [3]: Correlation between Neuron-specific Enolase [NSE] and NIHSS

DISCUSSION

The aim of the present study to assess the impact of treating stroke patients with rTPA on serum levels of NSE, the marker of neuronal degeneration. In the present study, rtPA treated patients were found to have significantly lower NSE serum levels than controls. To the best of our knowledge, only one study led by Wunderlich and colleagues[11] investigated the effect of treating stroke patients with rtPA on NSE. The results of their 66-patient study revealed that patients who received intravenous thrombolysis exhibited lower serum NSE levels than controls, but this difference did not reach statistical significance. Moreover, the present study found a statistically significant positive correlation between NSE serum level and stroke severity assessed by NIHSS. These conclusions are in line with other studies. The experimental research of Lui et al.[4] provided evidence of the effect of rtPA administration on corticorubral and corticospinal tract axonal remodeling, which was correlated with the behavioral outcomes. Similar results were also reported by clinical studies[11-14].

However, other studies failed to document such a relation[15-16]**.** Probably, the discrepancy in the results among these studies can be attributed to the difference in time at which NSE was measured [17].

Another interesting finding is that our study found a statistically significant positive correlation between NSE serum level and infarction size in line with previous studies[18-19]**.**

On the other hand, other authors didn't find such a relation[15,20]. Also, the present study identified that patients with favorable outcomes had significantly lower NSE serum levels than patients with unfavorable outcome in conformity with many studies[13,18,21] and in discordance with others[20,22]. Again, the difference between the conclusions of various studies may be related to the time of NSE sampling.

Conclusively, the present study found that r-TPA treatment resulted in a significant decrease in NSE levels. These levels were significantly correlated with infarct size, NIHSS at 24 hours, and MRS at 90 days. In spite of the fact that this study is the first to report such conclusions in Egyptian patients, the study isn't without limitations. The sample size is relatively small, and the follow-up period needed to be prolonged. We recommend other multicentric studies with a larger sample size and longer follow-up period.

Financial and Non-financial Relationships and Activities of Interest

None

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