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ORIGINAL ARTICLES

The Prediction of the Increase in intracranial Pressure in Stroke Patients Given Recombinant Tissue Plasminogen Activator by Measuring the optic Nerve Sheath Diameter on bedside Ultrasound.

Serdar Hekimsoy*, Münire Hande Gölgeli, Nefise Büşra Çelik, Avni Uygar Seyhan

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Abstract

Background: The aim of this study is based on the effects of the treatment, the recombinant tissue plasminogen activator (rTPA), applied to stroke patients in Emergency Departments (ED) by intravenous, to optic nerve sheath diameter (ONSD) measurements.

Material and Methods: The study was designed as prospective and observational. A total of 41 patients were included in this study with the following diagnoses: an acute clinical stroke, known well-being within 4.5 hours, and who had a finding for rTPA. Ultrasonographic (USG) ONSD measurements have been performed on a voluntary basis with the consent of the patients and their relatives.

Results: A statistically significant difference has been found between the ONSDs measured at the 0th, 15th, 30th and 60th minutes of the patients who were admitted to the ED and were on rTPA treatment due to stroke ($p<0.05$). Due to a large number of positive differences, the ONSD at the 15th, 30th, and 60th minutes was found higher than at the 0th minute. A statistically significant difference has also been found between ONSD measured at the 15th, 30th, and 60th minutes during rTPA treatment ($p<0.05$). Since the existence of a large number of positive differences, the ONSD at the 30th and 60th minutes is found to be higher than at the 15th minute. Finally, the difference of statistically significant values between the 30th and 60th-minute ONSD was determined by the Sign Test. According to the result of the Sign Test, a statistically significant difference was found to be between the ONSD differences of the 30th and 60th minutes of rTPA treatment ($p<0.05$).

Conclusions: Serial ONSD measurements performed at the bedside during the early stage in order to follow up on the intracranial complications of stroke patients may be misleading for the follow-up of complications within the first 60 minutes, which is the most critical stage. In this stage, symptom monitoring should be used in combination with ONSD and the decision should be made for treatment continues, accordingly.

Keywords: Emergency Department, Stroke, Optic Nerve Sheath Diameter, Recombinant tissue plasminogen activator.

Introduction

Acute stroke is a leading cause of morbidity and mortality, with more than 750,000 patients and 140,000 deaths each year, worldwide [1]. While the studies over the past 25 years have greatly expanded our ability to minimize the causing of acute stroke and maintain neurological function in many cases, it will be the greatest contribution to treatment if could be able to achieve the preventing of strokes. The basis of this achievement is contained in primary care [2].

During the acute phase of ischemic stroke, that is, within the first hours, the practices involved in patient evaluation and management are the use of thrombolytic therapy, endovascular thrombectomy, treatment of patients unsuitable for reperfusion therapy, clinical diagnosis of various types of stroke, and subacute or long-term evaluation of stroke patients [3-5].

Early treatment is the primary factor in the accomplished reperfusion treatment of acute ischemic stroke. However, selecting suitable candidates for reperfusion requires a neurological evaluation and a neuroimaging study. In addition, reperfusion therapy for acute stroke requires a system that coordinates prehospital EDs, emergency medicine, stroke neurology, intensive care units (ICU),

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* ***Corresponding author:***
Dr. Serdar Hekimsoy
✉ *serdarhekimsoy@gmail.com*

** Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, TURKEY.*

interventional neuroradiology, and neurosurgery to provide an ideal treatment [6]. The immediate goal of reperfusion therapy for acute ischemic stroke is to restore blood flow to ischemic yet infarcted areas of the brain [7].

Ultrasound is used for diagnosis, treatment and follow-up of many different diseases in EDs [8]. Ultrasound measurement of optic nerve sheath diameter (ONSD) is a simple, non-invasive tool that provides a reasonable level of diagnostic precision for the estimation of intracranial hypertension (ICP) [9,10]. Since the subarachnoid space of the optic nerve is a continuum with the intracranial cerebrospinal fluid (CSF) spaces, it can be expanded by an increase of ICP and modify the ONSD [11]. Intracranial hypertension is confirmed by invasive intracranial monitoring, which is the baseline technique for the measurement of ICP [12]. In comparison with conventional neuroimaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), transorbital sonography (TOS) has the advantages of being low cost, with short investigation times, good reproducibility, and bedside availability, and most importantly of being non-invasive and simple [10]. Especially in the hyperacute phases of acute ICH (within 6 hours of the onset of symptoms), the presence of an enlarged ONSD can provide dynamic monitoring of the patient by ultrasonography.

This study aims to reveal the impact of intravenous rTPA treatment applied to stroke patients in the ED on ONSD measurements.

Material and Methods

This study was designed as an observational prospective open uncontrolled study. Patients who were admitted to ED at Kartal Dr Lütfi Kırdar City Hospital with acute stroke clinic between August 15, 2019, and May 31, 2020, and were applied rTPA were included in the study. All first-ever acute ischaemic stroke 41 patients admitted to the Emergency Department of Kartal Dr. Lütfi Kırdar City Hospital and were applied rTPA, enrolled between August 15, 2019, and May 31, 2020, were included in the study. USG ONSD measurements have been performed on a volunteer basis with the knowledge and consent of the patients and their relatives, without affecting the examination and treatment process. Patients younger than 18 years of age and patients with non-stroke disease who may increase intracranial pressure were excluded. Ethics Committee Approval was obtained from Kartal Dr Lütfi Kırdar City Hospital on 24.07.2019 (decision number: 2019-514-158-1).

In this study, intravenous or intra-arterial reperfusion therapy was performed at the physician's discretion. Patients were applied a recombinant tPA, alteplase (Activase, Genentech) at a dose of 0.9 mg/kg body weight (maximum 90 mg). 10% of this was given as a bolus at the first minute, and then the remaining 90% as a fixed intravenous infusion over 60 minutes. Serial sonographic ONSD measurement was performed in patients clinically diagnosed with acute stroke and indicated for rTPA treatment. Sonographic measurements have been achieved by certified clinicians (USG Training Certificates) and under the guidance of the American College of Emergency Physicians (ACEP). After receiving the patient's consent, serial measurements were performed at the 0th minute, 15th minute, 30th minute and 60th minute of rTPA application. Sony Esaote brand, MySevenLab model USG device was measured using a linear probe in a B-mode setting. During sonographic ONSD measurements, the patient was placed in a relaxed supine position with eyes closed. The eye socket was filled with USG gel, and the insonation was adjusted to 5-8 cm dept. By using a high-frequency linear transducer probe, a transverse view of the eyeball and retrobulbar structures was received sonographically without causing any pressure on the eyeball. After receiving the best image for the optic nerves and freezing the image, the cursor was placed 3 mm posterior to the papilla, and the measurement was completed [13].

This study determined basic statistics such as percentage, the number of observations, and mean and standard deviations of the relevant variables. Kolmogorov-Smirnov and Shapiro-Wilk Tests were used to test the normality of continuous variables. Since the obtained data were measured from the same patients at regular intervals, in case normality could not be achieved, dependent two-group non-parametric Sign Tests were practised to evaluate the relationship between categorical and continuous variables. The t-test analysed the relationship between the customarily distributed continuous and categorical variables with independent groups. The independent Mann-Whitney Tests were conducted for the non-normally distributed continuous variables. In addition, Pearson and Spearman Rho correlation coefficients were measured for continuous and categorical variables.

Results

The outcomes of the patients were as follows: 20% remained in their current clinic, 64% recovered (modified Rankin score mRS of 0-2), 4% non-survivor, and 12% were admitted to the intensive care unit (ICU). While 53.7% (n=22) of the patients had no lesion, a left parietal localization was observed in 4 (9.8%) and right parietal localization in 7.3% (n=2). No complications were observed in 87.8% (n=12) of the patients. In some patients, it has been observed that skin ecchymosis (n=1; 2.4%), desaturation (n=1; 2.4%), embolism to the femoral artery (n=1; 2.4%), haematuria (n=1; 2%), 4) and intracranial haemorrhage (n=1; 2.4%).

The mean age of 41 patients in the study was 72.91, with the youngest patient 44 years old and the oldest 89 years old. 41.5% (n=17) of the patients were female, and symptom onset was observed in 68.29% between 08:31 and 20:00.

Normality tests of ONSD values have been made by using Kolmogorov-Smirnov Test and Shapiro-Wilk Test. The results are presented in *Table 1*.

The values of the nerve sheaths measured at the time of admission are normally distributed ($p>0.05$), yet the

ONSD (mm)	***Kolmogorov-Smirnov***			***Shapiro-Wilk***		
	Value	SD	***P***	Value	SD	***P***
Admission	0.135	27	***0.200***	0.941	27	***0.126***
rTPA 0^{th} min	0.178	27	***0028***	0.905	27	***0.017***
rTPA 15^{th} min	0.142	27	***0.169***	0.922	27	***0.044***
rTPA 30^{th} min	0.177	27	***0.029***	0.923	27	***0.047***
rTPA 60^{th} min	0.187	27	***0.016***	0.922	27	***0.043***

rTPA; *tissue plasminogen activator,* ***ONSD;*** *optic nerve sheath diameter* ***SD;*** ***s****tandard deviation*

Table 1 Normality tests for Optic Nerve Sheath Diameter (ONSD)

ONSD	***Negative Difference Observation Number***	***Positive Difference Observation Number***	***Equal Observation Number***	***Total Observation Number***	***Z Value***	***P Value***
0^{th} min.	6	22	11	39	-2.835	0.005
15^{th} min.	4	27	6	37	-3.951	0.000
30^{th} min.	5	24	2	31	-3.343	0.001
30^{th} min.	2	23	3	28	-3.248	0.000

ONSD; *optic nerve sheath diameter*

Table 2: The Results of Sign Tests to compare ONSDs measured at patient's admission and other rTPA treatment times

ONSD		***Negative Difference Observation Number***	***Positive Difference Observation Number***	***Equal Observation Number***	***Total Observation Number***	***Z Value***	***P Value***
rTPA 0^{th} min	rTPA 15^{th} min-rTPA 0^{th} min	2	20	15	37	-3.517	***0.000***
	rTPA 30^{th} min-rTPA 0^{th} min	4	23	4	31	-3.464	***0.001***
	rTPA 60^{th} min-rTPA 0^{th} min	1	27	0	28	-4.725	***0.000***
rTPA 15^{th} min	rTPA 30^{th} min-rTPA 15^{th} min	4	15	12	31	-2.075	***0.019***
	rTPA 60^{th} min-rTPA 15^{th} min	1	25	2	28	-4.511	***0.000***
rTPA 30^{th} min	rTPA 30^{th} min-rTPA 60^{th} min	0	23	4	27	-4.222	***0.000***

rTPA; *tissue plasminogen activator,* ***ONSD;*** *optic nerve sheath diameter*

Table 3: Results of Sign Tests performed to compare ONSD measured at rTPA treatment times

diameter values measured during rTPA treatment are not normally distributed ($p < 0.05$). Therefore, comparisons of two dependent groups were conducted by the non-parametric Sign Test. The results are shown in *Table 2*.

ONSDs were measured at the patient's admission and 0th, 15th, 30th and 60th minutes of rTPA treatment. When the measured ONSDs were compared to the Sign Test, it was found that ONSDs differed significantly from the measurements at the time of admission ($p<0.05$). It can be stated that the number of positive difference observations for all minutes is high, and the ONSD width of the patients have been increased significantly during rTPA treatment. The

Sign Test was continued to notice the difference between the minutes of rTPA treatment. The ONSD differences between the 0th minute and the other minutes of the treatment, Sign Test results, are given in *Table 3*.

There was a statistically significant difference between ONSD measured at the 0th minute of rTPA treatment and the 15th, 30th, and 60th minutes ($p<0.05$). Due to many positive differences, the ONSD at the 15th, 30th and 60th minutes is higher than at the 0th minute. rTPA treatment was continued to analyse with the Sign Test for the significance of the differences between the ONSDs received at the 15th and 30th, and 60th minutes. A statistically significant difference was found between ONSDs measured at the 15th minute of rTPA treatment and the 30th and 60th minutes ($p<0.05$). Due to many positive differences, the ONSD at the 30th and 60th minutes is higher than at the 15th minute. Finally, Sign Test determined whether the difference between ONSD at 30th and 60th minutes was significant. According to the result of the Sign Test, there was a statistically significant difference between the ONSD differences of the 30th and 60th minutes of rTPA treatment ($p<0.05$). Due to the significant positive difference, the diameters of the nerve sheaths measured at the 60th minute are higher than those measured at the 30th minute. In summary, the Sign Test shows that the ONSDs measured in patients increase while rTPA treatment continues. It was conducted that the ONSDs have increased statistically significantly during rTPA treatment.

The mean NIHSS score of the patients at the time of admission was 9.97±5.542, the mean NIHSS score after 24 hours was 3.73±4.252, and the mean NIHSS score at discharge was 3±4.147. In order to examine the neurological functions of the patients, initially, the normality tests of the scores were achieved to examine whether there was a difference between the scores received from the NIHSS scale practised at the time of admission, the 24th hour of treatment and discharge. The results of the normality test revealed that the scores were not normally distributed ($p<0.05$) (Table 4).

NIHSS Score	***Kolmogorov - Smirnov[a]***			***Shapiro-Wilk***		
	Value	***SD***	***P***	***Value***	***SD***	***P***
Admission	0.247	26	0.000	0.883	26	0.007
24 hours	0.197	26	0.011	0.793	26	0.000
Discharge	0.249	26	0.000	0.716	26	0.000

NIHSS; *national institutes of health stroke scale*

Table 4: Normality Tests for NIHSS Scores

Since NIHSS scores were not normally distributed, dependent group non-parametric Sign Tests were used to reveal the differences between scores. The Sign Test results demonstrated that there was a statistical difference between the NIHSS scores received at the time of ED admission and the NIHSS scores received after 24 hours and at discharge ($p<0.05$). The sign Test was applied again to determine the difference between the scores received at 24 hours and discharge. The Sign Test results showed a statistically significant difference in NIHSS scores between the 24-hour and discharge. The high number of negative difference observations indicates that the NIHSS scores received at 24 hours and discharge are lower than those measured during admission. A large number of observations with a negative difference indicates that the NIHSS scores received at discharge are lower than the NIHSS scores received after 24 hours. In other words, NIHSS scores are gradually decreasing. As a result, it was determined that the NIHSS scores progressively reduced at admission, 24 hours and discharge status, and this decrease in NIHSS scores was statistically significant.

Discussion

All patients diagnosed with acute ischemic stroke treated with intravenous thrombolysis should be admitted to the ICU or specialized stroke unit for at least 24 hours of close neurologic and cardiac monitoring [14]. Intravenous (IV) thrombolysis treatment within 4.5 hours of the onset of acute ischemic stroke is associated with an increased risk of early ICH in the range of 5% to 7% [6]. Therefore, symptomatic ICH should be suspected in any patient whose neurological deterioration appears suddenly, decreased level of consciousness, new headache, nausea and vomiting, or a sudden increase in blood pressure, especially within the first 24 hours of treatment after thrombolytic therapy. Guidelines advise that alteplase infusion be discontinued in patients with suspected ICH and non-contrast head computed tomography (CT) or magnetic resonance imaging (MRI) scanning. However, in patients with suspected intracranial events in ED, ONSD measurement with bedside ocular ultrasonography can be valuable in determining the increase and severity of ICP [15]. ONSD is a non-invasive ICP measurement method of clinical interest [16]. In this study, it was observed that the ONSDs of the patients extended, mainly after the onset of rTPA. It has been determined that this enlargement occurs in patients with bleeding and without complications, and the most apparent difference occurs in the 30th minute. Two basic situations are questioned here. First, rTPA can increase ONSD without complications. Another concern is that the initial half-life of rTPA is 5 minutes (not bound to fibrin), and the final half-life is 72 minutes [17]. However, in this study, it is effected that ONSD is evident, especially in the first 60 minutes. The change in ONSD can be used safely to predict malignant cerebral oedema. Still, the increase in ONSD within the first 60 minutes may be identified as the measurements and changes made in this process are not very suitable for complication follow-up, even if the patients assigned rTPA do not occur complications due to rTPA [18].

In this context, ONSD and clinical symptoms of the patient should be evaluated concurrently rather than the increase in ONSD independently, particularly for

the follow-up of ICH from the first onset of rTPA. Since these clinics and symptoms occur within the first 24 hours after the initiation of rTPA treatment, close monitoring of patients is required during this period. Based on the clinical condition of patients with symptomatic ICC, nurses and physicians argue that the patient should be alert against to decreased consciousness, increased weakness, increased systolic blood pressure and pulse pressure, or new headache and vomiting complaints [19]. In this context, the disadvantageous situation for ONSD was İts ineffectiveness' to gender. ONSD was greater in females at the 60th minute of treatment. It was believed that this could be misleading in patient follow-ups.

Specifically in this study, NIHSS follow-ups of the patients who were treated rTPA were achieved at their ED admission, at the 24th hour of the treatment and their discharge, and it was conducted that the NIHSS score decreased significantly at discharge. Thus, it was confirmed that an effective and accurate treatment strategy was accomplished. Since the present research is a single-centre study, the generalizability of the outcomes is limited. The complication rate was very low and intracranial bleeding was seen in only one patient. This patient has not been evaluated separately, which this is one of the limitations of the study.

Conclusion

Serial ONSD measurements executed at the bedside in the early stage for monitoring intracranial difficulties of stroke can be misleading for the follow-up of complications in the patient within the first 60 minutes, which is the most critical stage. In this stage, symptom monitoring should be used in combination with ONSD, and the decision on a continuous treatment strategy should be made based on this.

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