Seizure: European Journal of Epilepsy 62 (2018) 91–94

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Estimation of seizures prevalence in ischemic strokes after thrombolytic therapy

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ARTICLE INFO

Keywords:
Ischemic stroke
Thrombolytic therapy
Post-stroke seizures

ABSTRACT

Purpose: Post stroke seizures are a complication that occur in 5-20% of acute ischemic stroke (AIS) patients, cause a reduction in quality of life and a greater burden on the health system. There is not enough data regarding an association between today's standard of care treatment in AIS: recombinant tissue plasminogen activator (r-tPA) and the risk for post stroke seizures. Our aim in this work is to reveal such a connection.

Method: A non-randomized retrospective cohort-controlled study of 234 patients, who were hospitalized with acute ischemic stroke at Kaplan Medical Center in the years 2009-2015 and were divided into two different treatment groups: r-tPA and antiaggregant therapy(n = 141) and antiaggregant therapy only (n = 95) was conducted by us. Information regarding demographics, medical history, nature of the event, including NIHSS values on admission, discharge, and post stroke seizures, were obtained for each group. Follow-up was done for one year.

Results: During the year of follow-up, 19 patients (8.1%) of the overall cohort, developed seizures: 12 of them (12.6%) belonged to the control group and 7 (5%) to the study group $p < 0.05$). Results showed a decrease in the risk for developing seizure when treated with r-tpA, comparing to antiaggregants (odds ratio = 0.64).

Conclusion: This study suggests there is an association between r-tPA treatment and reduction of the risk for post stroke seizures.

1. Background

Epilepsy is a common neurologic disorder which affects about 1% of the U.S. population [1]. Most new cases of epilepsy occur in the elderly, with an annual incidence rate of 240 per 100,000 in people aged 65 and older in the United States [1]. Among patients with new-onset epilepsy, almost 50% of the causes can be explained by an underlying etiology, such as vascular diseases, tumors or metabolic disorders [2]. Around 30–40% of new epilepsy cases among the elderly are accounted for by previous cerebrovascular hemorrhages or ischemic accidents. This makes cerebrovascular strokes the most common cause of secondary epilepsy in adults [3].

The risk of developing post-stroke seizures ranges from 5 to 20% in patients older than 35 years old [4,5]. Risk factors for developing secondary seizures or epilepsy have been well studied [4,6,7]. The stroke characteristics, such as subtype, severity, hemorrhagic transformation and cortical involvement, correlate with the risk of secondary epilepsy. A large lesion, severe presentation (higher National Institute of Health stroke score (NIHSS) on admission) and signs of cortical injury, such as dysphasia or visual neglect, all enhance the risk to develop future post-stroke epilepsy (PSE) [3,6].

After a stroke, the risk of developing a seizure or (PSE) is 20 times higher in the first year after the event [7]. Post-stroke seizures are classified as 'early onset' seizures, if they occur within two weeks after the stroke. The peak incidence of 45% is at 24 h past the cerebrovascular event [17]. If the seizures occur after two weeks, it is classified as a 'late onset'. Late-onset seizures usually occur within the first year after the stroke, and they have a stronger correlation with post-stroke-epilepsy (PSE) [8,9].

Today's standard of care for treating an arterial ischemic stroke (AIS) is early reperfusion with a fibrinolytic antithrombotic factor, such as the recombinant tissue plasminogen activator (r-tPA). The National Institute of Neurological Disorders and Stroke has shown a statistically significant beneficial result in r-tPA treatment compared to placebo

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https://doi.org/10.1016/j.seizure.2018.09.001
Received 14 April 2018; Received in revised form 2 September 2018; Accepted 4 September 2018

[10,11,15]. This should be the most likely recommended treatment, if the patient arrives at the ER within the 4.5-hour window of opportunity and does not present any contraindication for r-tPA. Treatment with r-tPA for ischemic stroke reduces infarct size, but it also increases the risk for hemorrhagic transformation. Seizures have also been described in patients who underwent thrombolytic treatment for acute myocardial infarctions [18].

Previous studies have tried determining the relation between thrombolytic treatment and post-stroke epilepsy or seizures. The overall incidence rate of seizures in patients treated with r-tPA ranges from 4% to 20% [12–14].

Conversely, thrombolytic treatment has been suggested as a relative protective factor from late-onset seizures, by virtue of its beneficial effect on brain tissue reperfusion [14,16]. It is known that r-tPA is a more effective treatment in AIS than anti-platelet agents, allowing for faster reperfusion, and therefore, shortening the ischemia and reducing injury to brain tissue [12].

The aim of the study was to determine the influence of thrombolytic treatment on the risk of developing secondary seizures in patients with acute ischemic stroke. It was also to examine whether the benefits of r-tPA treatment reduce the risk of developing post-stroke seizures, too, by examining the incidence rate of those events in post-stroke patients.

2. Patients and methods

This cohort-controlled, retrospective, non-randomized cohort study was conducted on 236 consecutive patients with an acute ischemic stroke admitted to the emergency department at Kaplan Medical Center, between September 2008 and September 2015. This study group was composed of 141 consecutive acute stroke patients treated with IV r-tPA, and 95 patients who did not receive thrombolytic therapy, as a control group and was approved by our institute's Helsinki Committee for Medical Experiments.

Data were collected for the entire cohort including: demographic factors, such as age and gender, and vascular risk factors. Both groups of patients were heterogenic and comprised of patients between 33–100 years old, from various ethnic origins and both sexes. The characteristics of infarct were defined as: type of infarct, location, size, and NIHSS at arrival and discharge.

The hospitalization files in the context of the emergence of early epileptic seizures and measures of severity of neurological injury (as reflected by NIHSS) were reviewed. Exclusion criteria included: patients with a history of epilepsy or seizures, use of antiepileptic drugs previous to admission, and a previous underlying disorder with involvement of seizures (metabolic disorders, SOL, etc.). In a paradigm comparable to post-traumatic seizures, an arbitrary cut point of two weeks after the stroke onset was considered to distinguish between early- and late-onset seizures [19,20].

Epilepsy was diagnosed using the description of clinical phenomena concordant with known types of seizures corroborated by relevant EEG findings. A possible underestimation of the real number of focal seizures with impaired awareness might have occurred, but this underestimation is true for both study and control groups. According to the family's or caregiver's description, the seizures were classified as focal with preserved awareness (formerly known as simple partial-SP), focal with impaired awareness (formerly known as complex partial- CP) and generalized tonic-clonic (TC), the latter probably being of focal onset with rapid secondary generalization.

The acute stroke protocol at our institution includes immediate brain imaging with a non-contrast brain CT and a decision whether the patient is suitable for intravenous thrombolysis or not. Those patients treated with IV r-tPA are closely monitored for 24 h and undergo another brain CT during this period if there is suspicion of neurological worsening as reflected by an increase in their NIHSS. Those who are stable or are improving, undergo another brain CT 24 h after the r-tPA infusion. Afterwards, all patients undergo a thorough work-up to identify treatable vascular risk factors and secondary prevention with aspirin, clopidogrel or coumadin is started after the initial acute treatment (according to the suspected etiology of the stroke).

For at least two years, all the patients were followed-up and their neurological outcome and appearance of seizures were assessed. The information was collected from Kaplan's medical files and the hospital's virtual medical records (OFEK, dB Motion, Hod-Hasharon, Israel) which included a record of the emergency room visits, hospitalizations, and outpatient clinic visits.

The data was organized using the Excel (Microsoft, Redmond WA) program and analyzed using SPSS (ver. XXX, IBM, Armonk NY) for data processing. Statistical analysis included a homogeneity test using Pearson's chi-squared test for categorical variables. The primary endpoint was the incidence rate of seizure events after thrombolytic treatment compared to the control group, during one year follow-up, and the correlation between the type of treatment and the risk of developing such seizures. The correlation was calculated using Pearson's chi-squared test, as well as odds ratio and relative risk when there was statistical significance. A *t*-test and a Mann-Whitney test were used to compare means between the two groups.

3. Results

A cohort of 236 patients participated in the study, of which 141 patients were treated with r-tPA and formed the study group, and 95 patients, who did not receive r-tPA, were the control group. The two groups shared similar populations of various ethnic groups and similar ages (mean age 68.24 and 66.21, respectively). Risk factors for stroke including smoking, alcohol use, and underlying diseases, such as high blood pressure, diabetes and hyperlipidemia, were also similar in both groups.

It is important to note that despite our hope for a similar NIHSS score in both groups, mean admission NIHSS score of the study group was 10.82, significantly higher than the control group's 5.41 ($Z = -3.833$, $p < 0.001$).

Our results show a correlation between the location of the lesion and the risk for developing secondary seizures. When there was a cortical involvement of the lesion, a higher risk for post stroke seizures was found. This correlation was statistically significant in the overall cohort ($p = 0.028$) and the control group ($p = 0.035$), but not in the study group ($p = 0.68$) (Table 1). Odds ratio calculation showed that the risk for seizures after a cortical infract is 3.85 times higher in comparison to a sub-cortical infract. A correlation was also found between the incidence of seizures and the severity of the lesion, estimated by the NIHSS score at admission. Patients suffering from severe strokes, with a NIHSS score of 8 or more, were more likely to present with seizures in comparison to patients with mild-moderate strokes, with a NIHSS score of 7 or less ($p = 0.05$) (Table 2). The calculated odds ratio showed 2.748 times higher risk for developing seizures after a severe stroke.

In the one-year follow-up, 19 patients developed seizures, which made the overall seizure rate in this study 8.1%. When divided according to type of treatment, the incidence of seizures in the control group was significantly higher (12.6%) than the study group (5%) ($\chi^2 = 4.507$, $df = 1$, $p < .05$). In calculating odds ratio, a 64% decrease in the risk of developing post stroke seizures shown, when treated with r-tPA, in comparison to other treatments (Table 3).

There were no patients with early seizures in these series, and no patient developed status epilepticus during the follow-up period. An EEG was performed on all patients with seizures. Focal or diffuse slowing of the background was found in 80% of the patients, epileptic focal abnormalities (spikes, sharp waves) in 15% and 5% were normal.

As mentioned, the NIHSS score at admission (mean 10.82 and 5.41, respectively) and discharge (mean 6.74 and 5.78, respectively) was significantly higher in the study group than in the control group. The within-subjects effects tests revealed a correlation between the type of treatment and the improvement in neurological function, as measured