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Original article

The Use of Tenecteplase in Combination with Brain Scan Analysis in Thrombolysis of Acute Ischemic Stroke: A Moroccan Experience

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Abstract

Objective: Intravenous thrombolysis of acute ischemic stroke uses alteplase, which has long been approved for this indication. In the same context, studies on Tenecteplase have demonstrated the efficacy and safety of this molecule, which we use in our structure following clinical and radiological evaluation using non-enhanced computed tomography. Our aim is to share our institutional approach. ***Materials and Methods:*** Retrospective, descriptive, cross-sectional study in the neurology department of Casablanca over a 5-year period from 01 January 2018 to 31 December 2022. We included all patients with suspected acute stroke who underwent IVT with Tenecteplase with an Alberta Stroke Program Early CT Score greater than or equal to 7 on non-enhanced cerebral computed tomography. The Modified Rankin Scale was evaluated at 3 months. ***Results:*** During these 5 years, 140 patients (49% were females) had received Tenecteplase thrombolytic therapy. The mean age was 67 years, mean National Institutes of Health Stroke Scale was 13/42, mean Alberta Stroke Program Early CT Score was 8/10. 97% of the patients received a dose of 0.25mg/kg of Tenecteplase in a mean time of 210min from the onset of symptoms. The Modified Rankin Scale between 0 and 2 at 3 months was in 46% and 13% of death. ***Conclusion:*** We are satisfied with the results of Intravenous thrombolysis with Tenecteplase. However, we are convinced of the limited information provided by a non-enhanced cerebral computed tomography to brain magnetic resonance imaging which remains difficult to access in our context.

Keywords: ***intravenous thrombolysis, ischemic stroke, Tenecteplase, brain scan***

Introduction

Intravenous thrombolysis (IVT) for ischemic stroke uses alteplase, which has marketing authorization, but the Norwegian Tenecteplase Stroke Trial (NOR-TEST) phase III and other studies have demonstrated the efficacy and safety of using Tenecteplase (TNK) in this indication [1]. Non-enhanced cerebral computed tomography (CT) could be sufficient for radiologic eligibility according to European and American recommendations, but brain CT still has its multiple limitations in contrast to magnetic resonance imaging (MRI) with angiographic study, which provides additional information and allows the indication of IVT in a larger pool of patients [2,3]. This article presents the outcomes of our experience.

Materials and methods

This is a retrospective, cross-sectional, descriptive study of the medical records of the neurology department at the Ibn Rochd University Hospital of Casablanca over a 5-year period from January 1, 2018 to December 31, 2022. We included all patients who presented with a sudden neurological deficit within 4.5 hours of the onset of their symptoms, and in whom the thrombolysis alert triggered on admission led to IVT with TNK. Informed consent was signed by the patient or a family member before administration of the fibrinolytic agent. Radiologic eligibility was based on an Alberta Stroke Program Early CT Score (ASPECTs) greater than or equal to 7 on CT. Clinical neurological assessment was based on the National Institutes of Health Stroke Scale (NIHSS). All patients underwent follow-up CT at H24. We studied sociodemographic characteristics, IVT timeline, radiological and clinical characteristics, and the Modified Rankin Scale (mRS) score at 3 months.

Results

During this 5-year period, 5800 patients presented with a sudden neurological deficit suggestive of ischemic stroke. Among them, 11% (n=650) experienced a delay between symptom onset and door to admission (DTA) of less than 4.5 hours, leading to the initiation of a thrombolysis alert. After excluding patients who underwent MRI and assessing neurological and radiological eligibility, intravenous thrombolysis (IVT) was initiated in 22% (n=140) of the alerts. The mean age was 67 years [7-90], with women comprising 49% of the cohort. Arterial hypertension was found in 49% (n=69), diabetes in 23% (n=32), known embolic heart disease in 25% (n=35), active smoking in 20% (n=28), a history of ischemic stroke in 7% (n=10), eight patients (6%) were taking an antiplatelet drug with half of the patients discontinuing and 6% (n=8) were on anti-vitamin K with poor compliance (INR<1. 7). A transient ischemic attack less than 7 days old was found in 1% (n=2) of patients. All patients experienced their deficits during daytime activity, with a mean time to arrival at the neurological emergency department "Door to Admission" (DTA) of 156 minutes [25-315]. The mean NIHSS was 13/42 [3-23] with severity being mild in 8%, moderate in 52%, moderate to severe in 29% and severe in 11%. The electrocardiogram showed atrial fibrillation in 17% (n=25), of which one patient had atrial flutter and another had a myocardial infarction associated with the ischemic stroke. The mean ASPECTs was 8/10. The mean time to IVT onset to needle (OTN) was 210 minutes [75-245] with 68% exceeding 3 hours. The intra-hospital time from admission to needle (ATN) was 56 minutes [10-220]. Except for two patients who received 0.4 mg/kg tenecteplase due to myocardial infarction or a large proximal thrombus, the remaining patients received 0.25 mg/kg tenecteplase as a single intravenous bolus injection. Minimal immediate adverse events were observed, including nausea and vomiting in 2 patients and gingival bleeding in 1 patient. One patient developed extensive bruising shortly after the therapeutic injection. Fatal outcomes were observed in 8 patients, 2 due to extension of ischemia following IVT ineffectiveness and 6 due to symptomatic intracranial hemorrhage (ICH) in the hours following IVT. Twenty-four-hour control imaging after IVT objectified asymptomatic intracranial hemorrhage (aICH) in 12% (n=17) of cases. Stroke mimics were found in 4 patients, including acute myelitis, nonpainful paralytic sciatica, Todd's paralysis after motor epileptic seizure in a low-grade cortical glioma, and a case of sensory epileptic seizures. The mean mRS at 3 months was 2.67, 46% of which were between [0-2], with a death rate of 13% including all causes. The main results are summarized in Table 1.

Table 1: Demographic, clinical and stroke characteristics.

Patients (Total)	140 (100%)
Age (years)	67 (7-90)
Women	69 (49%)
Stroke risk factors	
Hypertension	69 (49%)
Diabetes	32 (23%)
Cardiac disease	35 (25%)
Smoking	28 (20%)
Previous stroke	10 (7%)
Previous transient ischemic attack	2 (1%)
Discontinuation of antiplatelet agents	9 (6%)
Under-dosed anti-vitamin K	8 (6%)
NIHSS score	
Mean	13
Mild (1-5)	11 (8%)
Moderate (6-14)	73 (52%)
Moderate to severe (15-20)	40 (29%)
Severe (>20)	16 (11%)
ASPECTs	
Mean	8
ASPECTs to 7	29 (21%)
ASPECTs to 8	36 (25%)
ASPECTs to 9	29 (21%)
ASPECTs to 10	46 (33%)
Tenecteplase dose	
0.25mg/kg	138 (98,6%)
0.4mg/kg	2 (1,4%)
Thrombolysis circuit delays (min)	
Door to admission	156 (15-240)
Admission to needle	56 (10-220)
Onset to needle	210 (75-345)
Complications	
Immediate related to the infusion	3 (2%)
Nausea/vomiting	2 (1,4%)
Gingivorrhagia	1 (0,7%)
Extension of the ischemia	2 (1,4%)
sICH	6 (4%)
24-hour Control CT scan	
aICH	17 (12%)
Stroke mimics	4 (3%)
Ischemic stroke constituted	119 (85%)
mRS (3 months follow-up)	
Mean	2.67
0-2	64 (46%)
3-4	30 (21%)
5	5 (4%)
6 (fatal)	18 (13%)
Lost to follow-up patients	23 (16%)

Discussion

The initiation of IVT for ischemic stroke at our institution started 23 years after the publication of the first positive therapeutic trial (NINDS) of IVT with alteplase in 1995 [4]. TNK, long considered a "cardiologic" fibrinolytic agent and therefore reserved for myocardial infarction, has gained considerable ground in IVT for ischemic stroke in several aspects, including efficacy, safety, and ease of administration [5]. The NOR-TEST clinical trial randomized more than 500 patients in each group to tenecteplase versus alteplase in patients with a low NIHSS of 4 and showed similar safety and better efficacy of the TNK arm in this clinical setting [6]. Superior efficacy of TNK over alteplase was also demonstrated in large vessel occlusion and in combined treatment or IVT followed by mechanical thrombectomy [7]. On the basis of these two large studies, TNK was for the first time included in the American recommendations (2019) for IVT in minor ischemic stroke [8]. In the post-hoc analysis of the NOR-TEST trial, TNK was associated with better outcomes in IVT for moderate and severe ischemic stroke [9]. And more recently, based on the AcT (Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke) and TASTE-A (Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance) trials, the European Stroke Organization recommended the use of TNK at a dose of 0.25 mg/kg, considering it to be as effective and safe as well as alteplase with significant superiority in ischemic stroke due to large vessel occlusion [10-12]. An additional advantage of TNK is its rapid onset of action, as early as 3 minutes, and its ease of administration, since it is a direct intravenous bolus injection compared to alteplase which is administered in a self-

feeding syringe over an hour after a bolus of 10% of the total dose in a direct intravenous injection [13]. The economic aspect is very important especially for centers with limited resources. However, the cost of TNK is less than half the cost of alteplase and therefore remains relatively more accessible with a still interesting profitability after the possibility of performing two IVTs from the same box if two eligible patients are present on the same time [14]. In our experience, safety outcomes were aligned with the literature with an ICH rate of 4% and aICH of 12% with few immediate and systemic infusion-related complications. The mRS at 3 months in our patients was slightly higher than in the NINDS study, probably explained by two major factors, the delayed for timeline IVT and the severity of NIHSS in our patients. The mortality rate at 3 months in our series was lower than international standards (**Table 2**), reaching 18% [15]. The possibility to perform only CT without injection was not an obstacle to start IVT in our structure. Initially, a hypoattenuation not exceeding 1/3 of the sylvian territory was required; this setting showed a high interindividual variability and was therefore replaced by the evaluation of ASPECTs, which is a score on 10 points and therefore more objective, causing less interindividual variability [16,17]. Studies have shown that a score lower than 7/10 is associated with a higher risk of bleeding. Therefore, this cutoff has been adhered to in our practice. The analysis of ASPECTs on CT does not give an idea of the state of the vessels, the presence or absence of large vessel occlusion, the various mismatches, the number of microbleeds and a higher risk of stroke mimics. Our rate of stroke mimics was much lower than those reported in the literature and may exceed 20% in some series [18]. Wake-up stroke is also a clear limitation of using CT, even with a favorable ASPECTs of 10 points [19]. The average time between symptom onset and IV thrombolysis (OTN) is at the upper limit of the therapeutic window, indicating several factors contributing to delay, particularly during the prehospital phase. This OTN delay was greatly increased during the COVID-19 pandemic, during which the CT evaluated several patients with respiratory symptoms, in addition to the time devoted to disinfecting the premises, resulting in a delay in IVT. There is a challenge in upgrading the management of ischemic stroke in our context, particularly focusing on neuroimaging and addressing various timelines. Establishing a more specialized network dedicated to acute ischemic stroke management is crucial to improving the quality of care and IV thrombolysis outcomes.

Table 2: Comparison of the efficacy and safety of thrombolysis with Tenecteplase with studies published in the literature.

Studies	NOR-TEST (n=382)	ATTEST (n=47)	EXTEND-IA TNK (n=150)	Australia -TNK (n=50)	Haley et al (n =31)	Haddouali and al. (n=140)
mRS (0-1)	64%	28%	49%	54%	48.4%	23.8%
mRS 6	5%	17%	15%	8%	22.6%	13%

Conclusion

The availability of Tenecteplase and non-enhanced CT was sufficient to initiate IVT for ischemic stroke at our institution. This combination appears to be a fairly reassuring option in terms of efficacy and safety, but excludes a large pool of patients due to the limited information provided by non-enhanced CT.

Abbreviations

OTA (Onset to Admission)
ATN (Admission to Needle)
NIHSS (National Institute of Health Stroke Score)
NOR-TEST (the Norwegian Tenecteplase Stroke Trial)
OTN (Onset to Needle)
ASPECTs (Alberta Stroke Program Early CT Score)
TNK (Tenecteplase)
CT scan (Computed Tomography scanner)
mRS: modified Rankin Scale
aICH: asymptomatic intracranial hemorrhage
sICH: symptomatic intracranial hemorrhage

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None

Statements and Declarations

Conflict of interest

The authors declare no conflict of interest regarding this case report.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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