REVIEW ARTICLE

Efficacy of tenecteplase compared to alteplase in acute ischemic stroke treatment. A narrative review

Nilson Alexander Cedillo-Reyes[1,c], María del Carmen Cuadra-Campos[1,c], William Alejandro Cosio-Mosqueira[1,c], Gustavo Adolfo Vásquez-Tirado[1,a,b]

ABSTRACT

Introduction: *Intravenous thrombolysis with alteplase (ALT) is recommended as standard treatment, being the only thrombolytic agent approved by the FDA. Tenecteplase (TNK), a modified tissue plasminogen activator, is emerging as an alternative antithrombotic agent. This narrative review assesses the current evidence and addresses practical issues regarding the efficacy and safety of tenecteplase compared to alteplase.* ***Methodology:*** *A systematic and analytical search of the literature was performed, providing a qualitative synthesis of meta-analyses and completed clinical trials comparing the effectiveness and safety of tenecteplase with alteplase in AIS, using articles indexed in MEDLINE, the Cochrane Library, and Scopus.* ***Results:*** *Randomized clinical trials mostly agree in finding TNK to be at least as or more effective than ALT for neurological improvement after AIS; while the meta-analyses agree that patients who received TNK had more successful recanalization, they differ in terms of the findings of early neurological improvement, functional outcome at 90 days, and mortality at 90 days.* ***Conclusion:*** *Tenecteplase is at least as effective as alteplase with regard to neurological improvement after treatment of acute ischemic stroke.*

Key words: *Acute ischemic stroke, tenecteplase, alteplase, intravenous thrombolysis.*

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[1] Escuela de Medicina, Universidad Privada Antenor Orrego, Trujillo, Perú.
[a] Médico Internista.
[b] Médico Intensivista.
[c] Estudiante de Medicina.

INTRODUCTION

Acute ischemic stroke (AIS) causes significant morbidity and mortality in the population, defined as the acute onset of neurological focalization caused by the sudden loss of blood supply in a vascular territory, ranking as the second most common cause of mortality in adults and the third most common cause of disability worldwide, with up to 50% of survivors with neurological sequelae and chronic disability[1,2]. In low- and middle-income countries, it represents a critical situation due to the increase in its incidence, associated disability and high mortality in recent decades. In Peru, it is estimated that 15% of all premature deaths are caused by stroke[3]. In health systems such as ours, with saturated services and a slow response capacity, providing the appropriate and early care that stroke patients require is a pending task but one that cannot be postponed.

Current clinical guidelines indicate that revascularization interventions are the cornerstone in the acute management of AIS, including intravenous thrombolysis and endovascular treatment with mechanical thrombectomy[4,5]. As time is the main defining factor of clinical outcomes, it also emphasizes the importance of early revascularization as soon as possible to avoid further functional impact or fatal consequences[6].

Intravenous thrombolysis with alteplase is recommended as standard treatment for guideline-eligible patients with AIS, being the only FDA-approved thrombolytic agent in this setting[4,5,7]. Although it significantly improves the prognosis for recovery without disability, alteplase has several limitations, including a low recanalization rate, risk of intracranial hemorrhage, and a short plasma half-life requiring continuous infusion over a period of approximately 1 hour[4,8].

Tenecteplase (TNK), a modified tissue plasminogen activator, has higher fibrin binding affinity, higher resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1), lacks procoagulant effects, and has a longer free half-life, allowing it to be administered as a single bolus instead of the bolus and continuous infusion required for alteplase[9]. These characteristics of TNK imply that it is a promising agent for AIS, since theoretically, due to the higher affinity for fibrin and the ease of administration, TNK has the potential to be superior in efficacy and safety compared to ALT for stroke.

The latest guidelines of the American Heart/Stroke Association included as a new recommendation that TNK could be considered an alternative to ALT in selected patients with AIS with minor neurological deterioration and no significant intracranial occlusion due to the pharmacodynamic differences already described. However, this recommendation was based on informal considerations rather than a meta-analysis of randomized controlled clinical trials[4]. At present, several studies have compared the efficacy of tenecteplase and alteplase with respect to the treatment of AIS[9,10]. The purpose of this article is to review the most recent evidence, as well as other practical issues regarding the use of tenecteplase and alteplase, and to determine whether tenecteplase is more effective than alteplase.

METHODS

A systematic search of the literature was performed, and a qualitative synthesis of meta-analyses and completed clinical trials was provided, which compared the effectiveness and safety of tenecteplase with alteplase in AIS, using articles indexed in MEDLINE, Cochrane Library and Scopus from January 2010 to November 2021. We used the following keywords: alteplase, tenecteplase, acute ischemic stroke, alteplase compared to tenecteplase, and thrombolysis. The search strategy was ((Acute Ischemic Stroke) OR (Acute Ischaemic Stroke) OR (Cerebrovascular disease) OR (Cerebrovascular accident)) AND ((Thrombolysis) OR (Intravenous thrombolysis) OR (Fibrinolytic)) AND ((Tenecteplase) OR (TNKase) OR (Metalyse)) AND ((Alteplase) OR (rt-PA) OR (Tissue Plasminogen Activator)). Case reports, editorials and comments were excluded,

and there were no restrictions regarding language, obtaining 22 studies for the purposes of the present review.

Generalities

Stroke is the second leading cause of death after malignant tumors, with thrombotic acute ischemic stroke being the most common variety. Reperfusion therapies with thrombolysis and endovascular thrombectomy are effective treatment methods for AIS, have improved the prognosis of patients by reducing disability and are highly cost-effective[4,5].

Tissue plasminogen activator (rTPA) facilitates the conversion of plasminogen to plasmin, promoting the lysis of fibrin clots to restore cerebral perfusion. Thrombolytic therapy with rTPA within the first 4.5 hours of symptom onset has shown early clinical neurological improvement and functional improvement 90 days after the event[4,5].

Alteplase as standard for intravenous thrombolysis in ais

Early administration of rtPA to patients who meet the selection criteria is the main treatment for AIS. The FDA approved alteplase (rtPA) for the treatment of ST-segment elevation myocardial infarction and subsequently for the treatment of acute massive pulmonary embolism, occluded central venous catheters, and ischemic stroke. However, numerous complications, such as severe bleeding, limited recanalization rates, and rapid clearance requiring continuous infusion, have prompted the development of thrombolytics with more desirable properties.

Although alteplase has been shown to provide benefit when administered to some patients presenting with AIS symptoms within 4.5 hours of symptom onset, its administration increases the patient's risk of intracranial hemorrhage, which is one of the complications more serious of its use; however, the benefits clearly outweigh the risks[4,6,7]. Hacke et al. evaluated the safety and effectiveness of ALT in 821 patients with a mean age of 65 years and found that the incidence of any intracranial hemorrhage was 27%, only 2.4% presented symptomatic hemorrhages, and 52% achieved functional independence at 90 days, defined as a score of 0-1 on the modified Rankin scale[11]. Rha et al., in a study with 591 patients, found that 1.9% presented symptomatic intracranial hemorrhage, and 62.5% reached functional independence in three months[12].

Tenecteplase as an emerging agent

TNK is a new generation fibrinolytic agent, a modified variant of ALT, which, compared to ALT, is easier to administer due to its pharmacokinetic profile, higher specificity for fibrin, longer half-life and reduced binding to PAI-1, implying greater resistance to inactivation by PAI-1[13]. Given these characteristics, TNK is a promising agent for acute ischemic stroke, as it theoretically has the potential to be superior in efficacy and safety compared to ALT for stroke. However, even if it is only equivalent to ALT rather than better, TNK would still be a useful alternative agent to AIS.

Since TNK only requires a one-time bolus for administration, compared to the 60-minute continuous infusion required for ALT, TNK could be delivered more efficiently in patients with large vessel occlusion, allowing for faster initiation. of endovascular mechanical thrombectomy, especially in drip-and-ship patients, who could receive the thrombolytic in a peripheral health center and then be immediately transferred in an ambulance with standard personnel such as paramedics, rather than having to wait for the availability of an ambulance equipped for critical care with nurses operating the continuous infusion pump[13,14].

Tenecteplase compared to alteplase

Neurological improvement

Among the published clinical trials that compared alteplase and tenecteplase in AIS, those by Parsons et al., Huang et al. and Campbell et al., who administered TNK at a dose of 0.25 mg/kg and standard doses of ALT within a window of 6, 4.5, and 4.5 hours, respectively, found that the TNK group had superior neurological improvement

outcomes in terms of clinical improvement at 24 hours and functional independence at 90 days compared to those who received alteplase[15,16]. Additionally, Campbell found that 22% of the TNK group achieved reperfusion above 50% of the affected vascular territory, compared to 10% treated with alteplase[17]. In contrast, Logallo et al. compared TNK at a dose of 0.4 mg/kg and ALT at a standard dose within a 4.5-hour window in a significantly larger population than other clinical trials, finding no differences between both groups for the outcome of functional independence at 90 days[18].

Based on the clinical trials described above, four meta-analyses were performed, reporting no statistically significant difference in 90-day neurological functional recovery and no difference between tenecteplase and alteplase in mortality[19-22]. However, the Thelengana and Kheiri meta-analyses reported better rates of early neurological improvement with TNK (RR 1.56; 95% CI, 1-00-2.43; p=0.05)[20,21], and the Kheiri meta-analysis reported a significantly higher rate of complete recanalization (OR 2.01; 95% CI, 1.04-3.87; p=0.04)[21].

The latest meta-analysis by Katsanos et al. included 4 selective randomized clinical trials, limited only to the subset of patients with confirmed large-vessel AIS, treated within 4.5 hours from the time of stroke onset. The meta-analysis reported that patients receiving TNK were more likely to have lower Modified Rankin Scale scores of 0 to 2 (OR 2.06; 95% CI, 1.15-3.69), three times more likely to have successful recanalization (OR 3.05; 95% CI, 1.73-5.40), and good functional outcome at 90 days (OR 1.84; 95% CI, 1.18-2.87) than patients receiving ALT; however, they did not find differences in early neurological improvement or mortality from any cause at 90 days[23].

Regarding neurological improvement, most randomized clinical trials agree that TNK is at least as or more effective than ALT for neurological improvement after AIS[15-18], while meta-analyses agree that patients who received TNK had higher rates of successful recanalization but differed in terms of early neurological improvement findings, 90-day functional outcome, and 90-day mortality[19-22].

Adverse effects

The clinical trials and meta-analyses mentioned above, when comparing the adverse effects between these thrombolytics, measured the rates of total and symptomatic intracranial hemorrhage. This complication is considered the most feared and devastating due to the high morbidity and mortality it entails, and although the overall benefits of tPA for stroke outweigh the risks, up to 3-4% of patients treated for stroke will develop this complication[24]. To this end, for intracranial hemorrhage, the AHA/ASA recommends replacing coagulation factors with cryoprecipitate and transfusing with platelets, but it acknowledges the lack of evidence to support a specific therapy[25,26].

None of the meta-analyses found a statistically significant difference in rates of total or symptomatic intracranial hemorrhage between TNK and ALT[21-23], but there was a trend toward lower rates of intracranial hemorrhage with tenecteplase (OR; 0.81 95% CI, 0. 56-1.17, p=0.26)[14]. Although this was calculated by pooling all the doses of tenecteplase used in the different studies, there is evidence that the 0.4 mg/kg dose of tenecteplase could lead to higher rates of intracranial hemorrhage compared to the 0.25 mg/kg dose. mg/kg[21,27]. Therefore, there would be a stronger trend toward lower rates of intracranial hemorrhage if patients receiving tenecteplase at a dose of 0.4 mg/kg were excluded.

Although studies usually focus on intracranial bleeding as the main adverse effect, it is necessary to consider the rates of other bleeding events associated with the administration of both thrombolytics. A large number of cardiology studies compare the adverse effects of TNK and ALT in patients with acute coronary syndrome (ACS). Since the rates of adverse events other than intracerebral hemorrhage for both thrombolytics are likely to be the same for patients with AIS as

for SICA, we will summarize the relevant literature below.

Three randomized clinical trials compared TNK with ALT for patients with acute coronary syndrome and reported major bleeding, including other than intracerebral bleeding, as an adverse effect. The largest study found that TNK patients had lower rates of noncerebral bleeding complications (26.43 vs 28.95%, p=0.0003) and less need for blood transfusion (4.25 vs 5.49%, p=0.0002)[28]. A meta-analysis that included these three clinical trials found a statistically significant reduction in major bleeding with TNK compared with ALT (RR 0.79; 95% CI, 0.69-0.90; p=0.0002)[28,29].

Regarding adverse effects, the available literature has not reported statistically significant differences in intracranial hemorrhage rates for tenecteplase versus alteplase in patients with AIS. Furthermore, the use of tenecteplase is associated with lower rates of noncerebral bleeding than alteplase[28-30].

This review strongly suggests that tenecteplase is an alternative to alteplase for thrombolysis in patients with AIS within the first 4.5 hours of evolution and at a dose of 0.25 mg/kg. Although the superiority of TNK for 90-day performance status cannot be demonstrated, the confidence intervals for these results are strongly skewed toward a beneficial effect of tenecteplase. To reinforce this finding, a beneficial effect of tenecteplase was observed on two important secondary outcomes, the rate of recanalization and early neurological improvement. Not only did the efficacy findings suggest a potentially beneficial effect of TNK in patients with AIS, but no deficiencies in terms of safety were also observed, with rates of mortality and intracranial hemorrhage being comparable between the two thrombolytics. Evidence also suggested that the 0.25 mg/kg dose of tenecteplase is preferable to other doses, as it was associated with higher rates of early neurological improvement, a trend toward better functional outcome at 3 months, and lower rates. of intracerebral hemorrhage[15-17]. However, these results should be interpreted with caution, as the included studies differ in important aspects, such as the use of advanced imaging for patient selection, the presence of large vessel occlusion, and the time window for drug administration or endovascular therapy, which makes indirect comparisons less conclusive.

To incorporate all the evidence, we chose to include randomized clinical trials, systematic reviews, and meta-analyses. All of these studies focused on patients with ischemic stroke undergoing thrombolysis; however, they differed in several aspects related to patient selection, intervention and study design, which represents a limitation to the review.

CONCLUSIONS

Tenecteplase is at least as effective as alteplase in regards to neurological improvement after treatment of acute ischemic stroke. Furthermore, tenecteplase might be associated with fewer bleeding complications than alteplase; however, more studies need to be performed to compare the safety of both drugs. Therefore, the use of tenecteplase instead of alteplase should be considered for intravenous thrombolysis in patients with acute ischemic stroke. If used, the recommended dose of tenecteplase is 0.25 mg/kg (maximum 25 mg).

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Correspondence:
María del Carmen Cuadra Campos
Pedro Urraca 394 Urb. San Andrés, Trujillo, Perú.
Phone: 974156370
Email: makicuadra30@gmail.com