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Indications and risks of the treatment fibrinolytic in accident patients Ischemic cerebrovascular

Indicaciones y riesgos sobre el tratamiento fibrinolítico en pacientes con accidente cerebrovascular isquémico

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73 - 96

Abstract

Introduction: Stroke causes functional limitation, worsening status, frailty and demand for health care; Objective: To assess the quality of scientific evidence from a systematic review focused on the efficacy of stroke treatment. Objective: To assess the quality of scientific evidence from a systematic review focused on the efficacy of fibrinolytic fibrinolytic treatment in patients with ischemic stroke; Methodology: Systematic review of meta-analyses published between 2018 - 2023, in English and Spanish; Results: Fibrinolysis is fundamental in the reduction of disability secondary to the event. The use of tenecteplase leads to complete recanalization (38.5%); while alteplase 29%. A hemorrhagic risk of 3.05% for tenecteplase and 2.86% in alteplase, statistically alteplase, statistically significant (RR: 1.27 with 95% CI [1.02 - 1.57], p = 0.03). Therefore, tenecteplase is an effective option for treatment considering its minimal likelihood of producing bleeding; Conclusions: Both drugs are effective and adequate. However, tenecteplase ensures a lower risk of bleeding.

Keywords: stroke, fibrinolysis, cerebral ischemia, treatment.

Resumen

Introducción: Un accidente cerebrovascular produce una limitación funcional, empeorando el estado, fragilidad y demanda de atención en la salud; Objetivo: Valorar la calidad de evidencia científica a partir de una revisión sistemática enfocada en la eficacia del tratamiento fibrinolítico en pacientes con accidente cerebrovascular isquémico; Metodología: Revisión sistemática de metaanálisis publicados entre 2018 – 2023, en idioma inglés y español; Resultados: La fibrinólisis, es fundamental en la reducción de discapacidad secundaria al evento. El uso de tenecteplasa conduce a una recanalización completa (38,5%); mientras que la alteplasa un 29%. Un riesgo hemorrágico de 3,05% para tenecteplasa y 2,86% en alteplasa, estadísticamente significativos (RR: 1,27 con IC 95% [1,02 - 1,57], p = 0,03). Por lo tanto, la tenecteplasa es una opción eficaz para el tratamiento considerando su mínima probabilidad de producir una hemorragia; Conclusiones: Los dos medicamentos son eficaces y adecuados. Sin embargo, la tenecteplasa asegura un menor riesgo de hemorragia.

Palabras clave: accidente cerebrovascular, fibrinólisis, infarto cerebral, tratamiento.

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
74 - 96

1. Introduction

Stroke (ACV) is defined as a functional alteration of the brain, whether transient or permanent, whose main cause is vascular in origin, affecting one or more parts of the brain. According to the World Health Organization (WHO), there are 15 million people with stroke every year worldwide, most of whom die or are left with permanent sequelae, radically affecting their environment (1-4).

It is currently one of the main causes of morbidity and mortality worldwide, and is therefore considered the main reason for consultation in emergency neurological care (12). It is a "time- dependent" pathology, in which 87% of cases are of ischemic origin, of which 80% have an atherosclerotic origin (1,2).

An ischemic stroke is triggered in people with vascular narrowing, and older adults are the ones who develop vascular sclerosis due to the patient's age. A hemorrhagic stroke results from the rupture of a blood vessel, associated with risk factors such as the presence of aneurysms, hypertension, use of anticoagulants and patients with amyloid angiopathy (5,6).

Based on this premise, it is necessary to mention the determining risk factors when it comes to producing a cerebrovascular event in a person, which can be modifiable or non-modifiable.

Within the group of modifiable factors are arterial hypertension, sedentary lifestyle, overweight, malnutrition and the consumption of substances such as tobacco, increasing the probability of developing a stroke by 2.5% - 4.1% in men and 3.6% - 5.8% in women (7,13). Among the non-modifiable factors, the age of each patient is mentioned, being the most important since a higher risk is seen in adults who are between 65 - 80 years old; where women maintain a certain protective factor due to the production of estrogens until before menopause (1,7,13).

According to the "National Institute of Neurological Disorders and Stroke" (NINDS), an ischemic stroke, also known as STROKE, is a sudden and emergent episode requiring immediate action due to the proportional relationship of injury, "time is brain," since irreversible neurological damage will not necessarily be observed in the first few minutes of clinical deficiency, so effective treatment

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
75 - 96

will preserve the affected brain cells and reduce brain damage by up to 80%, and in some cases even reverse it (9,10).

2. Methodology

2.1. Study design

2.1.1. Eligibility criteria

For the development of this criterion, a research question was posed: What is the current level of scientific evidence related to fibrinolytic treatment applied in patients suffering from ischemic stroke? Therefore, specific points were established to take into account when selecting each publication.
Studies included:

a) They were published in databases such as PubMed, Scopus, Redalyc and ScienceDirect, within the period 2018 – 2023.
b) Publications written in English and Spanish.
c) Studies that belong to medical societies and provide a scientific approach related to the objective of the work.
d) Meta-analysis and systematic reviews, based on the Oxford scale, considering the into account ranges 1a – 2b.

Studies were excluded:

a) They do not explain the methodological process of precision.
b) They present a discussion with incongruent information.
c) They mention some type of conflict of interest.
d) They focus on a population under 40 years of age.

2.2. Data extraction

2.2.1. Information sources

Based on the PRISMA 2020 model, an appropriate and correct methodological process was carried out for the selection of publications in order to exemplify and quantify these studies.

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
76 - 96

2.2.2. Search strategies

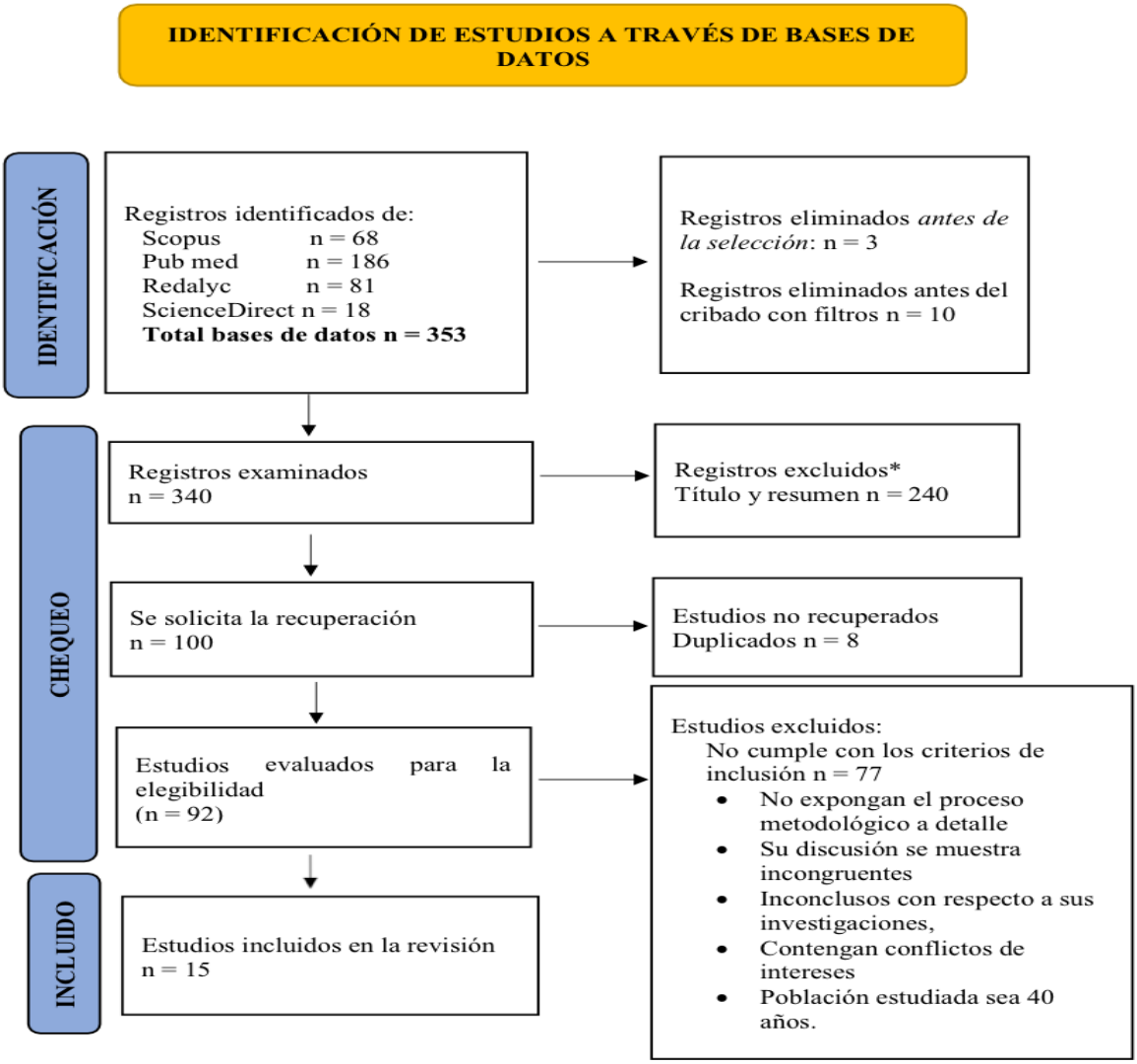
By using Boolean operators, known as AND, OR, NOT, the information search process was facilitated, ensuring that the collection of data and information is up-to-date, relevant, and related to the topic of study.

2.2.3. Summary of results

The identification of the selected studies began with a general search of the topic, obtaining 353 general works, of which 68 belonged to Scopus, 186 to PubMed, 18 to ScienceDirect and 81 to Redalyc. Through the evaluation of bibliographic records and various criteria, a total of 341 works was excluded. Finally, the inclusion criteria were considered, reaching a selection of 15 studies that met each established point, were approved and evaluated to be used in the bibliographic review (Figure 1).

Subsequently, a second analysis was carried out, in which a detailed reading of the segments of each study was carried out: methodology, development, discussion, conclusions and recommendations. To avoid duplicate documents and to have a better organization, the Zotero tool was used, a platform that allows storing the studies, finding them more quickly and having the most relevant information.

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
77 - 96



2.2.4. Methodological quality

To ensure the adequate quality of information in the study, the Oxford Quality Scale was used, a tool that allows for standardizing information, ranking each study, identifying any type of bias present and assessing the limitations found. The scale has 5 levels that consider the type of study, the clinical problem in question and its thematic area in order to classify it and give it an adequate value.

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
78 - 96

Level 1: High Quality Evidence

- 1a: Meta-analysis of well-designed randomized controlled trials (RCTs).
- 1b: At least one well- designed RCT.
- 1c: "All-or-nothing" therapies (when all patients die without treatment and some survive with treatment).

Level 2: Moderate Quality Evidence

- 2a: Systematic review of high-quality cohort studies.
- 2b: Cohort study (including follow-up studies of RCTs).
- 2c: Results of outcome-based research (e.g., case studies) database).

Level 3: Limited Quality Evidence

- 3a: Systematic review of case-control studies.
- 3b: Case-control study.

Level 4: Low Quality Evidence

- 4: Case series (and low-quality cohort and case-control studies).

Level 5: Expert Opinion

- 5: Expert opinion without explicit critical evaluation, or based on physiology, laboratory research or theoretical principles.

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
79 - 96

3. Development

Bibliometric studies

Table número 1. Compilation of studies according to their year of publication.

BASE OF DATA	YEARS															
	2016		2019		2020		2021		2022		2023		2024		TOTAL	
	F	%	F	%	F	%	F	%	F	%	F	%	F	%	F	%
Scopus	1	6,7	0	0	1	6,7	0	0	0	0	1	6,7	0	0	3	20
Pubmed	0	0	0	0	0	0	0	0	3	20	1	6,7	2	13,3	6	40
Redalyc	0	0	1	6,7	0	0	1	6,7	1	6,7	0	0	0	0	3	20
Sciencedirect	0	0	0	0	0	0	0	0	0	0	1	6,7	2	13,3	3	20
TOTAL	1	6,7	1	6,7	1	6,7	1	6,7	4	26,7	3	20	4	26,7	15	100

Note. Source: authors

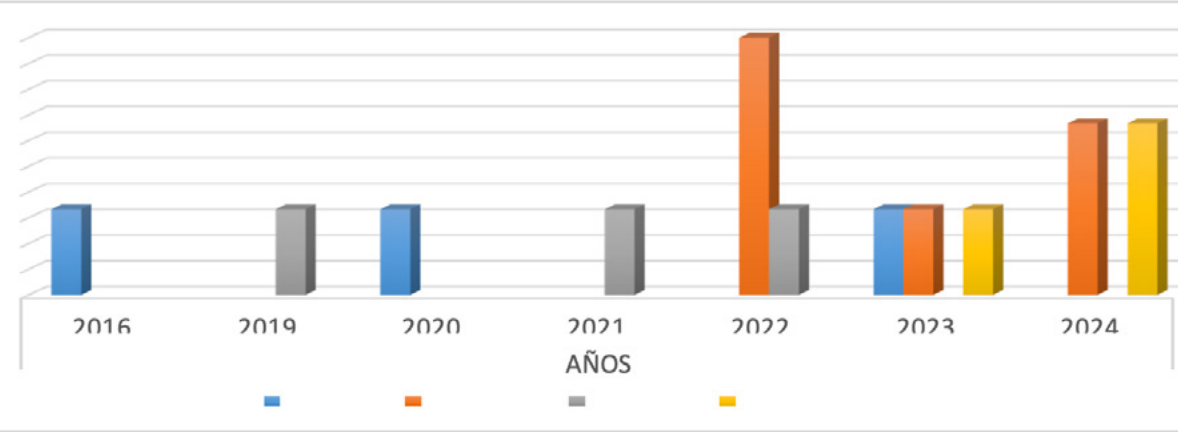


Figure 1. Database Studies of the Systematic Review, after selection filter by years. **Source:** Authors

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
80 - 96

The articles used for this study were obtained from the scientific databases PubMed, Scopus, Redalyc and ScienceDirect. Most were published in 2022, followed by some from 2024, and one study from 2016 was included because its results were statistically significant when using a wider therapeutic window. The chosen research articles were obtained through a systematic review in the following scientific databases: ScienceDirect (3 articles, 20%), PubMed (6 articles, 40%), Scopus (3 articles, 20%) and Redalyc (3 articles, 20%).

Data collection:

After completing the systematic research flow, specific tables are prepared in accordance with the PRISMA 2020 guide.

Table 2: Data collection on fibrinolytic therapy.

N.º	ISSUE	BASE OF DATA	YEARS PUBLISH	AUTHORS	STUDY	DRUG	LINK
1	Safety and efficacy of tenecteplase versus alteplase in patients with acute ischemic stroke (TRACE): A multicenter, randomized, open-label, blinded, controlled phase II study (PROBE)	Pubmed	2022	Li S, Pan Y, Wang Z, et al. (28)	Clinical trial: multicenter, prospective, randomized, open, blinded and phase II	tenecteplasa TNK alteplasa rt-PA	https://pubmed.ncbi.nlm.nih.gov/34429364/

2	The efficacy and safety of tenecteplase versus alteplase for acute ischemic stroke: an updated systematic review, pairwise, and network meta-analysis of randomized controlled trials.	Pubmed	2023	Abuelazm M, et al. (30)	Metaanálisis ECA	tenecteplasa TNK alteplasa rt-PA	https://pubmed.ncbi.nlm.nih.gov/36449231/
3	Alteplasa intravenosa	Pubmed	2020	Thomalla G, et al. (29)	Metaanálisis ECA: WAKE-UP, EXTEND, THAWS y ECASS-4.	PLACEBO alteplasa rt-PA	https://pubmed.ncbi.nlm.nih.gov/33176180/
4	Intravenous fibrinolysis of ischemic stroke in a medium complexity municipal hospital in the city of General Villegas, province of Buenos Aires.	Sciencedirect	20016	Hawkes MA, et al. (36)	Retrospective studies	alteplasa t-PA	http://www. scielo.org.ar /scielo.php?script=sci_arttext&pid=S0025-
5	Intravenous thrombolysis in acute ischemic stroke patients with pre- stroke disability: A systematic review and meta-analysis.	Pubmed	2023	Bao Q, et al. (37)	Metaanálisis	alteplasa rt-PA	https://on linelibrary.wiley.c om/doi/10.1002/brb3.3431

6	Tenecteplase versus alteplase for patients with acute ischemic stroke: a meta-analysis of randomized controlled trials.	Pubmed	2023	Zhang X, et al. (32)	Metaanálisis ECA	tenecteplasa TNK alteplasa rt-PA	https://www .ncbi.nlm.ni h.gov/ pmc/a rticles/PMC 10781500/
7	Comparative efficacy and safety of tenecteplase and alteplase in acute ischemic stroke: a pairwise and network meta-analysis of randomized controlled trials	Pubmed	2022	Rehman AU, et al. (33)	Metaanálisis ECA	tenecteplasa TNK alteplasa rt-PA	https://pubmed. ncbi.nlm.nih.go v/36630803/
8	Tenecteplase versus alteplase for intravenous thrombolytic treatment of acute ischemic stroke: a systematic review and meta-analysis.	Pubmed	2023	Shen Z, et al. (34)	Metaanálisis	tenecteplasa TNK alteplasa rt-PA	https://pubmed. ncbi.nlm.nih.go v/37552459/
9	Efficacy of tenecteplase compared with alteplase for treatment of acute ischemic stroke. A narrative review	Redalyc	2023	Cedillo-Reyes N, et al. (42)	Metaanálisis ECA	alteplasa rt-PA tenecteplasa TNK	https://www.scielo.cl/ scielo.php?script=sci_ arttext&pid=S0717- 92272023000300363 &lng=en&nrm=iso&tl ng=en

10	Efficacy and safety outcomes of Tenecteplase versus Alteplase for thrombolysis of acute ischemic stroke: a meta-analysis of 9 randomized controlled trials.	Sciencedirect	2024	Wang Y, et al. (35)	Metaanálisis ECA	tenecteplasa TNK alteplasa rt-PA	https://www.sciencedirect.com/science/article/abs/pii/S0022510X24000479
11	Pharmacological Fibrinolysis in Acute Ischemic Stroke: Experience in a Tertiary Hospital in Ecuador.	Redalyc	2019	Scherle Matamoros C, et al. (38)	Prospectivo, longitudinal ECA	alteplasa rt-PA	http://sci elo.senescyt.gob.e c/scielo.php?script=sci_artt
12	Uso y resultados de la fibrinololisisis intravenosa en una unidad cerebrovascular / Use and results of intravenous fibrinolysis in a stroke	Pubmed	2021	Rosales Julieta S, et al. (39)	Retrospectivo observacional ECA	alteplasa rt-PA	http://www. scielo.org.ar /scielo.php?script=sci_arttext&pid=S0025-
13	Results of bridging intravenous thrombolysis versus endovascular therapy alone in acute late window ischemic stroke.	Pubmed	2024	Demeestere J, et al. (40)	Retrospectivo Multicéntrico	alteplasa rt-PA	https://www.ahajourn als.org/doi/10.1161/STROKEAHA.124.04

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87

14	Predictors of poor outcome in acute ischemic stroke patients treated withalteplase, a multicenter randomized trial	Sciencedirect	2024	Zeinhom MG, et al. (41)	ECA	alteplasa rt-PA	https://pubmed.ncbi.nlm.nih.gov/38472241/
15	Benefits of thrombolysis with rtPA in patients with ischemic cerebrovascular event, according to age group.	Sciencedirect	2024	Cedeño Almeida LY, et al. (42)	Metaanálisis	alteplasa rt-PA	https://doi.org/10.1038/s41598-024-56067-5

Source: Review sheets

Author: Andrés Esteban Pesantez Coronel

Indications on the application of fibrinolytic treatment in patients with ischemic stroke.

The systematic review analysed 15 studies that showed similarities in the therapeutic regimens used for the treatment of ischaemic stroke internationally. The dose of alteplase was 0.9 mg/kg, while that of tenecteplase varied between 0.1, 0.25 and 0.32 mg/kg, administered within a therapeutic window of less than 4.5 hours in all the studies reviewed.

Efficacy of different drugs used in fibrinolytic treatment in patients with ischemic CVD.

Eight studies comparing the efficacy of the different drugs used were compiled, 7 of these studies compared tenecteplase and alteplase, while one study compared alteplase with placebo. The results indicate recanalization rates ranging from 28% to 54% for tenecteplase. For alteplase, the results range from 24% to 47%. It is observed that in the study comparing alteplase with placebo, a recanalization rate of 39% is presented in favor of placebo.

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
85 - 96

Likewise, the early neurological improvement presented by patients is stated, which has results ranging from 23% to 56% for tenecteplase.

Comparing it with alteplase we have figures that range between 26% and 56%. In the placebo study it gives us a value of 29% (25,26,27,29,30,31,32,39).

Risks of applying fibrinolytic treatment in patients with ischemic stroke

The administration of alteplase and tenecteplase in stroke carries risks such as intracerebral hemorrhage, serious adverse events and death. According to 8 studies (Table 5), tenecteplase was associated with arrhythmias (3-5%), hypotension (12-20%), severe hypersensitivity (2-12.3%), mortality (3-10%) and hemorrhage (2-5%). Alteplase was associated with arrhythmias (1.7-6.7%), hypotension (1-13%), severe hypersensitivity (1-18%), mortality (1.2-10.2%) and hemorrhage (1.7-3.7%) (25,29,30,31,34,36,37,38).

Indications on the application of fibrinolytic treatment in patients with ischemic stroke

Alteplase was approved in 1996 by the Food and Drug Administration to treat acute ischemic stroke following the National Institute of Neurological Disorders and Stroke (NINDS) study, which demonstrated that rtPA administered during the first 3 hours resulted in complete recovery in patients (1,2,3,4,16,18).

In the European Cooperative Acute Stroke Study (ECASS I, II, and III), the extension of the treatment window in patients with ischemic stroke was evaluated. The results showed that those treated with rt-PA within four hours of the event were more likely to achieve favorable functional recovery, according to the mRS 01 scale, at 90 days of follow-up (1,2,3,4,25,26).

The study “Extending the Time for Thrombolysis in Emergency Neurological Deficits” (EXTEND) demonstrated that treatment with alteplase for 4.5 to 9 hours, in patients with salvageable brain tissue, resulted in a greater likelihood of functional independence at 90 days, according to the mRS 01 scale. However, the group receiving rt-PA showed a non- significant increase in cases of symptomatic cerebral hemorrhage (1,2,3,4,25,26).

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
86 - 96

A 2014 meta-analysis evaluated 6756 patients with ischemic stroke randomized to receive rt- PA or placebo in several studies. The primary endpoint was the mRS 0-1 score at 90 days. The results showed that alteplase administration within the first 3 hours was associated with a better outcome (33%) compared with the control group (23%) (OR 1.75, 95% CI 1.35-2.27).

By extending the therapeutic window to 3-4.5 hours, the percentage of positive results was 35% with rt-PA vs 30% in the control group (OR 1.26, 95% CI 1.05-1.51). Neither age nor severity of the event had a significant influence. However, treatment with rt-PA increased the risk of intracranial hemorrhage to 6.8% vs 1.3% in the control group (OR 5.55, 95% CI4.01-7.70) (1,2,3,4,25,26).

The Tenecteplase vs Alteplase Safety and Efficacy in Patients with Acute Ischemic Stroke (TRACE) study found that use of alteplase TNK resulted in better outcomes. Recanalization was achieved in 28% of patients treated with a dose of 0.32 mg/kg (OR 1.16 [95% CI 1.14-2.13]; p=0.014), with excellent neurological recovery (RR 1.14; 95% CI 1.06-1.12; p=0.03). However, use of low-dose tenecteplase (0.1 mg/kg) was associated with a 12% rate of disability as an adverse event (27).

Although international protocols state that the therapeutic window for treating ischemic stroke should not exceed 4.5 hours for administering fibrinolytics, in practice, the time of onset of the disorder is often unknown. One study demonstrated that intravenous alteplase offers better functional outcomes at 90 days compared with placebo or standard care, with high recanalization rates in TNK (OR 1.49 [95% CI 1.10-2.03]; p=0.011) and excellent neurological recovery (OR 1.50; 95% CI 1.06-2.12; p=0.022). Although a net benefit in functional outcomes was observed, an increased risk of symptomatic intracranial hemorrhage was also reported. Tenecteplase (TNK) shares administration criteria with alteplase and is in phase III clinical trials, showing similar results.

The study conducted by Julieta Rosales indicated that the use of TNK reduced the hospitalization time from 9 to 5 days ($p < 0.00001$) and shortened the door-to-needle time from 75 minutes with alteplase to 53 minutes with TNK ($p < 0.00001$), in addition to 76% of patients receiving treatment within 60 minutes in the TNK group versus 36% in the alteplase group ($p < 0.00001$) (28).

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
87 - 96

Efficacy of different drugs used in fibrinolytic treatment in patients with ischemic stroke

People who have suffered an ischemic stroke with unknown onset time have been excluded from thrombolysis. However, intravenous alteplase has been shown to be safe and effective in these cases, provided salvageable tissue is identified by biomarker imaging. In addition, improved functional outcome has been observed at 90 days compared to placebo or standard care. There is a net benefit in all functional outcomes, despite the increased risk of symptomatic intracerebral hemorrhage. It is also mentioned that the door-to-needle time is reduced regardless of the therapeutic window, which increases the delay in prehospital time (38).

Comparison of the efficacy and safety of tenecteplase and alteplase in ischemic stroke is ongoing. Preliminary results indicate that TNK is significantly associated with complete recanalization (RR: 1.27 with 95% CI [1.02, 1.57], P = 0.03). However, no differences were found in early neurological improvement (RR: 1.07 with 95% CI [0.94, 1.21], P = 0.33) or excellent neurological recovery (RR: 1.03 with 95% CI [0.96, 1.10], P = 0.42 (27).

Risks of applying fibrinolytic treatment in patients with ischemic stroke

Tenecteplase (TNK) is a newer fibrinolytic agent with greater specificity for fibrin and a longer half- life than alteplase. Both TNK and rt-PA are associated with adverse events, including prolonged hospitalization, disability, dysfunction, intracerebral hemorrhage, and mortality.

The Safety and Efficacy Study of TNK versus Alteplase in Patients with Acute Ischemic Stroke (TRACE) showed that adverse events were more frequent with low doses of TNK, reporting 12.3% disability and 5% serious adverse events. In terms of morbidity, the risk was similar between TNK and rt-PA at doses of 0.1 mg/kg and 0.9 mg/kg, respectively (27).

4. Conclusions

The use of TNK (Tenecteplase) compared to rtPA (Alteplase) in the treatment of ischemic stroke presents notable differences in the time of administration, where TNK is applied in a single dose of 0.32 mg/kg as a bolus, being equally

DOI: https://doi.org/10.58995/redlic.rmic.v3.n1.a87
88 - 96

safe and effective as alteplase, which is administered as a bolus and over one hour at a dose of 0.9 mg/kg.

TNK does not increase intracerebral hemorrhage relative to alteplase; however, procedure-related mortality is identified in 15 studies as a risk that must be mitigated. Therefore, tenecteplase can be administered in the absence of alteplase, without the risk of causing intracranial hemorrhage or patient death. Door-to-needle time is reduced to 53 minutes, and the treatment window is extended to 4.5 hours, resulting in fewer complications for patients with difficulties in the initial evaluation.

The prognosis of ischemic stroke is determined by its severity, which establishes the functional prognosis, the risk of disability and the response to fibrinolytic treatment that facilitates cerebral recanalization and reperfusion in the patient.

Therefore, the evaluation of neurological deficit is crucial, using scales such as the NIHSS (National Institutes of Health Stroke Scale) that predict the efficacy of treatment in terms of sensitivity and specificity.

5. Authors' contribution

PC first author: basic structure of the research, analysis of the information.
FR third author: review, correction and configuration of the article
AB fourth author: review and restructuring to article format.
NC fifth author: review and restructuring to article format.
CB sixth author: review and restructuring to article format.

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96 - 96