

## Thrombolytic management versus endovascular in ischemic stroke

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### ABSTRACT

**Introduction:** ischemic stroke is an endemic condition; its approach has been the subject of study and new techniques and technologies have been developed for its treatment. Currently there are two types of therapies, thrombolysis and thrombectomy. Although both therapies have been extensively studied, there is controversy as to which of these has better recanalization rates and functional outcomes. **Objective:** to characterize ischemic stroke by comparing the therapeutic approaches for the management of the pathology. **Method:** a literature review was performed for which PubMed, Cochrane and SciELO databases were consulted, using the descriptors "Stroke", "Thrombolytic Therapy" and "Thrombectomy" and the following selection criteria: systemic reviews, meta-analyses, clinical and preclinical trials, clinical practice guidelines and literature reviews published from 2015 to 2020, with a total of 32 articles and 4 books consulted with adequate quality and validity. **Development:** mechanical thrombectomy has generated good functional results, with better recanalization rates and longer therapeutic window period, compared to thrombolysis, being direct aspiration cost-effective, with better results than stentriever application. **Conclusions:** primary management of acute ischemic stroke with mechanical thrombectomy by direct aspiration is cost-effective, with better functional results than just thrombolysis and it is effective with or without thrombolysis.

**Keywords:** Ischemic Stroke; Thrombolytic therapy; Thrombectomy.

Ischemic stroke is an acute neurological lesion that is classified according to its etiology into: cerebral ischemia and cerebral hemorrhage. Cerebral ischemia is an injury resulting from decreased cerebral perfusion and nutrition due to insufficient blood supply. It may present as a transient ischemic attack (TIA), which is a type of focal neurological ischemia lasting less than 60 minutes, or as a permanent cerebral infarction. Cerebral hemorrhage is an injury resulting from the accumulation of blood within the cranial vault; it may present as intracerebral hemorrhage (ICH) if the bleeding is focal and occurs from a vessel into the parenchyma or as subarachnoid hemorrhage (SAH) if it is within the subarachnoid space<sup>1,2</sup>.

Although hemorrhagic stroke has a worse prognosis, ischemic stroke has a higher incidence. Stroke

is the second leading cause of mortality worldwide (9,7 %) and the second most common cause of disability. Eighty percent of cases are of ischemic origin (ITA 20 %, cerebral infarction 80 %) and 15-20 % are hemorrhagic (ICH 10-15 %, SAH 5-7 %)<sup>3</sup>.

Currently, the two main therapeutic approaches are intravenous thrombolysis (IVT) and mechanical thrombectomy (MT). Although both therapies have been extensively studied, there is controversy as to which of these has better recanalization rates and functional outcomes. The aim of this review is to characterize ischemic stroke by comparing both therapeutic approaches in the management of the pathology.

### METHOD

A literature review was conducted in August 2020. The search strategy was automated, in the databases: PubMed, Cochrane and SciELO. The descriptors used for the search were: "Accidente Cerebrovascular", "Terapia Trombolítica" and "Trombectomía", in Spanish; for English: "Ischemic stroke", "Thrombectomy", "Thrombolytic Therapy".

The selection criteria were: systemic reviews, meta-analyses, clinical and preclinical trials, clinical practice guidelines, and literature reviews published from 2015 to 2020, in English and Spanish. Two search strategies were used, one for Spanish: (Accidente Cerebrovascular) AND (Terapia Trombolítica) AND [(Accidente Cerebrovascular) AND

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### Conflict of interests

The authors declare no conflict of interests.

(Trombectomía)]; and another for English: [(Ischemic Stroke) AND (Thrombolytic Therapy)] AND [(Stroke) AND (Thrombectomy)].

The initial search, taking into account the selection filters, yielded a total of 8738 results, of which duplicates were eliminated. Of the publications most relevant to the object of the study, the text was entirely read and 32 articles were included; in addition, 4 books with adequate quality and validity for the purpose of the review were consulted.

## DEVELOPMENT

Arterial hypertension is the most important risk factor associated with the onset of stroke, present in 55-81 % of patients. Other factors are related to increased cardiovascular risk, such as hyperlipidemia, diabetes mellitus and smoking<sup>3,4</sup>.

The classification of etiologic subgroups of ischemic stroke is constantly advancing. The current etiological classification system consists of two main categories: phenotypic classification (PC) and causal classification (CC)<sup>5</sup>.

PC is based on the organization of all abnormal test results found, without weighting to the most likely cause, i.e., it assigns a degree of probability for each possible etiology of the stroke. The ASCO system (atherothrombosis, small vessel disease, cardiac and other rare causes) is an example of this type of classification. On the other hand, CC assigns the patient into a single category, its objective being to establish the most probable cause, without focusing on other associated diseases. The TOAST system is a clear example of this classification<sup>5</sup>.

There is a system that integrates both PC and CC: the causative stroke classification system (CCS), which has been shown to be less limiting than the others and classifies patients according to specific etiological groups<sup>5</sup>.

### Pathophysiology

The main pathophysiological component of ischemic stroke is decreased blood flow in a segment of the brain or brain stem (Figure 1).

Excitotoxicity refers to the common final pathway for neuronal injury and death that is caused by excessive glutamate activity and effects that are mediated by this receptor. The interaction of glutamate with one of its receptors, N-methyl-D-aspartate (NMDAr) is directly involved in neuronal injury. It opens a large-diameter calcium channel that allows calcium to enter the intracellular space (ICS) and potassium to exit into the extracellular space (ECS), triggering a prolonged action potential. However, the amount of glutamate is strictly and tightly regulated, since its concentration in the ICS is 16 times higher than

in the ECS<sup>6,7,8</sup>.

Ischemia causes the transport and regulation of glutamate to stop and an increase in its extracellular concentration, which causes its interaction with NMDAr and the opening of these receptors with the consequent excessive entry of calcium into the ICS. Calcium triggers a series of events referred to as the "calcium cascade", which induces the release of intracellular enzymes that degrade proteins, form free radicals, cause mitochondrial injury, fragment deoxyribonucleic acid (DNA), promote lipid peroxidation, nuclear breakdown, apoptosis and brain edema<sup>7</sup>.

Mitochondrial injury follows the calcium cascade as calcium accumulates in the mitochondria, altering their function and allowing the opening of the mitochondrial permeability transition pore (mtPTP) and release of cytochrome C leading to mitochondrial collapse, promoting apoptosis<sup>6</sup>.

When calcium enters, it activates the production of nitric oxide (NO), a type of reactive nitrogen species (RNS), by the enzyme nitric oxide synthase. Once formed, it can interact with superoxide (a type of reactive oxygen species or ROS) to form peroxynitrite (ONOO<sup>-</sup>), which is a potent nitrating agent<sup>6,9</sup>. When ROS and RNS interact, NO decreases, and thus vasodilation, further decreasing brain perfusion<sup>6,9</sup>.

When ischemia ceases due to the resolution of any of its etiologies, nerve cell perfusion returns, and with it, the possibility of generating tissue injury, because when the tissue is deprived of oxygen, the cells resort to anaerobic glycolysis, generating lactate, which alters the brain acid-base balance, which can lead to cell destruction<sup>9,10</sup>.

Likewise, ischemia has repercussions on the mitochondrial electron transport chain (ETC). This requires oxygen as the final electron acceptor, so that electrons are trapped in the chain complexes, becoming saturated and increasing the mitochondrial membrane potential. Once ischemia ceases, oxygen is reintroduced into the ETC, with the consequent excessive production of reactive oxygen species (ROS), overcoming physiological antioxidant mechanisms and causing damage to intracellular structures (lipids that constitute the cell membrane and DNA) and extracellular structures (blood vessels and blood-brain barrier [BBB])<sup>9,10</sup>.

Oxidative stress and lack of ATP alter endoplasmic reticulum (ER) function, specifically the sarcoplasmic/ER calcium ATPase pump (SERCA), preventing optimal protein synthesis, producing misfolded proteins and chaperone dysfunction<sup>6</sup>.

The cascade of inflammatory cells and factors results in BBB dysfunction. Under physiological conditions neutrophils, monocytes and B and T lymphocytes do not usually penetrate this barrier,

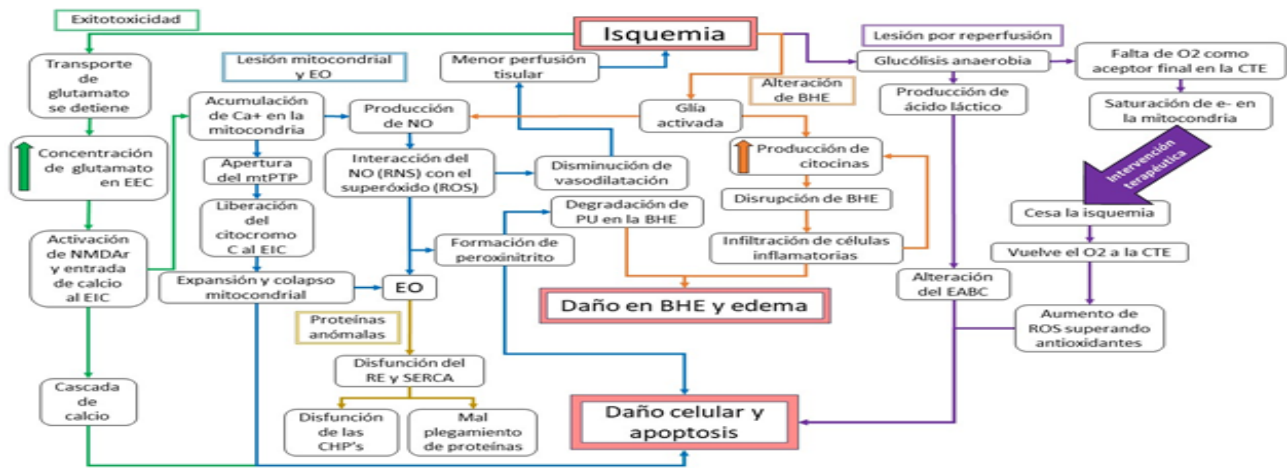


Figure 1. Description of pathophysiological events in ischemic stroke, from ischemia to cellular and BBB damage, apoptosis and edema.

Abbreviations: BBB: blood-brain barrier, CHP's: chaperone proteins, ETC: electron transport chain, DNA: deoxyribonucleic acid, e<sup>-</sup>: electrons, ABSB: acid-base state of the brain, ECS: extracellular space, ICS: intracellular space, EO: oxidative stress, mtPTP: mitochondrial permeability transition pore, NMDAR: N-methyl-D-aspartate receptor, NO: nitric oxide, mtPTP: mitochondrial permeability transition pore, NMDAR: N-methyl-D-aspartate receptor, NO: nitric oxide, O<sub>2</sub>: oxygen, PU: binding proteins, ER: endoplasmic reticulum, RNS: reactive nitrogen species, ROS: reactive oxygen species, SERCA: sarcoplasmic/ER calcium ATPase pump.

Symbology: green arrows: excitotoxicity. Blue arrows: mitochondrial injury and oxidative stress. Golden arrows: mechanism of abnormal proteins. Purple arrows: reperfusion injury.

thanks to all the components of the neurovascular unit (NVU) that comprise it<sup>11</sup>.

After ischemia, microglia and astrocytes are activated, increasing the production of cytokines, chemokines, vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) in the ischemic tissue, causing disruption of the BBB, which allows the aforementioned cells (especially neutrophils) to penetrate, resulting in the release of more cytokines and activating more glial cells<sup>11,12</sup>.

Early identification of the characteristic symptoms of ischemic stroke is essential for timely care<sup>13</sup>.

The clinical picture present at the time of initial evaluation depends on the anatomical location and extent of the lesion. The main altered vascular territories and their corresponding signs and symptoms are<sup>2</sup>:

#### Anterior circulation

Anterior cerebral artery: contralateral hemiparesis and hypoesthesia, dysarthria, urinary incontinence, apathy, abulia and disinhibition.

Middle cerebral artery:

Portion M1: contralateral hemiplegia and hypoesthesia, homonymous hemianopsia, forced gaze deviation, altered consciousness and aphasia if the dominant hemisphere is affected.

Portion M2 and M3: contralateral hemiparesis and hypoesthesia, dysarthria and homonymous

hemianopsia

Portion M4: involvement of cortical functions such as language (dysgraphia, dyscalculia, agraphesthesia and apraxias).

#### Subsequent circulation

Posterior vertebral artery: contralateral visual field involvement, visual agnosia, or cortical blindness or visual seizures.

Vertebrobasilar territory: cerebellar or brainstem involvement according to the affected artery.

The National Institute of Health Stroke Scale (NIHSS) allows objective measurement of the patient's clinical status, quantification of neurological deficit, identification of which patients are candidates for fibrinolytic or mechanical intervention and which are at greater risk of complications<sup>2,13</sup>.

To establish the diagnosis, the use of simple cerebral computed axial tomography (CT) is recommended as the initial study and should be performed within the first 20 minutes of hospital admission and before initiating any specific therapy. The CT is used to obtain the ASPECTS score, which is used to measure early signs of cerebral ischemia. For thrombolytic therapy to be beneficial, candidates must obtain a score greater than or equal to 7 (0-10 scale)<sup>2</sup>. Likewise, computed tomography angiography (CT angiography) of the brain and neck vessels allows evaluation of the large intracranial vessels, identification of occlu-

ded or stenotic areas and collateral circulation. This should be performed in those patients who are candidates for endovascular therapy<sup>2,13</sup>.

On the other hand, conventional magnetic resonance imaging (MRI) can detect diffusion or cerebral perfusion abnormalities and determine the time course of a stroke, making it useful to exclude ICH before intravenous administration of thrombolytics<sup>14,15</sup>.

### Therapeutic Management of Ischemic Stroke

Current guidelines for the early management of acute ischemic stroke indicate two strategies for restoring circulation: thrombolysis and thrombectomy. The former consists of the administration of thrombolytic drugs, either intravenously (IVT) or intra-arterially (IAT) and the latter is performed using various devices (catheters or stents) to eliminate the occlusion. The therapeutic window depends on the used method<sup>16,17,18</sup>.

However, the main risk of these cerebral reperfusion therapies is the transformation of the infarct into symptomatic intracranial hemorrhage (ICHs), as hematomas cause an occupational (or "mass") effect, affecting adjacent structures and favoring cognitive impairment and even death<sup>19,20</sup>.

The most current guidelines on the early management of ischemic stroke from the American Stroke Association (ASA) recommend that, as a first action, IVT with alteplase should be used in patients who are candidates for it, before neuroimaging or other studies are performed, since the benefit of therapy is proportional to the speed with which it is started. For therapy to be successful, it has to be administered 3-4,5 hours after the onset of symptoms (reperfusion window). In addition, it is mentioned that patients who are candidates for treatment with IVT should receive it, even if the use of MT is being considered<sup>2,13,21</sup>.

Likewise, Campbell BC et al.<sup>22</sup> compared tenecteplase versus alteplase as pre-MT management in ischemic stroke. They concluded that tenecteplase administration was faster than alteplase, and was not inferior in restoring perfusion where arterial occlusion was present. However, functional outcome was better with tenecteplase than with alteplase (according to the modified Rankin scale) and, finally, the incidence of recovery to independent function did not differ significantly for tenecteplase compared to alteplase.

Thrombectomy has a longer therapeutic window than IVT, specifically within the first 6 hours of symptom onset. In addition, such treatment was also effective in large vessel occlusion, with an extended time window period (up to 12 hours)<sup>23</sup>. According to their mechanism of action, endovascular techniques are classified into four groups: thrombus rupture techniques, thrombectomy, stent recanalization and retrievable stents

(stent-retriever)<sup>17,24</sup>.

Among thrombus rupture techniques, the most commonly used technique is to probe the thrombus with a microneedle and/or approach a microcatheter to the thrombus. Others, such as percutaneous transluminal balloon angioplasty (PTA), the EKOS system (which uses ultrasonic vibration applied to the thrombus) and the EPAR system (which uses laser technology to emulsify the thrombus) are grouped in this category, although they are used less frequently<sup>17,25</sup>.

Thrombectomy devices enter the site of occlusion, and depending on where force is applied to the thrombus, they are divided into proximal or distal thrombectomy<sup>17</sup>. Within proximal thrombectomy, suction devices are the most commonly used; they eliminate the occlusion by applying force adjacent to the thrombus and suctioning it through a guide catheter. On the other hand, distal devices include the Coil retriever, which, once it reaches the thrombus, introduces a microcatheter into it and wraps around it, deploying it backwards to extract it and eliminate the occlusion<sup>26,27,28</sup>. Although proximal devices are faster and have a lower complication rate, distal devices have shown greater success in removing the thrombus<sup>17</sup>.

The stent or intracranial stent is an expandable device that is generally introduced from the femoral artery until it reaches the affected artery and is permanently placed. It compresses the thrombus against the vessel wall in such a way that it restores blood flow immediately once in place, without the need to pass repeatedly at the site of occlusion (as in thrombectomy devices mentioned above). However, it has been reported that the stent can cause stenosis in 30 % of cerebral arteries with intracranial atherosclerosis to which the device is placed<sup>19</sup>.

The stent-retriever or stentriever is a more modern device for recanalization of blood flow; it combines two mechanisms of action: it immediately restores blood flow (by expansion of the stentriever in the thrombus) and captures and removes the clot (due to the mesh that is embedded in the thrombus). In this way, complications arising from permanent stent implantation can be avoided<sup>17,18</sup>. It is similar to the intracranial stent, however, the stentriever does not remain in the blood vessel, but is inserted for 5 to 10 minutes, so that the thrombus docks within the interstices of the device, and is then removed (allowing the thrombus to recede with it)<sup>17,29</sup>.

### Comparison of endovascular approaches

Although various endovascular techniques have shown promising results, currently, the two main techniques for the treatment of ischemic stroke are direct aspiration thrombectomy and stentriever<sup>20</sup>.



In several recently published articles, these two interventions are compared, and although both have good results, with recanalization rates greater than 80 % and minimal disability at 90 days post-intervention, direct aspiration thrombectomy has been shown to have better rates of successful recanalization and lower mortality, as well as fewer ICH events<sup>21,24</sup>. Also, direct aspiration as the first method of intervention is safe and effective, in addition to allowing the use of stentriever as salvage therapy if aspiration does not achieve successful recanalization and can achieve shorter procedure times<sup>22,30</sup>.

### Cost-effectiveness of aspiration thrombectomy versus stent-retriever thrombectomy

The cost-minimization analysis by Malhotra et al.<sup>20</sup> reveals that the cost of direct aspiration as first-line endovascular treatment is lower than first-choice management with stentriever. Likewise, the study by Turk et al.<sup>24</sup> comparing both interventions as first-line alternatives in long vessel occlusion indicates that their clinical results were achieved with significantly lower device costs in the management of thrombectomy by aspiration than by stentriever.

### Mechanical thrombectomy with or without intravenous thrombolysis

Evidence suggests that patients undergoing early endovascular therapy have better functional benefit than with or without just medical therapy<sup>31,32,33</sup>. In patients with acute ischemic stroke due to large vessel occlusion, TM alone is not inferior, with respect to functional outcome, to TM preceded by intravenous alteplase<sup>34</sup>. Moreover, TM in conjunction with IVT is cost-effective compared to IVT alone<sup>33,35</sup>.

Therefore, if the patient is a candidate for endovascular intervention, it should be considered as standard medical care in the management of acute ischemic stroke in the first 8 hours after symptom onset<sup>16,36</sup>.

### Therapeutic alternatives and innovation

Mild cerebral hypothermia (MCH) at 33 Celsius degrees has been positioned as a promising neuroprotective therapy in ischemic stroke. Although there is extensive preclinical evidence of its effectiveness, the benefit in humans has not been established<sup>6,12</sup>.

For each Celsius degree decrease, oxygen and glucose consumption decreases by 5 %, preventing the loss of energy and metabolic substrates.

It also limits excitotoxicity by decreasing the accumulation of glutamate in the ECS and the deregulated entry of calcium into the ICS. It also prevents the activation of MMPs, which degrade BBB binding proteins causing edema<sup>6,12</sup>.

### Cell therapy: stem cell treatment

Stem Cell Therapy (SCT) is aimed at aiding post-ischemic stroke neuronal rehabilitation and regeneration<sup>26</sup>.

There are two modalities of this therapy for ischemic stroke: endogenous (with the individual's own neural progenitor cells [NPCs]) and exogenous (with transplantation of cells from a source outside the individual). The endogenous approach stimulates the growth, mobilization and stabilization of NPCs that can differentiate into oligodendrocytes, astrocytes and ependymal cells. Cells capable of replacing dying neurons exist in the dentate gyrus and subventricular zone. However, most of the cells that are formed do not integrate and die<sup>6,26,27</sup>. In the exogenous approach, neural progenitor cells are transplanted from an external source, which through pathotropism (innate ability to migrate) integrate into the injured tissue, leading to replacement of damaged cells, plasticity, immunomodulation and trophic effects. However, as in the endogenous approach, most of these cells also fail to integrate and thus die<sup>6,26</sup>.

## CONCLUSIONS

The primary management of acute ischemic stroke with direct aspiration mechanical thrombectomy is cost-effective (compared to stentriever), with better functional results than thrombolysis alone and is effective with or without thrombolysis, pointing out the better outcome, longer window time and better recanalization rates.

## AUTHORSHIP

**Carlos Martínez-Zarazúa:** conception, bibliographic research, methodology and design of the article, supervision, drafting, revision and editing.  
**María Gabriela Torres-Rivera:** conception, bibliographic research, methodology and design of the article and draft writing.

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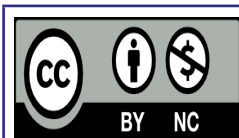
## Manejo trombolítico versus endovascular en el accidente cerebrovascular isquémico

### RESUMEN

**Introducción:** el accidente cerebrovascular isquémico es una afección endémica; su abordaje ha sido objeto de estudio y se han desarrollado nuevas técnicas y tecnologías para su tratamiento. Actualmente existen dos tipos de terapias, la trombólisis

y la trombectomía. Pese a que ambas terapias han sido ampliamente estudiadas, existe controversia sobre cuál de estas tiene mejores tasas de recanalización y resultados funcionales. **Objetivo:** caracterizar el accidente cerebrovascular isquémico comparando los abordajes terapéuticos para el manejo de la patología. **Método:** se realizó una revisión bibliográfica para la que se consultaron las bases de datos PubMed, Cochrane y SciELO, empleando los descriptores "Accidente Cerebrovascular", "Terapia Trombolítica" y "Trombectomía" y los siguientes criterios de selección: revisiones sistémicas, meta-análisis, ensayos clínicos y preclínicos, guías de práctica clínica y revisiones bibliográficas publicadas del 2015 al 2020, con un total de 32 artículos y 4 libros consultados con calidad y validez adecuada. **Desarrollo:** la trombectomía mecánica ha generado buenos resultados funcionales, con mejores tasas de recanalización y mayor periodo de ventana terapéutico, en comparación con la trombólisis, siendo la aspiración directa costo-efectiva, con mejores resultados que la aplicación del stentriever. **Conclusiones:** el manejo primario del accidente cerebrovascular isquémico agudo con trombectomía mecánica por aspiración directa, es costo-efectivo, con mejores resultados funcionales que la trombólisis por si sola y es eficaz con o sin la misma..

**Palabras clave:** Accidente Cerebrovascular; Terapia Trombolítica; Trombectomía.



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