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FIBRINOLYTICS: INDICATIONS AND TREATMENT OF HEMORRHAGIC COMPLICATIONS

FIBRINOLÍTICOS: INDICAÇÕES E TRATAMENTO DAS COMPLICAÇÕES HEMORRÁGICAS

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ABSTRACT

Fibrinolytics belong to a class of drugs specialized in promoting lysis of fibrin and consequent dissolution of the thrombus. This effect is based on the conversion of plasminogen into plasmin, a potent proteolytic enzyme. Its application in different acute cardiovascular syndromes has changed the natural course of acute myocardial infarction, pulmonary embolism, and acute ischemic stroke. In practice, three generations of fibrinolytics are available: streptokinase, alteplase, and tenecteplase (the latter having high affinity to fibrin). Hemorrhagic complications, although rare, must be identified and treated early. This is due to coagulation disorders, especially the decrease in fibrinogen and other coagulation factors, more prevalent with streptokinase. Correction is based on the administration of cryoprecipitate and fresh plasma, which are rich in fibrinogen and coagulation factors, respectively. Inexperience in administering these drugs and hemorrhagic fear are aggravating factors of disease progression. Educational programs can mitigate such scenarios, especially in centers that lack technological resources.Inexperience administering such medicines and hemorrhagic fear has been an aggravating factor in the lives of these diseases. Educational campaigns will be able to mitigate such a scenario especially in the most lacking centers of technological resources.

Keywords: Fibrinolytics; Hemorrhagic Complications; Treatment of Hemorrhagic Complications.

RESUMO

Os fibrinolíticos pertencem a uma classe de medicamentos especializada em promover a lise da fibrina e a consequente dissolução do trombo. Esse efeito baseia-se na transformação do plasminogênio em plasmina, potente enzima proteolítica. A sua aplicação nas diferentes síndromes cardiovasculares agudas alterou o curso natural do infarto agudo do miocárdio, da embolia pulmonar e do acidente vascular cerebral isquêmico agudo. Na prática, temos três gerações de fibrinolíticos disponíveis: estreptoquinase, alteplase e tenecteplase, essa última com alta afinidade à fibrina. As complicações hemorrágicas, embora raras, devem ser identificadas e tratadas de forma precoce. Isso se deve aos distúrbios da coagulação, especialmente, queda do fibrinogênio e outros fatores de coagulação, mais predominantes com a estreptoquinase. A correção baseia-se na administração de crioprecipitado e plasma fresco, ricos, respectivamente, em fibrinogênio e fatores de coagulação. A inexperiência ao administrar tais medicamentos e o receio hemorrágico tem sido fator agravante na sobrevida dessas doenças. Campanhas educacionais poderão amenizar tal cenário, especialmente, em centros mais carentes de recursos tecnológicos.

Descritores: *Fibrinolíticos; Complicações Hemorrágicas; Tratamento.*

INTRODUCTION

The development of fibrinolytics is among the major advances in medicine in the recent decades. In 1948, English physician and researcher Dr. William Tillet isolated and identified streptokinase (SK) from cultures of ß-hemolytic streptococcal strains (Figure 1). The hematologist, Dr. Sol Sherry, demonstrated its clinical benefits in patients with hemothorax and pleural empyema in whom intrapleural infusion led to fibrin lysis and sequelae such as pleural thickening and pulmonary incarceration, were avoided.

In the 60s and 70s, researchers found that SK could promote experimental lysis of thrombi located in the caudal arteries of mice. Several studies were conducted in the cardiovascular field after this finding was reported. With the increasing availability of new generations of this class of medication, these drugs are widely indicated in acute cases of myocardial infarction, pulmonary embolism, ischemic stroke, and arterial and venous obstructions.[1]

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MECHANISM OF ACTION

Fibrinolytics are molecules that activate plasminogen in plasmin, whose powerful lytic action on the fibrin mesh can remove the thrombus. Fibrinolysis is physiologically self-limited by counter-regulatory mechanisms, e.g., plasminogen activator inhibitor (PAI-1) and α_2-antiplasmin that allow local lytic action (Figure 2).

Two fibrinolytics are continuously synthesized by the vascular endothelium: 1. tissue plasminogen activator (tPA or alteplase) and 2. urokinase (small amounts), also synthesized by the urogenital epithelium, inhibit clot formation in this system.[2,3]

Although thrombus formation and lysis are dynamic events, lysis does not always occur timely. Thus, systemic infusion and therapeutic doses of fibrinolytics can restore the desired blood flow (Figure 3).

Figure 1. Dr. William Tillet, a pioneer in research on streptokinase.

FIBRINOLYTICS

Fibrinolytics are generally classified according to their mechanism of generation and fibrin specificity.[4,5]

First generation

SK (*Streptase*® - *CLS Bering*): An antigenic streptococcal-derived molecule that activates both circulating and fibrin-bound plasminogen that is not fibrin-specific and lyse several coagulation factors. Allergic reactions and hypotension are noted in 5% of the cases.

Second generation

tPA (*Actilyse*® - *Boehringer Ingelheim*): a recombinant molecule identical to that synthesized by the human endothelium. It is fibrin-specific, is not antigenic, and rarely causes allergic reactions or hypotension.

Third generation

Tenecteplase (TNK; *Metalyse*® - *Boehringer Ingelheim*): some modifications of the rtPA molecule yielded with an increased half-life, increased resistance to PAI, and high affinity for fibrin (Table 1).

Doses and infusion times vary according to the indication in the different acute cardiovascular syndromes (Table 2).

Although rare, side effects are more prevalent with SK.

- Hypotension: pause the infusion for 15 min and raise the lower limbs.
- Mild/moderate allergy: methylprednisolone 125 mg administered intravenously
- Severe allergy, glottis edema: methylprednisolone 125 mg + 50 mg diphenhydramine (*Benadryl*®) + ranitidine 50 mg administered intravenously + adrenaline 0.1% 0.3 mL administered subcutaneously or 0.5 mL through inhalation.

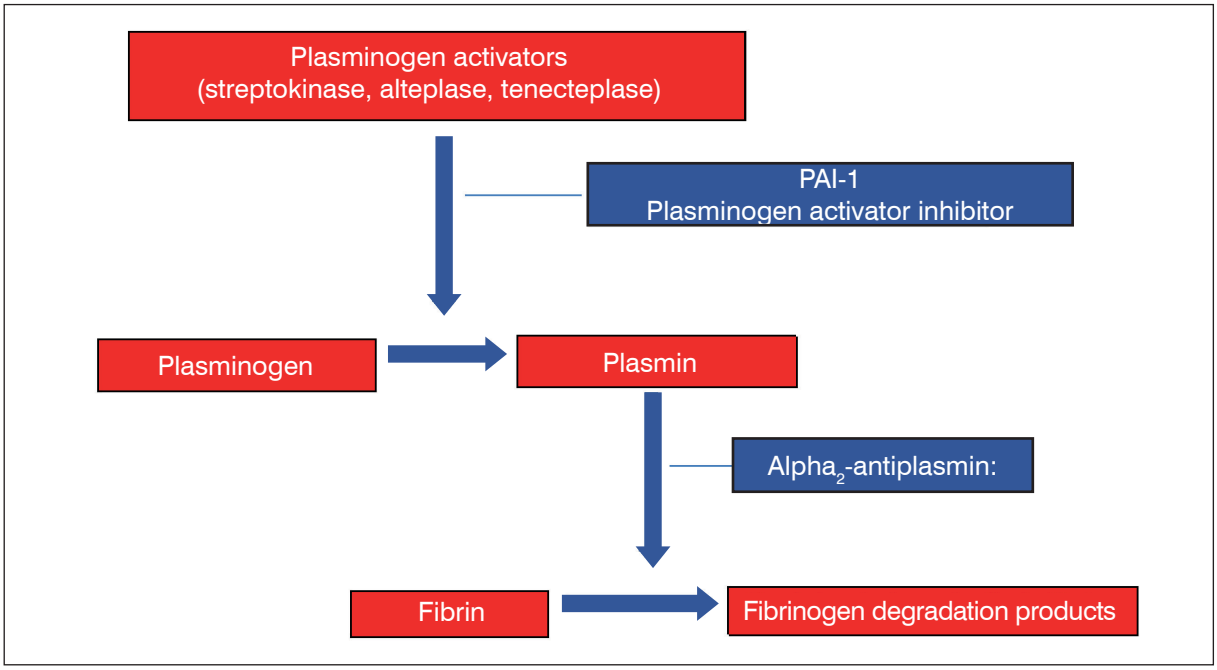

Figure 2. Mechanism of action of fibrinolytics.

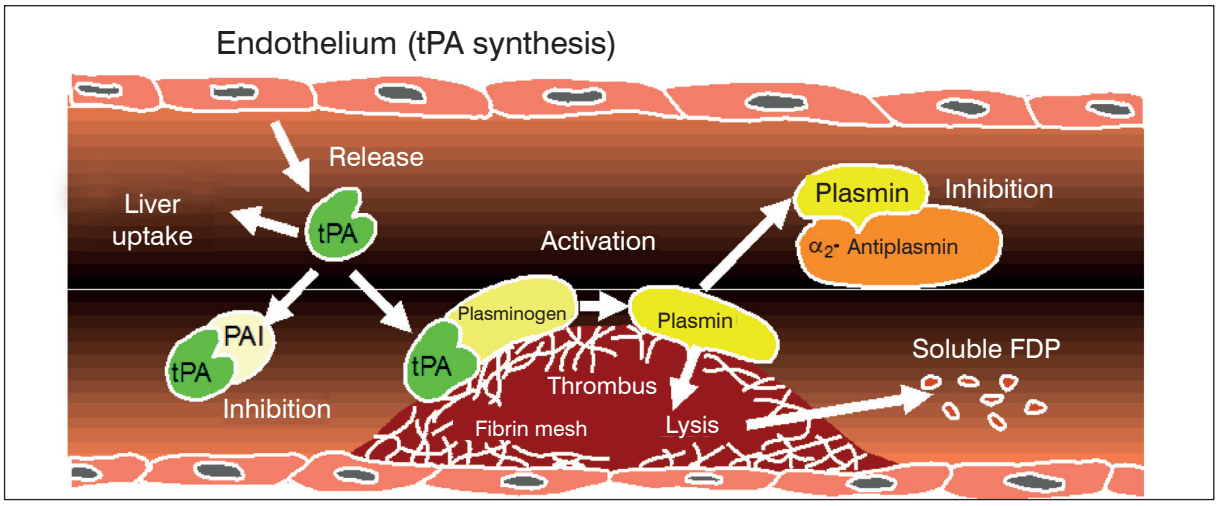

Figure 3. Dynamic action of fibrinolytic on the thrombus.

Table 1. Characteristics of fibrinolytics.

	Streptokinase	Alteplase	Tenecteplase
Molecular weight (Daltons)	47.000	65.000	65.000
Activation of plasminogen	Indirect	Direct	Direct
Half-life (min)	20	5	20
Coronary flow with TIMI 2 or 3 at 90 min of infusion	60-68%	73-84%	85%
Fibrinogen depletion	++++	+	-
Fibrin-specific	No	++	++++
Resistance to PAI-1	No	No	Yes
Hypotension	Yes	No	No
Antigenic	Yes	No	No

TIMI, Thrombolysis in Myocardial Infarction; PAI, plasminogen activator inhibitor.

Table 2. Clinical indications for fibrinolytics.

	SK Estreptoquinase	Alteplase	Tenecteplase
ST-elevation AMI (up to 12 h)	1.500.000 UI (60 min)	Accelerated infusion (90 min) 15 mg (bolus) + 0.75 mg/kg (30 min) (maximum 50 mg) + 0.5 mg/kg (60 min) (maximum 35 mg) Do not exceed 100 mg	Fast infusion (1-2 min) 0.53 mg/kg (bolus): <60 kg = 30 mg, ≥60 to 70 kg = 35 mg ≥70 to 80 kg = 40 mg ≥80 to 90 kg= 45 mg ≥ 90 kg = 50 mg
VTE (up to 30 days)	100,000 UI/hour (24 to 120 hour)	100 mg (120 min)	0,53 mg/kg (bolus): <60 kg = 30 mg, ≥60 to 70 kg = 35 mg ≥70 to 80 kg = 40 mg ≥80 to 90 kg= 45 mg ≥ 90 kg = 50 mg
AIS (up to 4.5 hour)	Contraindicated	Peripheral intravenous infusion: 0.9 mg/kg (60 min) (10% bolus) Intravenous infusion: 0.5 mg/kg (60 min) (10% bolus)	Wait for approval

AMI, acute myocardial infarction; VTE, venous thromboembolism; AIS, acute ischemic stroke For patients ≥ 75 years, administer 50% of the total dose of tenecteplase.

MAIN CLINICAL INFORMATION

ST-segment elevation acute myocardial infarction

Fibrinolytics are indicated in the first 12 hours after symptom onset and with specific electrocardiographic changes (Figure 4). With limited benefit, it can be administered between 12 and 24 hours in the presence of persistent pain and ischemic signs.[6]

Two decades ago, a review of nine studies of more than 1,000 patients - *The Fibrinolytic Therapy Trialist Collaborative Group* (FTT) - observed a reduction in mortality rates of 18–25% in the first 6 hours of infarction compared to control at 35 days of treatment. The earlier the use of fibrinolytics, the more lives were saved.[7]

Two other studies, LATE (*Late Assessment of Thrombolytic Efficacy*) and EMERAS (*Estudio Multicéntrico*

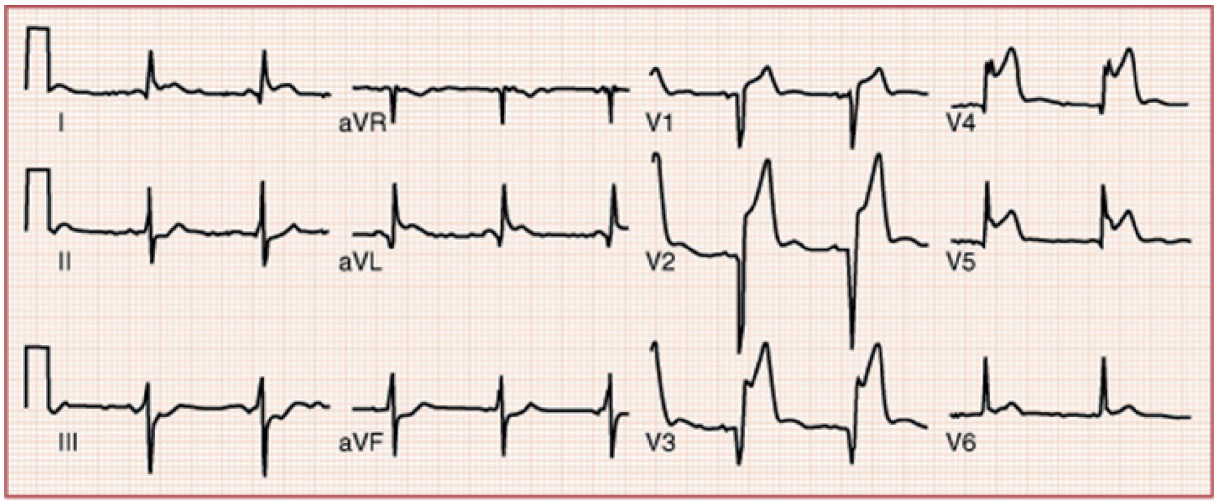

Figure 4. ST-elevation ≥ 2 mm on the anterior wall with symptoms for 60 minutes.

Estreptoquinasa Repúblicas de América del Sur), concluded that this benefit could be extended between 6 and 12 hours and is limited between 13 and 24 hours. [8,9]

In a recent meta-analysis, the PROSPERO study (*The International Prospective Register of Systematic Reviews*) compared 12 different fibrinolytic regimens in 40 studies with approximately 128,000 patients regarding mortality and major bleeding (according to the BARC scale) at 30–35 days of evolution.[10] The BARC (*Bleeding Academic Research Consortium*) scale incorporated clinical and laboratory criteria used by GUSTO (*Global Use of Strategies to Open Occluded Arteries*) and TIMI (*Thrombolysis in Myocardial Infarction*), excluding, respectively, the terms "moderate or severe bleeding; greater or lesser bleeding" (Table 3).[11,12]

In this study, the best results were obtained with TNK (bolus) and accelerated rtPA (90 min), both associated with systemic heparin. Mortality was similar at 6%, while hemorrhagic risk (BARC scale type 3a, b, or c) was 3.5% and 4.5%, respectively, favoring TNK. It was concluded that, among the fibrinolytics used, TNK was the safest with an efficacy similar to that of accelerated rtPA.

Also, in the recent STREAM study (*Strategic Reperfusion Early After Myocardial Infarction*), 1,892 patients with up to 3 hours of onset of symptoms and no possibility of primary angioplasty within 60 minutes were randomized between TNK (associated with aspirin, clopidogrel, and enoxaparin) and primary angioplasty, with doses corrected for age ≥ 75 years (50% reduction in total dose).

In those of the fibrinolytic group, angioplasty was electively performed between 6 and 24 hours except in the rescue condition (ST-segment depression < 50% at 90 min of its infusion). At 30 days, there was no difference in mortality rate due to any etiology (4.4 × 4.4%, p = 0.88), hemorrhagic stroke (0.5 × 0.3%, p = 0.45), major hemorrhagic events (6.5 × 4.8%, p = 0.11), and need for blood transfusion (2.9 × 2.3%, p = 0.47). We interrupted angioplasty due to the low rates of intracranial hemorrhage we found, especially with dose adjustment for patients ≥ 75 years.[13]

Hemorrhagic risk

One of the main complications of fibrinolytics use is hemorrhage, with intracranial hemorrhage having the highest morbidity and mortality rates. The risk of intracranial hemorrhage ranged from 0.5 to 1% in different studies, especially in the first 24 hours of treatment. This is an event with an estimated mortality rate of 50%.

Table 3. Bleeding type by Bleeding Academic Research Consortium scale.

	Bleeding characteristic
Type 0	Absent
Type 1	No need for medical intervention: nasal, oral, cutaneous, hemorrhoidal
Type 2	Requires diagnostic tests, hospitalization, or treatment
Type 3a	Hb drop of 3-5 g/dL, relative need for transfusion
Type 3b	Hb drop ≥ 5g/dL, cardiac tamponade, requires surgical intervention (except nasal, oral, and hemorrhoidal), vasoactive drugs
Type 3c	Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; ocular hemorrhage with visual impairment
Type 4	Bleeding within 48 hours of myocardial revascularization surgery
Type 5	a. Probable fatal bleeding b. Definitive fatal bleeding

This risk was also estimated almost two decades ago, considering different clinical and fibrinolytic variables of first (SK) and second (rtPA) generation (Table 4).

The risk of intracranial hemorrhage ranged according to score: 0 or 1 (0.7%), 2 (1.0%), 3 (1.6%), 4 (2.4%), and ≥ 5 (4.1%). Pressure control and history of coagulopathy should be checked before treatment, as should other contraindications.[14]

In practice, fear of hemorrhage and inexperience with fibrinolytics administration have compromised the benefits of pharmacological reperfusion in STEMI. Although intracranial hemorrhage was the greatest fear, it accounted for only 0.5% of cases in the STREAM study.

Pulmonary Embolism

The onset timing of symptoms of pulmonary embolism, unlike acute myocardial infarction, is not always accurate. The patient usually complains of dyspnea for hours, days,

Table 4. Hemorrhage risk score.

Factor	Points
Age ≥ 75 years	1
Black ethnic group	1
Female sex	1
Previous history of stroke	1
Systolic blood pressure ≥ 160 mmHg	1
Weight: women < 65 kg and men < 80 kg	1
INR > 4 or prothrombin time > 24 sec	1
Alteplase administration	1

INR, international normalized ratio.

or weeks interspersed with moments of improvement. This reflects the dynamic nature between thrombus formation, fragmentation, and lysis. The histopathological findings confirm their different stages of organization, the most recent being proximally arranged to the pulmonary arterial flow.

Since the response to fibrinolytic infusion in a disease with dynamic thromboembolic events, different stages of organization, and increased thrombus mass cannot be specified, treatment with SK has some advantages over those with rtPA and TNK. As it is a slow and continuous infusion regimen (between 24 and 120 hours), it provides a permanent lytic state with progressive reduction of pulmonary artery systolic pressure (PASP). This is monitored on 24/24-hour echocardiography, interrupting when PASP ≤ 40 mmHg (Figure 5). Sometimes, treatment with rtPA and TNK does not reduce pressure as desired because of the short period of exposure of the thrombus to the fibrinolytic. The rtPA is infused over 120 min and the TNK is administered by bolus, which is "little time for so much thrombus."

Thrombolysis is indicated in the presence of hypotension (systolic blood pressure [SBP] ≤ 90 mmHg) in selected cases of right ventricular dysfunction associated with elevation of biomarkers (troponin and/or BNP) and signs of clinical deterioration (hypoxemia, tachycardia).[15,16]

Hemostatic disorders are more pronounced with SK, commonly having reduced fibrinogen < 100 mg/dL and other coagulation factors. It is not a fibrin-specific drug and hemostasis is re-established at 1–3 days, which is the time necessary for the hepatic synthesis of these factors. When fibrinogen > 100 mg/dL, oral anticoagulation is initiated. The incidence of intracranial hemorrhage in the fibrinolytic treatment of pulmonary embolism is 1–2%, while that of others is 6–8%.[17] Mechanical, surgical, or even ultrasonic thrombectomy is indicated (under clinical evaluation) when fibrinolytic therapy is contraindicated.

Acute ischemic stroke

Acute ischemic stroke (AIS) is a neurological emergency. With arterial obstruction, the necrosis wave progresses from a central area to more peripheral ischemic and still viable areas. The administration of rtPA aims at reestablishing blood flow and saving the neurons from the ischemic area, minimizing neurological sequelae.[6]

The main causes of AIS are: 1. atherothrombosis (60%) secondary to plaque rupture and atheroma; 2. embolism (20%), usually emboli from the left heart chambers and great vessels; and 3. small vessel disease (20%).

The only approved fibrinolytic is rtPA, whose efficacy was evaluated in a randomized study conducted by the National Institute of Neurological Diseases and supervised by the United States National Institutes of Health (NIH) for nearly 2 decades.[19] Although it did not lead to a decrease in mortality rates at 3 months and 1 year of follow-up, there was a significant decrease in the incidence of neurological sequelae (40%). Compared to that in the control group, the risk of central nervous system bleeding was 6%, with no increase in mortality rates.

It is indicated in the first 4.5 hours after symptom onset and peripheral venous line infusion. Other protocols have been tested, including TNK (0.4 mg/kg bolus intravenous administration) and mechanical thrombectomy with specific stents (6–24 hours after symptom onset) with good results.[20-22]

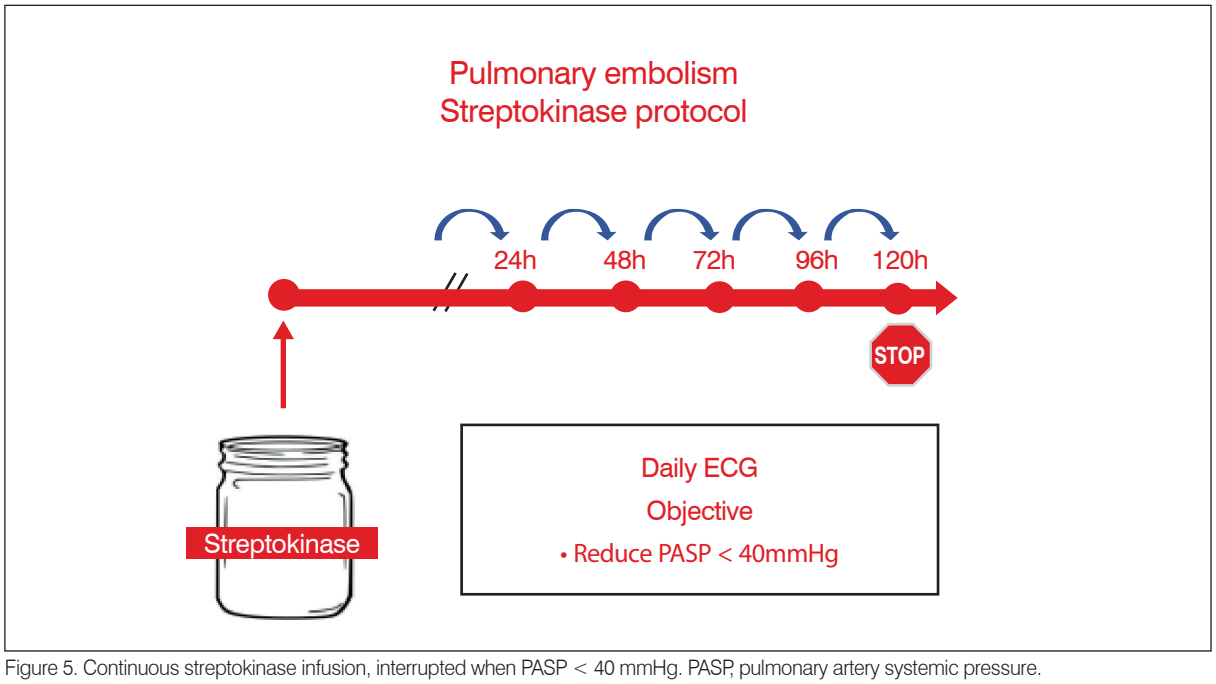

Figure 5. Continuous streptokinase infusion, interrupted when PASP < 40 mmHg. PASP, pulmonary artery systemic pressure.

Aspirin is administered 24 hours after rtPA and at 24–48 hours in those who did not undergo thrombolysis. Glycoprotein IIb/IIa inhibitors are contraindicated.

Computed tomography of the skull is mandatory and performed within 20 min of the patient's arrival at the emergency room (door-to-ECG time ≤ 20 min) and a medical report issued in 10 min (door-to-diagnosis time ≤ 30 min). Once the diagnosis is confirmed, the door-to-needle time should not exceed 60 min. The earlier the infusion, the better the results (Figure 6).

Magnetic resonance imaging (diffusion-perfusion technique) can also be performed by identifying ischemic areas that are still viable.

Some subsidiary tests are recommended, e.g., blood glucose, electrolytes, complete blood count, troponin, coagulation, kidney function, liver function, chest X-ray, and ECG.

The inclusion and exclusion criteria for fibrinolytic therapy are as follows.

Inclusion

- Age ≥ 18 years;
- Onset of symptoms ≤ 4½ h;
- Tomographic confirmation: absence of bleeding, expansive lesions, mass effect; and
- Family understanding of the risks/benefits.

Exclusion

- Stroke with few symptoms (≤4 points on the NIH scale);
- Stroke with rapid neurological improvement;
- History of AIS or head trauma < 3 months;
- Surgery of the CNS < 3 months;
- Endocarditis;

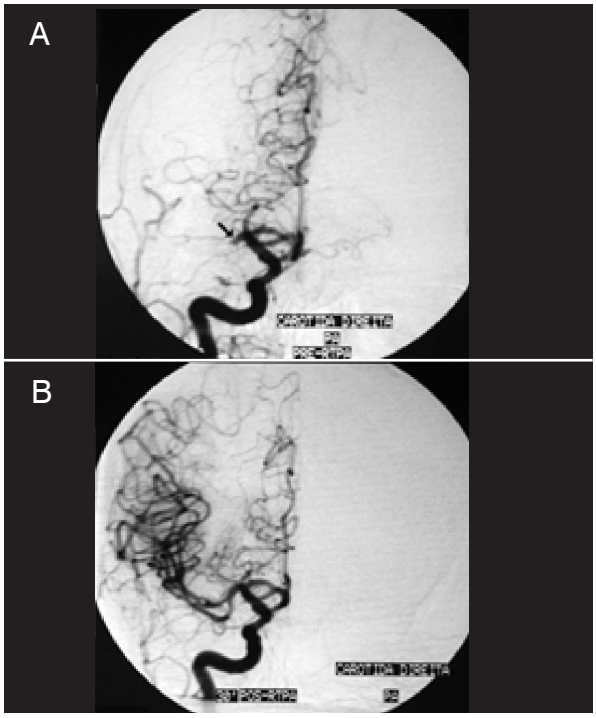

Figure 6. A. Thromboembolic occlusion of the right middle cerebral artery. B. Complete recanalization of recombinant tissue plasminogen activator (rtPA) infusion at 30 min.

- Previous intracranial bleeding;
- Symptoms suggestive of subarachnoid hemorrhage;
- Seizure crisis at symptom onset;
- Full anticoagulation with heparin, warfarin (international normalized ratio > 1.7);
- Platelets ≤ 100,000/mm^3;
- Current use of platelet antiaggregant (except aspirin);
- Use of therapeutic heparin ≤ 48 hours (except normal TTPa); New oral anticoagulants ≤ 48 hours (check kidney function);
- Blood glucose ≤50 mg/dL or ≥ 400 mg/dL;
- Major surgery in the last 14 days;
- Active internal bleeding;
- Urinary or digestive tract bleeding < 21 days;
- Arterial puncture in a non-compressible site < 7 days;
- Suspected aortic, carotid or vertebral dissection;
- Recent myocardial infarction (between 24 hours and 3 months);
- SBP ≥185 and diastolic blood pressure (DBP) ≥ 110 mmHg without hypotensive effect;
- NIH score >25 points.

The rtPA should be administered as soon as possible, while the patient is still in the emergency room, and the patient should be referred for neurological and hemodynamic follow-up in the intensive care unit.

Dose: 0.9 mg/kg (maximum 90 mg), with 10% bolus (1 min) + remainder in 60 min.

Intensive Care

- Continuous neurological observation;
- Cardiac and pressure monitoring;
- Avoid central venous catheterization, arterial puncture, and bladder and nasogastric intubation;
- Serial pressure control in the first 24 hours:
  - 15/15 min in the first 2 hours;
  - 30/30 min in the next 6 hours;
  - 60/60 min until the course of 24 hours;
- Maintain SBP < 180 mmHg and DBP < 105 mmHg;
- Do not administer anticoagulants or antiplatelet agents in the first 24 hours of rtPA infusion;
- Perform CT of the skull 24 hours after rtPA; and
- Glycemic control (140–180 mg/dL).

Treatment of bleeding complications

Hemorrhagic complications in the central nervous system are prevalent in the first 24 hours and patients with neurological worsening should be suspected of having it.

Regardless of their indication, coagulation disorders should be rapidly corrected, especially those corresponding to BARC scale type 3.

Treatment begins with transfusion of cryoprecipitate and fresh plasma, recomposing levels of serum fibrinogen and other coagulation factors. If adequate control is lacking, which is rare, it is followed by platelet transfusion, antifibrinolytic, and red blood cell (RBC) concentrate as follows:[23]

1. Cryoprecipitate: Transfuse 10 units rich in fibrinogen and factor VIII, each unit increases the serum fibrinogen level by 10 mg/dL. Repeat at levels > 100–150 mg/dL, with hemostatic safety;
2. Fresh plasma: Transfuse 2–4 units rich in coagulation factors;

3. Platelets: Transfuse a unit by apheresis (if coagulation time ≥ 9 min) to reverse platelet dysfunction induced by fibrinolytics regardless of its absolute count;
4. Epsilon-aminocaproic acid (Ipisilon®): Antifibrinolytic, 4–5 g in 60 min, repeat 1 g/hour until bleeding is controlled;
5. Tranexamic acid (Transamin®) – 1 g extravascularly in 20 min; and
6. RBC concentrate to treat anemia.

If intracranial hemorrhage is suspected, request a neurosurgery evaluation, perform diagnostic confirmation, correct hemostasis, and provide surgical intervention.

CONCLUSION

Fibrinolytics have changed the natural history of the main acute cardiovascular syndromes: myocardial infarction, pulmonary embolism, ischemic stroke, and venous and arterial obstructions. Due to fear of hemorrhagic events and practical inexperience, it has been underutilized in several emergency services, compromising its prognosis. Only educational campaigns and process restructuring can change this scenario.

Hemorrhagic events are treatable, most commonly with SK, and reversed with the administration of cryoprecipitate and fresh plasma. In selected cases, platelet transfusions, antifibrinolytics, and RBC concentrates are used as treatments.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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