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Fibrinolytic Treatment for Pulmonary Thromboembolism: A Systematic Review

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1. Introduction

Pulmonary embolism is a relatively common cardiovascular emergency involving occlusion of the pulmonary vascular bed, which can lead to life-threatening right ventricular failure [1]. In addition, venous thromboembolism, clinically presented as deep vein thrombosis or pulmonary embolism, is the third most frequent acute cardiovascular syndrome globally, second only to acute myocardial infarction and stroke [2,3]. In addition, this disease is often linked to persistent dyspnea and poor physical capacity 6 months to 3 years after an acute episode 4.

Primary therapy for pulmonary embolism consists of hemodynamic and respiratory support. In addition, once the patient with venous thromboembolism has been diagnosed and stabilized, if necessary, anticoagulation should be started unless this therapy is contraindicated [5,6]. There are also reperfusion therapies consisting of surgical thrombectomy and thrombolysis [1,3], which will be the focus of this review.

In thrombolytic therapy, thrombolytic drugs are used to break up the thrombus that is occluding the pulmonary vascular bed in order to quickly re-establish pulmonary circulation, which is accompanied by an improvement in right ventricular function6. Thrombolytic therapy can be carried out either systemically or by percutaneous intervention using a catheter to carry out more localized therapy. In catheter-directed thrombolysis, lower doses of fibrinolytic drugs are used and ultrasound can also be used to facilitate thrombus fragmentation, as well as mechanical fragmentation [3].

Despite all the possibilities that thrombolytic therapy presents, it is related to an increase in the occurrence of adverse events that can be fatal, such as major hemorrhages and intracranial hemorrhages [7,8], so great caution is needed when considering this therapy in cases of intermediate risk pulmonary embolism, since its benefits may not outweigh the risks it brings [7]. In addition, when reading and analyzing studies on the subject, the reader should be cautious, as the studies are very heterogeneous, and definitions for major or minor bleeding and hemodynamic instability or shock are not standardized, or even described in the studies [9].

Therefore, this therapy is only routinely recommended in cases of high-risk pulmonary embolism. In intermediate-risk cases, there is still no indication for routine thrombolysis since, apparently, the risk of bleeding related to thrombolysis is very high compared to its possible benefits [3,10].

However, many studies aim to assess the impact of thrombolytic therapy in conjunction with anticoagulation in high and intermediate risk pulmonary embolism, comparing its efficacy and safety with anticoagulants used alone or with different modalities of thrombolysis in order to establish the best therapy to treat the disease in different forms of presentation, as well as assessing the impact of different therapies on the long-term prognosis of the

disease. All this effort is being made in order to establish a treatment for PE with the best possible clinical outcome, given that this disease has a high global incidence and is linked to sequelae that have the potential to reduce patients' quality of life in the long term. Therefore, this study aims, through a systematic review of the current literature, to expose the state of the art of thrombolytic treatment in order to answer questions on the subject, such as which patients affected by pulmonary embolism are indicated to receive thrombolytic therapy and which is the most beneficial modality of this therapy. In addition, it raises questions that could guide further studies on the subject.

2. Methodology

This study is a systematic review aimed at evaluating the efficacy of fibrinolytic treatment for PTE.

The inclusion criteria for this study were: randomized controlled clinical trials published from 2010 to June 2021 that address fibrinolytic treatment for PTE, written in English. The exclusion criteria used were: studies that were off topic, other types of study that were not randomized controlled clinical trials, repeated articles and articles in other languages.

To construct the search strategies, the PICO strategy was used to define the research question. The study population will be patients diagnosed with pulmonary thromboembolism, the intervention will be fibrinolytic therapy and the terms of comparison and outcome will not be used due to the objectives of the study. The databases that will be used for collection will be: PubMed and Embase. The descriptors used for fibrinolytic therapy were: Thrombolytic Therapy; Fibrinolytic Therapy; Fibrinolytic Therapies; Therapeutic Thrombolyses; Therapeutic Thrombolysis; Therapies, Fibrinolytic; Therapies, Thrombolytic; Therapy, fibrinolytic; Therapy Thrombolytic; Thrombolyses, Therapeutic; Thrombolysis, Therapeutic; and Thrombolytic Therapies. For pulmonary thromboembolism, the following descriptors will be used: Pulmonary Embolism; Embolism, Pulmonary; Embolisms, Pulmonary; Pulmonary Embolisms; Pulmonary Thromboembolism; Pulmonary Thromboembolisms; Thromboembolism, Pulmonary; and Thromboembolisms, Pulmonary. The descriptors used to set up the strategy were taken from the DeCS and MeSH platforms. Thus, for the search, these descriptors will be connected using the Boolean operators "AND" and "OR" to form the search strategies to be used, which are "(thrombolytic therapy OR fibrinolytic therapy OR Fibrinolytic Therapies OR Therapeutic Thrombolyses OR Therapeutic Thrombolysis OR Therapies, Fibrinolytic OR Therapies, Thrombolytic OR Therapy, fibrinolytic OR Therapy Thrombolytic OR Thrombolyses, Therapeutic OR Thrombolysis, Therapeutic OR Thrombolytic Therapies) AND (Pulmonary Embolism OR Embolism, Pulmonary OR Embolisms, Pulmonary OR Pulmonary Embolisms OR Pulmonary Thromboembolism OR Pulmonary Thromboembolisms OR Thromboembolism, Pulmonary OR Thromboembolisms, Pulmonary)". Finally, the date of publication of the articles was restricted to after 2010 and the type of article to randomized controlled clinical trials. Articles published until June 2021 were searched for.

The articles found using the above search strategy were first downloaded and then identified by title, name of the main author and year in an Excel® table. In this table, the articles were identified as included or excluded from the review according to the selection made. The first part of the selection of articles will be to read their titles and abstracts in order to identify articles that meet the exclusion criteria set out above and exclude them. After this first selection, the articles that have not been excluded will be added to a folder in Mendeley where the second part of the selection will be carried out by reading the articles in full to select the articles that will be used for the literature review, based on the eligibility criteria. Two independent researchers took part in this stage and in the event of a disagreement over the eligibility of the studies collected, a third researcher was appointed.

The data was collected by reading and filing the selected articles. The information assessed in the articles was: level of risk of the disease, fibrinolytic agent used, method of application of the agent, dose used, adverse effects, clinical outcomes, indications and contraindications.

To analyze the risk of bias in the articles, we used the Cochrane Risk of Bias in Randomized Controlled Articles tool, RoB 2.0, updated on August 22, 2019. This tool assesses 5 domains that can generate bias in randomized clinical trials, namely: bias arising from the randomization process, bias due to divergence of the planned interventions, bias due to lack of data on the results, bias in the measurement of the results and bias in the selection of the results shown.

3. Discussion

Pulmonary embolism is a cardiovascular disease that occurs as a result of occlusion of the pulmonary arterial bed and can lead to acute and potentially fatal right ventricular dysfunction [11]. In this way, the disease interferes with both blood circulation and pulmonary gas Exchange 1. Pulmonary embolism is part of a larger syndrome called venous thromboembolism, which presents as pulmonary embolism or deep vein thrombosis and is the third most frequent acute cardiovascular syndrome in the world. In addition, studies from Western Europe, North America, Australia and Argentina have shown consistent annual incidence results ranging from 0.75 to 2.69 per 1000 individuals in their populations, which makes this syndrome the third most frequent cardiovascular disease in the world, with an incidence lower only than that of myocardial infarction and stroke. Therefore, venous thromboembolism causes a large burden of disease in countries at different levels of development [2]. Furthermore, when compared to deep vein thrombosis, pulmonary embolism is linked to higher mortality, a

higher incidence of recurrences and more severe long-term complications [5].

The clinical picture of pulmonary embolism is non-specific and the most common symptoms are dyspnea at rest, pleuritic chest pain, dyspnea on exertion and edema of the extremities suggestive of deep vein thrombosis. Syncope or hypotension can also occur, but these manifestations are less common. Other signs and symptoms may also be present, such as cough, diaphoresis, signs of increased respiratory effort, among others. The most common comorbidities related to pulmonary embolism, which represent possible risk factors, are hypertension, obesity, recent hospitalization and active malignancy [12].

Pulmonary embolism evolves with changes in circulation and pulmonary gas exchange, with an increase in pulmonary artery pressure from the occlusion of 30 to 50% of the cross-sectional area of the pulmonary arterial bed [13]. Mechanical obstruction and pulmonary vasoconstriction resulting from hypoxemia act as two factors that lead to an increase in pulmonary vascular resistance. This increase in vascular resistance causes right ventricular dilation, altering the contractile properties of the ventricle and generating dysfunction which, in turn, can lead to hemodynamic decompensation and death [14].

In pulmonary embolism, risk stratification is based on the estimated risk of early death, and is divided into high risk, intermediate-high risk, intermediate-low risk and low risk. Thus, high-risk PE, also commonly called massive PE, is characterized by the presence of shock or prolonged hypotension due to right ventricular failure. Intermediate-risk PE, on the other hand, can be subdivided into intermediate-high risk and intermediate-low risk. The parameters that define this class are: signs of right ventricular dysfunction on an imaging test and the presence of markers of myocardial damage on laboratory tests. Thus, when both parameters are positive, PE is classified as intermediate-high risk and when only one of the two is positive, PE is classified as intermediate-low risk. Finally, PE is classified as low risk when none of the aforementioned parameters are positive [1].

In addition, studies that have carried out long-term follow-up of patients who have suffered a PE have shown that these patients can have functional limitations and reduced quality of life even years after an episode of the disease [4]. Thus, patients may also have chronic thromboembolic pulmonary hypertension (CTEPH), which results in markedly reduced exercise capacity and patients often report dyspnea consistent with NYHA (New York Heart Association) functional class III or IV. CTEPH is defined by the presence of 2 criteria after 3 months of anticoagulation for acute PE. These are mean pulmonary arterial pressure >25mmHg measured invasively with pulmonary capillary cross-sectional pressure <15mmHg and at least one defect in pulmonary segmental perfusion detected by pulmonary angiography or pulmonary angiotomography [15].

Treatment for PTE is primarily based on hemodynamic and respiratory support. In addition, anticoagulants are also part of the treatment of this disease in order to prevent early death and recurrences [1]. Therefore, once a patient with venous thromboembolism has been diagnosed and stabilized, anticoagulation should be started whenever necessary, unless this therapy is contraindicated [5]. Anticoagulant therapy in PE should last at least 3 months [1,10].

In addition to hemodynamic and respiratory support, there are also reperfusion therapies. These are surgical thrombectomy, which consists of surgically removing the thrombus that occludes the pulmonary vascular bed, and thrombolysis3. Thrombolytic therapy, the main subject of this theoretical rationale, is a tool that enables faster restoration of pulmonary perfusion, and its use is better established when the patient with PTE has hemodynamic compromise. As such, it is considered one of the first-choice treatments in cases of high-risk PTE. However, in cases without hemodynamic compromise, the benefits of this therapy remain controversial1 since it is related to an increased risk of bleeding, which also contraindicates therapy in cases of intermediate-risk PE, since mortality in these cases does not justify exposure to the risks of therapy in these patients [7,8].

Thrombolytic therapy, in which thrombolytic drugs are used to break up the thrombus that is occluding the pulmonary vascular bed in order to quickly re-establish pulmonary circulation and improve right ventricular function [6]. This therapy can be carried out either systemically or by percutaneous intervention using a catheter to carry out localized therapy. In catheter-directed thrombolysis, lower doses of fibrinolytic drugs are used and ultrasound can also be used to facilitate the fragmentation of the thrombus in addition to its mechanical fragmentation [3].

In the latest Cochrane review on thrombolytic therapy for pulmonary embolism, the meta-analysis showed that, in the studies included, therapy with thrombolytic plus heparin reduces the risk of death and recurrence of pulmonary embolism when compared to therapy with heparin alone or with heparin plus placebo. However, this effect became less significant when excluding studies with a high risk of bias from the analysis. In addition, the incidence of major and minor bleeding was higher in the group receiving thrombolysis and the quality of life and length of hospital stay were similar between the groups [16].

4. Systemic Thrombolysis

The PEITHO clinical trial, the largest ever study of thrombolytic treatment for pulmonary thromboembolism, compared the efficacy and safety of thrombolysis with tenecteplase plus heparin versus placebo plus heparin in the treatment of intermediate-risk PTE. In this study, a lower incidence of death or hemodynamic decompensation was noted in patients who received thrombolysis, but an increase in bleeding was also observed in the same group. The study therefore concluded that caution is needed when considering

thrombolytic treatment for intermediate-risk PTE7. In a post hoc analysis of the study, there was no difference in mortality, residual dyspnea, functional limitation or persistent right ventricular dysfunction between the groups at 24 months [17]. In another post hoc analysis, which followed patients from 6 months to 3 years after the PTE episode, there were also no differences between the groups and the results showed that incomplete recovery or non-recovery of echocardiographic parameters 6 months after the PTE episode are predictors of chronic thromboembolic pulmonary hypertension (CTEPH) or long-term post-pulmonary embolism impairment (PPEI) [18].

Another smaller study which also evaluated thrombolysis with tenecteplase in intermediate-risk PTE with follow-up of up to 90 days also showed that thrombolytic treatment is linked to a higher probability of a positive outcome, but the study sample was too small to assess whether this treatment was linked to an increased incidence of bleeding. At the 90-day follow-up after the PTE episode, the only difference between the groups was that patients in the thrombolysis group rated themselves more highly on a scale of perceived general health from 1 to 10. [19] Another study also evaluated tenecteplase therapy in the treatment of intermediate-risk pulmonary embolism and observed a greater reduction in right ventricular dysfunction at 24 hours when compared to placebo; however, it was also not possible to define whether or not this benefit was related to an excessive risk of bleeding [20].

The TVASPE study evaluated the effects of thrombolysis with Alteplase or Streptokinase for PTE associated with pulmonary hypertension or right ventricular dysfunction. Its results showed that patients who received thrombolytics had a lower incidence of in-hospital death or clinical deterioration compared to those who only received anticoagulation. In addition, patients in the thrombolysis group also had lower pulmonary artery pressures at the time of hospital discharge, but there was no significant difference in the normalization of right ventricular function between the groups and at the end of the month when exertional dyspnea and NYHA functional class were assessed, there were also no differences between the groups [21].

Another study aimed to assess the impact of thrombolytic therapy with tenecteplase on quality-of-life outcomes in patients with submassive PTE, using the physical component summary (PCS) of the SF-36 questionnaire, at a follow-up 90 days after therapy. The results of this study showed that thrombolytic treatment improved quality of life compared to the placebo group in patients with previous comorbidities such as venous thromboembolism, heart failure, among others. In patients without these comorbidities, there were no differences between the thrombolysis and placebo groups [22].

Another smaller study compared thrombolytic treatment with alteplase plus anticoagulation with unfractionated heparin and placebo plus unfractionated heparin in patients with submassive PE, with echocardiographic follow-up up to 6 months after therapy. The results showed that patients who received alteplase had a faster reduction in right ventricular dysfunction and a tendency towards better clinical outcomes, although this effect has yet to be defined [23].

Another study compared treatment regimens with r-SK and urokinase for massive or submassive PE using pulmonary CT angiography scores with a 3-month follow-up. The results showed differences only in one of the two scores used 14 days after thrombolysis, in which Urokinase obtained a better score. Furthermore, there were no other differences between the treatments during the 3-month follow-up [24].

Another study aimed to compare convalescent inflammatory biomarkers at a 3-month follow-up in PTE patients treated with systemic thrombolysis or placebo. The results showed the acute inflammatory nature of PTE through the concentration of 4 inflammatory markers. In addition, a reduction in these markers was observed in more than 80% of patients and there were markers that suffered a greater reduction in the group that received thrombolysis, but the difference did not reach statistical significance [25].

Finally, another study assessed the levels of activated protein C (APC) in patients with submassive PTE treated with thrombolysis with activated alpha-dotrecogin or with placebo, with both groups receiving anticoagulation with enoxaparin. The results showed that the patients had low levels of APC and that these values did not change in the patients in the placebo group and increased in a dose-dependent manner in the thrombolysis group. Thus, the study concluded that activation of coagulation in submassive PTE does not lead to systemic activation of activated protein C [26].

5. Low-Dose Systemic Thrombolysis

One study compared the efficacy and safety of thrombolytic therapy with streptokinase performed with the normal dose of the drug and with a low dose in patients with submassive PTE with right ventricular dysfunction. A comparison was also made with a group receiving only anticoagulants. A significant improvement in echocardiographic parameters was observed in the groups receiving thrombolysis compared to the group receiving only anticoagulants 72 hours after treatment. However, there were no statistically significant differences in mortality between the groups and no significant differences in complications between the groups receiving fibrinolytic therapy [27].

Another study compared the efficacy and safety of low versus high doses of Alteplase in patients with high-risk PTE. The results of the study showed no significant differences in the efficacy of either regimen and both showed significant improvement in echocardiographic parameters, pulmonary perfusion and pulmonary artery obstruction. In addition, there were no significant differences in mortality, bleeding and recurrence of PTE; however, a lower trend of bleeding was observed in the group that was treated with a low

dose of thrombolytic [28]. Another study compared the use of intermittent low doses of urokinase for one week versus a bolus of alteplase. The results also showed that both modalities had similar efficacies and further studies are needed to determine whether or not the modality with intermittent low doses of urokinase reduces the risk of bleeding [29].

The "MOPETT" study evaluated the treatment of intermediate-risk PTE with thrombolysis and a low dose of tissue plasminogen activator versus anticoagulation alone. In the results, the occurrence of pulmonary hypertension or pulmonary hypertension and recurrence of PTE at 28 months was significantly higher in the control group when compared to the group that received thrombolysis. As for mortality, length of hospital stay, bleeding, PTE recurrence and the combination of PTE recurrence and mortality, the thrombolysis group had a significantly lower incidence of the combination of PTE recurrence and mortality and length of hospital stay. Thus, the study concluded that the results suggest that thrombolysis with a lower dose of tissue plasminogen activator is safe and effective in the treatment of moderate PTE with an immediate and significant reduction in pulmonary artery pressure that was maintained during the 28-month follow-up [30].

6. Localized Thrombolysis

One study aimed to analyze the efficacy and safety of intra-arterial pulmonary thrombolysis with streptokinase compared to systemic thrombolysis in patients with high-risk PTE. At the end of the study there were significantly more participants in the group that received intra-arterial thrombolysis who became asymptomatic when compared to the group that received systemic thrombolysis. In addition, intra-arterial thrombolysis was significantly more effective in reversing cardiogenic shock, had a greater reduction in the median heart rate of the group and had a significantly greater improvement in some cardiographic parameters when compared to the group that received systemic treatment. The results showed no significant difference in bleeding between the two groups, but mortality was significantly higher in the group that received systemic thrombolysis. Thus, the study concluded that local thrombolysis in high-risk PTE reverses hemodynamic damage quickly and safely, with a higher average clinical success rate when compared to systemic thrombolysis, as well as reducing morbidity and mortality [31].

The OPTALYSE-PE study aimed to compare the efficacy and safety of 4 doses and times of ultrasound-facilitated catheter-directed administration of tissue plasminogen activator (tPA) in order to identify the ideal treatment regimen for patients with submassive PTE. The results of the study showed that there was a significant improvement in right ventricular dilation in all groups, which led to the conclusion that treatment with lower doses and infusion times has good potential and should be further studied in future clinical trials [32]. In a study that followed up patients who took part in the OPTALYSE-PE study for a year to assess echocardiographic, functional and quality of life outcomes in the 4 groups that made up the OPTALYSE-PE study. The results of this follow-up showed that in all groups there was a reduction in the ratio between the diameters of the right and left ventricles up to 30 days after treatment, this reduction was maintained 90 days and 1 year after treatment and there were no significant differences between the groups. In addition, there was an improvement in all groups in the 6-minute walk test and in the scores used to measure the patients' functional status and quality of life at 1 year. Thus, the study concluded that the lower dose regimens of rt-PA in ultrasound-facilitated catheter-directed thrombolysis resulted in sustained improvement in right ventricular function during the 1-year follow-up in all treatment groups and the improvement in functional status and quality of life was parallel to the improvement in right ventricular function [33].

Another study compared ultrasound-facilitated catheter-directed thrombolysis using rt-PA (10-20mg/15h) and anticoagulation with unfractionated heparin versus anticoagulation with unfractionated heparin alone in patients with intermediate-risk PTE. In this study, the group that received thrombolysis showed a greater reduction in the ratio between the diameters of the right and left ventricles at 24 hours and there were no significant differences in mortality, bleeding and recurrence of PTE. Thus, the study concluded that a standard regimen of catheter-directed thrombolysis facilitated by ultrasound was superior to anticoagulation alone in reversing right ventricular dilatation in 24 hours without increasing the occurrence of bleeding [34].

7. Anticoagulants in Thrombolysis

One study compared two different anticoagulants, low molecular weight heparin and unfractionated heparin, in order to see what impact these drugs have on clinical outcomes in patients receiving fibrinolytic treatment with Alteplase for massive PTE. The results showed a lower incidence of adverse events for low molecular weight heparin, but the difference was not statistically significant, so further studies are needed to confirm the results [35].

8. Final Considerations

Finally, it can be seen that several studies have managed to show advantages of thrombolytic therapy similar to those shown in the 2018 Cochrane review on the subject. Despite this, even though most of the studies included in the rationale are randomized controlled trials, most studies have several limitations, such as low population samples, which often lead to statistically insignificant or dubious results. This shows that more studies and higher quality studies are needed to reach a consensus on the various doubts that still exist about thrombolytic therapy for pulmonary embolism.

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