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[Intervention Review]

Thrombolytic therapy for pulmonary embolism

Zhiliang Zuo[1,2], Jirong Yue[1,2], Bi Rong Dong[1,2], Taixiang Wu[3], Guan J Liu[4], Qiukui Hao[1,2]

[1]The Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China. [2]National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China. [3]Chinese Clinical Trial Registry, Chinese Ethics Committee of Registering Clinical Trials, West China Hospital, Sichuan University, Chengdu, China. [4]Cochrane China, West China Hospital, Sichuan University, Chengdu, China

Contact: Bi Rong Dong, birongdong@163.com.

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ABSTRACT

Background

Thrombolytic therapy is usually reserved for people with clinically serious or massive pulmonary embolism (PE). Evidence suggests that thrombolytic agents may dissolve blood clots more rapidly than heparin and may reduce the death rate associated with PE. However, there are still concerns about the possible risk of adverse effects of thrombolytic therapy, such as major or minor haemorrhage. This is the fourth update of the Cochrane review first published in 2006.

Objectives

To assess the effects of thrombolytic therapy for acute pulmonary embolism.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 17 August 2020. We undertook reference checking to identify additional studies.

Selection criteria

We included randomised controlled trials (RCTs) that compared thrombolytic therapy followed by heparin versus heparin alone, heparin plus placebo, or surgical intervention for people with acute PE (massive/submassive). We did not include trials comparing two different thrombolytic agents or different doses of the same thrombolytic drug.

Data collection and analysis

Two review authors (ZZ, QH) assessed the eligibility and risk of bias of trials and extracted data. We calculated effect estimates using the odds ratio (OR) with a 95% confidence interval (CI) or the mean difference (MD) with a 95% CI. The primary outcomes of interest were death, recurrence of PE and haemorrhagic events. We assessed the certainty of the evidence using GRADE criteria.

Main results

We identified three new studies for inclusion in this update. We included 21 trials in the review, with a total of 2401 participants. No studies compared thrombolytics versus surgical intervention. We were not able to include one study in the meta-analysis because it provided no extractable data. Most studies carried a high or unclear risk of bias related to randomisation and blinding.

Meta-analysis showed that, compared to control (heparin alone or heparin plus placebo), thrombolytics plus heparin probably reduce both the odds of death (OR 0.58, 95% CI 0.38 to 0.88; 19 studies, 2319 participants; low-certainty evidence), and recurrence of PE (OR 0.54, 95%

CI 0.32 to 0.91; 12 studies, 2050 participants; low-certainty evidence). Effects on mortality weakened when six studies at high risk of bias were excluded from analysis (OR 0.71, 95% CI 0.45 to 1.13; 13 studies, 2046 participants) and in the analysis of submassive PE participants (OR 0.61, 95% CI 0.37 to 1.02; 1993 participants). Effects on recurrence of PE also weakened after removing one study at high risk of bias for sensitivity analysis (OR 0.60, 95% CI 0.35 to 1.04; 11 studies, 1949 participants). We downgraded the certainty of evidence to low because of 'Risk of bias' concerns.

Major haemorrhagic events were probably more common in the thrombolytics group than in the control group (OR 2.84, 95% CI 1.92 to 4.20; 15 studies, 2101 participants; moderate-certainty evidence), as were minor haemorrhagic events (OR 2.97, 95% CI 1.66 to 5.30; 13 studies,1757 participants; low-certainty evidence). We downgraded the certainty of the evidence to moderate or low because of 'Risk of bias' concerns and inconsistency. Haemorrhagic stroke may occur more often in the thrombolytics group than in the control group (OR 7.59, 95% CI 1.38 to 41.72; 2 studies, 1091 participants).

Limited data indicated that thrombolytics may benefit haemodynamic outcomes, perfusion lung scanning, pulmonary angiogram assessment, echocardiograms, pulmonary hypertension, coagulation parameters, composite clinical outcomes, need for escalation and survival time to a greater extent than heparin alone. However, the heterogeneity of the studies and the small number of participants involved warrant caution when interpreting results.

The length of hospital stay was shorter in the thrombolytics group than in the control group (mean difference (MD) −1.40 days, 95% CI −2.69 to −0.11; 5 studies, 368 participants). Haemodynamic decompensation may occur less in the thrombolytics group than in the control group (OR 0.36, 95% CI 0.20 to 0.66; 3 studies, 1157 participants). Quality of life was similar between the two treatment groups.

None of the included studies provided data on post-thrombotic syndrome or on cost comparison.

Authors' conclusions

Low-certainty evidence suggests that thrombolytics may reduce death following acute pulmonary embolism compared with heparin (the effectiveness was mainly driven by one trial with massive PE). Thrombolytic therapy may be helpful in reducing the recurrence of pulmonary emboli but may cause more major and minor haemorrhagic events, including haemorrhagic stroke. More studies of high methodological quality are needed to assess safety and cost effectiveness of thrombolytic therapy for people with pulmonary embolism.

PLAIN LANGUAGE SUMMARY

Drugs to dissolve pulmonary embolism (blood clot in the lungs)

Background

A pulmonary embolus is a potentially fatal blood clot that lodges in the main artery of the lungs, straining the right side of the heart and affecting blood circulation. People with this condition are at risk of new emboli forming (recurrence). In the case of a massive pulmonary embolism, treatment to restore blood flow is urgently required. Heparin thins the blood, but newer drugs that actively break up the clots (thrombolytics) may act more quickly and may be more effective. These newer drugs include streptokinase, urokinase, and recombinant tissue-type plasminogen activator. The major complication of this treatment is bleeding.

Key results

We searched the literature and included 21 studies in this update (evidence current to 17 August 2020). These trials involved 2401 adult participants with pulmonary embolism, who were randomly assigned to a thrombolytic agent followed by heparin or heparin alone or heparin plus placebo. No studies compared thrombolytics versus surgical intervention. We were able to use data from 20 clinical trials with a total of 2371 participants. Thrombolytics may lower the likelihood of death and recurrence of blood clots compared to heparin. On the other hand, thrombolytics caused more side effects, including major and minor bleeding events (haemorrhagic events) and haemorrhagic stroke, than heparin alone. Limited information from a number of individual trials show that thrombolytics might be better at improving blood flow through the lungs, heart function, reducing the need for further treatment and time spent in hospital. None of the studies reported on post-thrombotic syndrome or compared the costs of the different treatments.

Certainty of the evidence

The certainty of the evidence is moderate or low, because of study design limitations (risk of bias), and small sample sizes. We need more large, well-designed trials to increase our confidence in any benefits of thrombolytic therapy for pulmonary embolism.