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Catheter-directed therapy as a treatment for submassive pulmonary embolism: A meta-analysis

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ABSTRACT

Aims: Catheter-directed therapy (CDT) is included in the guidelines for diagnosing and treating massive pulmonary embolism. However, few studies have evaluated the efficacy of CDT as a treatment for submassive pulmonary embolism (SPE). Therefore, we used evidence-based medicine to evaluate the effectiveness and safety of CDT in treating SPE.

Methods: Search terms describing CDT in SPE and patients with intermediate pulmonary embolism were entered into the PubMed, Embase and Cochrane Library databases to identify relevant articles without language restrictions published between January 1990 and December 2016. A quality assessment and data extraction were performed by two investigators. The clinical efficacy of and major complications associated with treatment were analysed using a fixed effects model.

Key findings: A total of 552 patients in 16 studies were included in this meta-analysis. The clinical success rate in CDT was approximately 100% (95% confidence interval (CI): 99%, 100%), the primary bleeding rate was 0.02% (95% CI: 0%, 0.05%), and mortality during hospitalization was approximately 0% (95% CI: 0%, 0.01%). The mean decrease in pulmonary artery systolic pressure after treatment was −14.9% (95% CI: −19.25%, −10.55%), and the mean post-treatment change in the ratio of the right to the left ventricle (RV/LV) was −0.35% (95% CI: −0.48%, −0.22%).

Significance: CDT is effective and safe as a treatment for SPE and could be a first-line treatment for SPE under specific conditions.

1. Introduction

Pulmonary embolism is a general term that describes a group of diseases or clinical syndromes caused by a variety of embolization-related obstructions of the pulmonary arterial system. Pulmonary thromboembolism (PTE) is the most common type of pulmonary embolism. Acute pulmonary embolism is a serious threat to the quality of life of affected people, and its incidence increases annually. According to the 2004 European Society of Cardiology report on the diagnosis and treatment of acute pulmonary embolism, individuals with this condition can be divided into the following three categories: high risk, moderate risk and low risk. The hazard indicators that serve to stratify these individuals include blood pressure, right ventricular morphology and functional and myocardial injury markers. The 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) statement describes treatments for “pulmonary embolism and chronic thromboembolic pulmonary hypertension” in patients classified with “massive, sub-massive and low-risk pulmonary embolism” [1]. In fact, massive pulmonary embolism indicates a high-risk patient, whereas sub-massive pulmonary embolism indicates an intermediate-risk patient. SPE is a type of pulmonary embolism observed in patients with right ventricular dysfunction (RVD) and/or elevated myocardial injury markers but without haemodynamic instability [1]. There is currently no uniform standard to diagnose RVD; however, the above-mentioned statement proposed that the presence of at least one of the following criteria indicates RVD: right ventricular enlargement (ratio of right ventricular diameter (RVd) to left ventricular diameter (LVd) > 0.9 in a cardiac four-chamber view) or a colour Doppler ultrasound showing right ventricular systolic dysfunction; computer tomography (CT) imaging showing right ventricular enlargement (RVd/LVd > 0.9 in a cardiac four-chamber view); increased BNP (> 100 pg/ml); increased NTpro-BNP (> 900 pg/ml); or electrocardiogram changes

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(e.g., a newly created complete or incomplete right bundle branch blockage, an increase or decrease in the ST segment of the atrioventricular septal lead, or T wave inversion in the atrioventricular septal lead). Additionally, the presence of either of the following criteria was defined as indicative of myocardial injury or necrosis: increased cTnI (> 0.4 ng/ml) or increased cTnT (> 0.1 ng/ml) [1].

The current treatment for PTE primarily comprises two components: thrombolysis and anticoagulation. Systemic thrombolysis occurs in massive pulmonary embolism, but its association with submassive pulmonary embolism (SPE) remains controversial [1–4]. Niwa et al. [5] studied 465 patients with SPE who were enrolled in a multicentre randomized controlled clinical trial to compare the efficacy of monteplase as a treatment for acute pulmonary embolism. Although the results of this study support the efficacy of this drug as a systemic thrombolytic therapy, serious bleeding complications (including intracranial haemorrhage) did occur in some patients. Kline et al. [6] found that in some patients with SPE alone, initiating anticoagulation treatment within 6 months resulted in a significant increase in pulmonary artery pressure, suggesting that anticoagulant treatment may have poor long-term efficacy in SPE.

The 2014 European Journal of Cardiology guidelines on acute pulmonary embolism suggest that catheter thrombolysis can be used in patients with massive pulmonary embolism resulting from absolute contraindications such as thrombolysis or thrombolysis failure [7]. A meta-analysis performed by William et al. [8] included 35 studies of catheter-direct therapy to treat massive pulmonary embolism (n = 594 individuals). The results showed that catheter thrombolysis can be used as a first-line treatment for massive pulmonary embolism. However, there are less data regarding the use of catheter-thrombolytic therapy to treat SPE. Lou BH et al. [9] recently published a meta-analysis that evaluated catheter intervention as a treatment for SPE in studies published between January 1, 2015 and May 31, 2016. Their search window was small, and some documents that met the requirements may have been omitted. Additionally, they did not evaluate biases (publication or otherwise) in their results. Here, we analysed the clinical success rate of CDT for primary pulmonary embolism rather than only analysing changes in the RV/LV ratio and pulmonary arterial pressure before and after treatment. When the data were merged and found to be heterogeneous, we actively engaged in subgroup analyses to identify heterogeneity sources to bolster our conclusions; none of the articles by Lou and colleagues were included. Hence, this meta-analysis follows up on these established publications to further evaluate the effectiveness and safety of catheter thrombolysis as a treatment for primary pulmonary embolism. However, these results provide support for implementing this clinical treatment in primary pulmonary embolism.

2. Materials and methods

2.1. Materials

The PubMed, Embase and Cochrane Library databases were searched to identify studies that describe the use of catheter thrombolytic therapy in submassive or intermediate-risk pulmonary embolism and were published between January 1990 and December 2016. Additionally, there were no language restrictions.

2.2. Literature search method

The following keywords were used to identify potentially relevant articles: patient-acute, submassive, intermediate-risk, pulmonary, embolism, thromboembolism; intervention-percutaneous, transvenous, thrombolysis, thrombolysis, treatment, device, pigtail, fibrinolysis, fibrinolysis, aspiration, fragmentation, enzymatic, embolectomy, tissue plasminogen activator; contrast-systemic thrombolysis, intravenous thrombolysis, intravenous thrombolytic, pulmonary embolectomy, outcome-death, death, mortality, clinical improvement, Miller index, shock index, pulmonary artery pressure, and pulmonary perfusion. We used the Boolean logical operators “OR” and “AND” to maximize the number of hits.

2.3. Inclusion and exclusion criteria

Two researchers independently evaluated the literature. All differences were resolved through discussion, and the following inclusion criteria were used: 1) sub-massive (intermediate-risk) pulmonary embolism; 2) sufficient details provided to meet the inclusion criteria; 3) use of pulmonary angiography, pulmonary perfusion scans or CT pulmonary angiography to obtain a diagnosis; 4) CDT administration in the treatment arm of the trial; and 5) reported outcomes of mortality, clinical efficiency, bleeding rate, or imaging. The following exclusion criteria were applied: inclusion of patients with massive (high-risk) or low-risk pulmonary embolism or incomplete data.

2.4. Data extraction

The following data were independently extracted from the selected studies by two researchers: 1) the number of patients with submassive (intermediate-risk) pulmonary embolism, 2) the number of deaths, 3) the number of cases of severe bleeding, 4) the number of cases of mild haemorrhage, 5) the number of cases of treatment failure, 6) the mean pulmonary arterial pressure before and after treatment, 7) the RV/LV ratio before and after treatment, and 8) the Miler index before and after treatment. The clinical success rate was defined as haemodynamic stability, improved pulmonary artery pressure and/or right ventricular pressure, or hospital discharge. Severe bleeding was defined as either fatal bleeding; bleeding in a vital site or organ, including intracranial, spinal, intraocular, intraperitoneal, intraocular, or retroperitoneal bleeding, after treatment was terminated; or required infusion of 2 or more units of red blood cells.

2.5. Document quality evaluation

Two researchers independently evaluated the quality of the included literature, and any differences were resolved through discussion. An RCT study was assessed using the following Cochrane Reviewer Handbook 5.1.0 RCT quality evaluation criteria: 1) whether the random sequence was fully described and whether the method was appropriate; 2) whether the blind method was used: 3) whether the allocation of the hidden sequence was fully described; 4) whether the description impacted the results; and 5) any other source of bias. If each of these items was deemed low-risk, the risk of bias in the study was also assumed to be low (level A); if one or more of these criteria were unknown, the risk of bias was considered moderate (Grade B); and if there was a high risk of one or more of these criteria, the risk of bias was considered high (C). Non-randomized controlled trials were evaluated using the Newcastle-Ottawa Scale (NOS) document quality assessment scale [10]. To strengthen our results more convincing, we excluded an article of relatively low quality.

2.6. Statistical processing

This meta-analysis of selected articles describes efficacy and safety indicators. The data were statistically processed using R-3.3.2 statistical software. When the incidence rate was 0 or 1, the Freeman-Tukey double-inverse sine conversion was used. The odds ratio (OR) and 95% confidence interval (CI) were calculated by performing a heterogeneity test (Q test and I^2 statistic) for each study effect. If there was no heterogeneity ($p \geqq 0.1$, $I^2 < 50\%$) among the studies, the fixed effects model was used to estimate the effect of the model. If there was heterogeneity among the studies ($p < 0.1$, $I^2 > 50\%$), the random effects model was used. A subgroup analysis was used to determine the source of heterogeneity in the included studies (e.g., the type of study and the