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Systemic Therapy versus Catheter Directed Techniques for the Treatment of Acute Massive Pulmonary Embolism

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SYSTEMIC THERAPY VERSUS CATHETER DIRECTED TECHNIQUES FOR THE TREATMENT OF ACUTE MASSIVE PULMONARY EMBOLISM

by

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ABSTRACT

Acute massive pulmonary embolism is characterized by obstruction of the pulmonary arterial tree that exceeds 50% of the cross-sectional area causing acute and severe cardiopulmonary failure from right ventricular overload. Systemic thrombolytic therapy is recommended as standard, first-line treatment in patients with massive pulmonary embolism unless contraindicated and catheter directed therapies, including low dose thrombolytic administration directly into thrombus and mechanical thrombectomy can be adjunctive or used as an alternative to systemic treatments. This literature review researched articles looking both systemic thrombolysis and endovascular techniques for the treatment of acute massive pulmonary embolism with an emphasis on long term clinical outcomes. Study results demonstrated the efficacy and safety of systemic thrombolysis and catheter directed therapies as well as adverse effects; however, further randomized trials are needed, as acknowledged by many of the authors included in this paper, comparing both treatment options for hemodynamically unstable patients with emphasis on long term sequalae.

Keywords: anticoagulation, prognosis, pulmonary embolism, thrombectomy, and thrombolytics.

Introduction

Systemic thrombolysis is standard, first-line treatment for a patient presenting with hemodynamically unstable pulmonary embolism, but data from randomized trials using catheter directed techniques is gaining attention as a viable option for patients who have contraindications to high-dose systemic thrombolysis. A meta-analysis of 594 patients from six prospective and 29 retrospective studies demonstrated a significant reduction in complication rates with catheter directed therapies and a clinical success rate of 86.5% compared to 77% following systemic thrombolysis (Kuo, et al., 2009). This study supported both safety and efficacy in treating massive pulmonary embolism with catheter directed thrombectomy and intraclot thrombolysis.

Long term outcomes following massive pulmonary embolism treatment provide beneficial statistical data for clinicians treating these patients. The use of quality of life surveys, dyspnea-questionnaires and a 6 minute walk test are tools that help measure outcomes and are valuable clinical and physiological predictors of long term prognosis (Kahn, et al., 2017). Data acquisition following pulmonary embolism could prove beneficial in determining appropriate treatment by looking at the long-term sequela of post massive pulmonary thrombus, especially those receiving systemic thrombolytics or endovascular therapies.

Statement of the Problem:

Deciding on a treatment plan for a patient presenting with an acute massive pulmonary embolism can be challenging for some clinicians. Systemic thrombolytic therapy continues to be standard, first-line therapy, but new technologies using catheter directed techniques with a combination of thrombectomy and intraclot thrombolysis are demonstrating safety and efficacy and are gaining support in the medical community. There is limited long term data regarding morbidity and mortality of patients treated for massive pulmonary embolism. This information

could help guide clinicians in deciding on a treatment option that could provide immediate therapy to hemodynamically unstable patients while at the same time providing improvement in quality of life long term.

Research Questions:

In patients presenting with acute massive pulmonary embolism, how does the use of systemic thrombolytics compare in efficacy and safety over catheter directed therapies? Is there improvement in quality of life, dyspnea, and functional capacity with catheter directed thrombolysis and thrombectomy compared to systemic thrombolysis?

This scholarly project looked at the efficacy and safety of both therapies for massive pulmonary embolism to determine the best option for clinicians when deciding treatment for their patients by comparing statistical data of short-term efficacy as well as long-term sequela.

Pathology of Pulmonary Embolism:

Pulmonary embolism (PE) is defined as obstruction of the pulmonary vasculature and risk factors that are acquired and inherited may contribute to someone developing this disease. Genetic risk factors typically involve disorders of clotting factors and include protein C deficiency, protein S deficiency, factor V Leiden, antithrombin deficiency, and hyperhomocysteinemia. Acquired risks include, but are not limited to obesity: age, estrogen therapy, pregnancy, prolonged immobility, cancer, trauma, and post-surgery (Giordano, Jansson, Young, Hogan, & Kabrhel, 2017).

Thrombus occurs when there is a disruption in the mechanisms between blood coagulation and anticoagulation, and PE can follow when thrombus from a deep vein thrombosis (DVT) breaks off and travels to the pulmonary circulation, although non-thrombotic material like fat, tumor or air can also be the source (Giordano, Jansson, Young, Hogan, & Kabrhel, 2017).

Therapy should be initiated promptly because of increased mortality and morbidity associated with PE and understanding the risks for venous thromboembolism (VTE) and how a patient may present can expedite diagnosis and subsequent treatment.

Venous stasis, hypercoagulability and local trauma to vessel walls are events known as Virchow's triad, and many patients with VTE are diagnosed with one of these during their history and physical examination. When DVT develops, usually in the lower extremities, vascular congestion can cause swelling and pain proximal to the site of obstruction, although these symptoms can be subtle or nonexistent. If the DVT forms in a large vessel, it is more likely to dislodge and embolize the pulmonary artery occluding some degree of the vasculature. Small emboli may only obstruct subsegmental arteries and spontaneously lyse without clinical consequences. However, large thrombi can straddle the bifurcation or obstruct the entire pulmonary outflow tract, increasing the strain on the right heart and leading to severe hypotension and death (Giordano, Jansson, Young, Hogan, & Kabrhel, 2017).

Diagnosis of Pulmonary Embolism

Turan et al. (2017), conducted a retrospective analysis of 196 patients suspected of having pulmonary embolism and a subsequent D-dimer and computed tomography angiography (CTA) was performed for diagnosis. This study used clinical scoring systems, comparing them to patients with and without pulmonary embolism to help guide clinicians in managing their patients and add to their ability to diagnose pulmonary embolism, especially practitioners in rural communities. It was noted by the authors that CTA is important in visualizing pulmonary embolism, but has a high radiation and contrast exposure.

The study tested a hypothesis that clinical scoring and D-dimers can aide in guiding clinicians in managing their patients with suspected pulmonary embolism by comparing their

findings to diagnostic imaging. The analysis employed an empirical scoring system as well as Geneva, Wells, and Miniati scoring systems to help classify patients as having low, intermediate or high clinical probability of PE and then compared the results to CT angiography for correlation. The study group included 107 males (54.6%) and 89 females (45.4%) suspected of PE; their mean age was 64.18 ± 17.44. There was no statistically significant relationship between the presence of PE and gender ($p = 0.064$). The sensitivity of the various scoring systems for PE was found as 94.9% for empirical scoring, 89.7% for the Wells criteria, 84.6% for Geneva scoring, and 92.3% for the Miniati system. There was no PE in any patient with a normal D-dimer level and a low probability score in any scoring system.

Treatment Options for Acute Massive Pulmonary Embolism

Treatment options for pulmonary embolism depend on the hemodynamic stability of the patient and the clot burden. Therapy consists of anticoagulation, systemic thrombolytics and endovascular therapies including mechanical thrombectomy and intraclot thrombolysis. Rheolytic thrombectomy removes clots by injecting high pressure saline into the thrombus and breaking it into fragments. The clot is then suctioned out of the artery. A retrospective study of 51 consecutive patients that presented with acute submassive or massive pulmonary embolism and were subsequently treated with AngioJet rheolytic therapy was conducted by Chechi et al. (2009) to appraise the impact of this therapy both clinically and angiographically. Figure 1 shows post-procedural angiographic data.

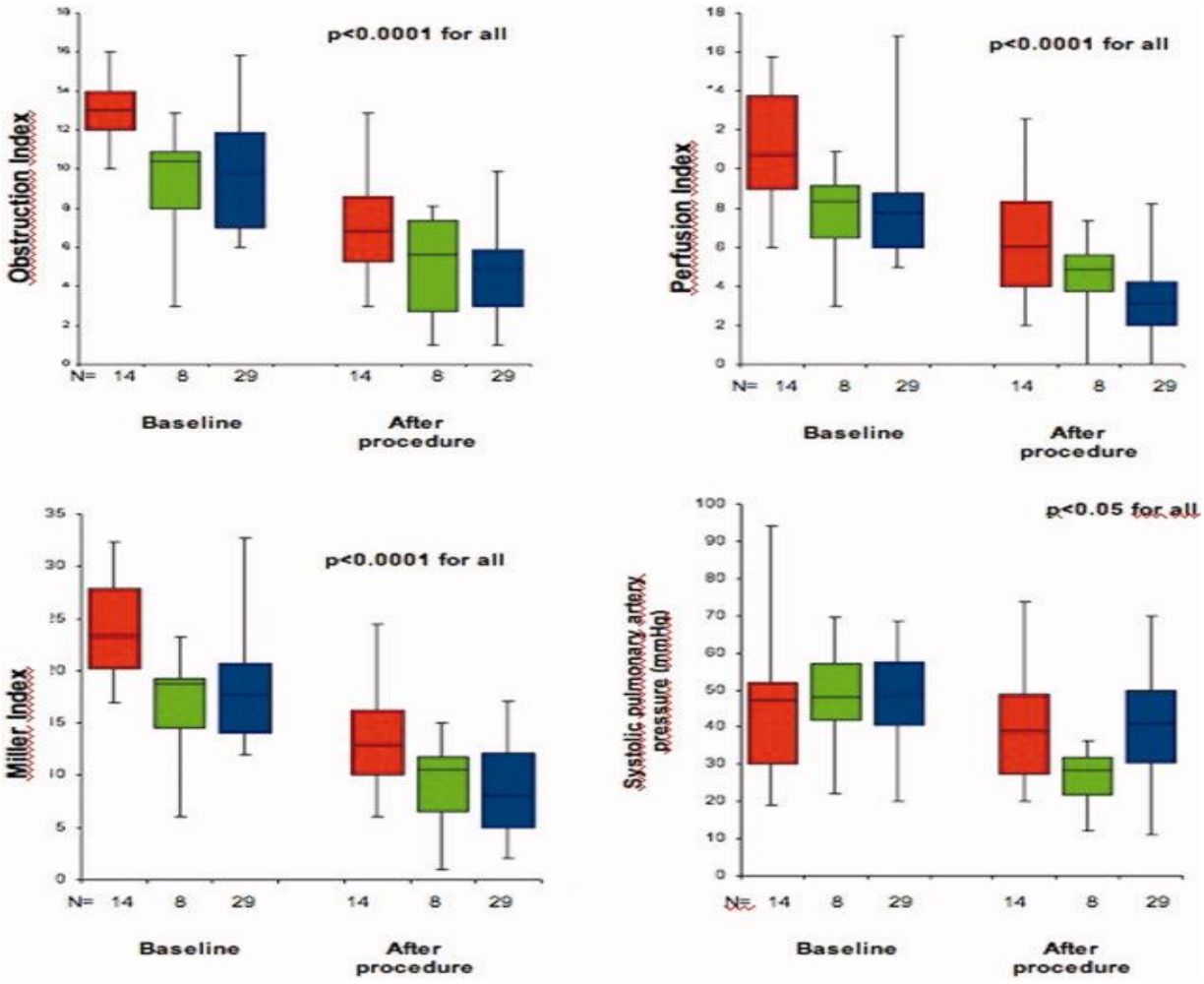


Figure 1

Improvement in obstruction, perfusion, Miller indexes, and systolic pulmonary artery pressure before and after rheolytic thrombectomy according to hemodynamic compromise (i.e., shock, red bars; hypotension, green bars; right ventricular dysfunction, blue bars) Chechi et al. (2009).

The study hypothesized that there was a significant clinical benefit to mechanical removal of the thrombus as opposed to management with systemic therapy in patients with hemodynamically significant compromise. The data demonstrated safety and efficacy in treating hemodynamically unstable patients with massive pulmonary embolism. Loco-regional fibrinolysis, as it has been carried out in historical trials, may carry a lower risk of bleeding,

because of the low dose of drug administration; however, due to its ease and availability, systemic route is currently recommended for thrombolysis in acute PE.

The use of systemic thrombolytics increases the risk of hemorrhage when compared to heparin alone or when thrombolysis was combined with placebo. A Cochran Review meta-anaylsis combined data from 17 trials with 2167 participants and looked at outcomes of patients randomly assigned to thrombolytic agents followed by heparin versus other therapies. The study showed low quality evidence that thrombolytics reduce death following acute pulmonary embolism compared to systemic heparin; however, the studies demonstrated a reduction in recurrance rates and an increased risk of hemorrhage when using thrombolytic therapies ($P = 0.001$) (Hao, Dong, Yue, & Liu, 2015). Major and minor bleeding remain a concern when using thrombolytics even though evidence suggest these agents dissolve clots more rapidly than heparin and reduce the death rate associated with PE.

Systemic thrombolysis also demonstrates an increased risk of hemorrhage when compared to catheter directed intraclot lytics. A meta-analysis of 594 patients from six prospective studies and 29 retrospective studies that met the inclusion criteria were included in this systematic review evaluating the safety and efficacy of catheter directed therapy techniques for massive pulmonary embolism. The study demonstrated a significant reduction in complication rates with the use of catheter directed therapies and a clinical success rate of 86.5% compared to 77% following systemic thrombolysis (Kuo et al., 2009). The authors of this paper reported an estimated 20% risk of major hemorrhage with systemic thrombolysis; however, only minor and major procedural complications of 7.9% (95% CI 5.0 to 11.3) and 2.4% (95% CI 1.9 to 4.3) respectively were given.

Safety of Systemic and Endovascular Therapy

Deciding on a treatment plan for a patient presenting with an acute massive pulmonary embolism can be challenging for some clinicians. Systemic thrombolytic therapy continues to be standard, first-line therapy, but new technologies using catheter directed techniques with a combination of thrombectomy and intraclot thrombolysis are demonstrating safety and efficacy and are gaining support in the medical community.

A meta-analysis of 594 patients from six prospective and 29 retrospective studies demonstrated a significant reduction in complication rates with catheter directed therapies and a clinical success rate of 86.5% (95% CI 82.2 to 90.2; 35 studies) compared to 77% following systemic thrombolysis (Kuo et al., 2009). The authors acknowledged treatment of massive pulmonary embolism with systemic thrombolysis is standard of care, but that contraindications and time constraints can increase the risks of adverse events associated with this therapy.

A retrospective, unblinded study was performed in Japan investigating the clinical outcomes of 221 patients diagnosed with acute pulmonary embolism and treated with systemic therapy. Anticoagulation therapy was performed in 100 patients and thrombotic therapy was performed in 121 patients. For patients with right heart strain, thrombolysis demonstrated a favorable outcome and no significant complications from hemorrhage when compared to anticoagulation alone (Nakamura et al., 2005). Figure 2 shows Clinical events during the hospital stay.

	Anticoagulation alone	Thrombolysis	P
With prolonged shock	1/4 (25%)	5/12 (42%)	>0.99
Hemodynamically stable	8/91 (9%)	10/100 (10%)	0.81
With RV afterload stress	4/15 (27%)	5/42 (12%)	0.22

Without RV afterload stress	4/30 (13%)	5/32 (16%)	>0.99
Major bleeding	6/100 (6%)	16/121 (13%)	0.11

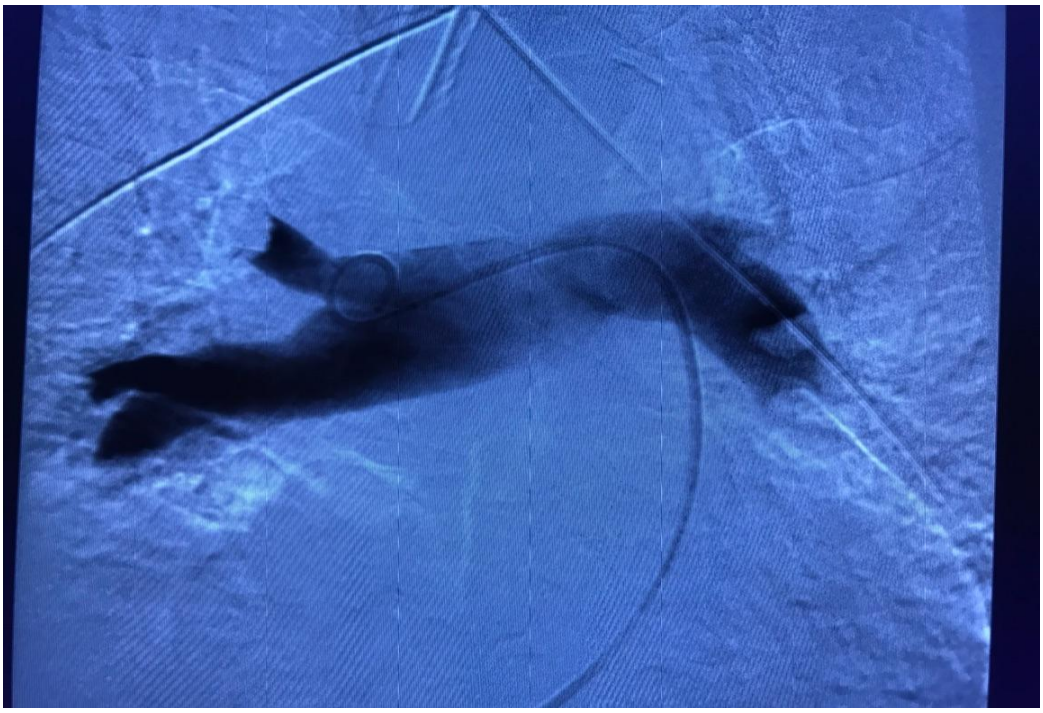
Values shown were (no. of death cases + no. of cases with recurrent APTE)/no. of total cases in each group. Only for major bleeding, values shown were no. of cases with major bleeding/no. of all study cases. RV=right ventricular, APTE=acute pulmonary thromboembolism (Nakamura, et al., 2005).

The rate of death and recurrence of acute pulmonary thromboembolism in the anticoagulation group was similar to that in the thrombolytic group (9% versus 10%, respectively, P-0.81). It was noted that the dosage of thrombolysis is less in Japan than that used in the United States. A potential source of bias was the non-randomized assignment of patients and the choice of treatment being at the discretion of the attending physicians.

Treating elderly patients can be challenging due to comorbidities and the increased risks of hemorrhage. Ipek, et al., evaluated the effectiveness and safety of thrombolytic therapy in elderly patients with pulmonary embolism. This study added to existing knowledge concerning hemorrhagic complications associated with thrombolysis by including elderly patients who historically receive inadequate treatment. The data collected on 363 patients recruited for the study, including 205 subjects > 65 and 158 subjects < 65, demonstrated comparable hemorrhagic complications versus patients who received heparin therapy. Three of 51 (5.9%) elderly patients who were treated with thrombolytic therapy died at 30 days follow-up. One (1.9%) additional death was seen at 1-year follow-up in this group. In contrast, 11 (7.1%) patients died at 30 days and 20 (12.9%) patients died during the follow-up among elderly non-thrombotic group. These results show the effectiveness and safety of thrombolytic therapy in the elderly (Ipek et al., 2015).

For those patients with relative contraindications to systemic high dose thrombolytic therapy, catheter directed procedures that employ mechanical thrombectomy as well as low dose intraclot thrombolysis have proven safety track records in both massive and submassive PE (figure 1). A multicenter registry and meta-analysis conducted by Bloomer et al. (2017), provided results in a paper investigating the safety of catheter-directed thrombolysis in the treatment of both acute massive and submassive pulmonary embolism. Comparison to systemic treatment was not conducted; however, the data demonstrated low bleeding complications with CDT. Of the 860 patients analyzed, 88% were considered submassive PE, potentially skewing the results of the safety data of massive PE treatment with CDT. The statistical analysis from the registry was combined with the pooled analysis from the 15 published studies and the data was justified in their conclusion.

A



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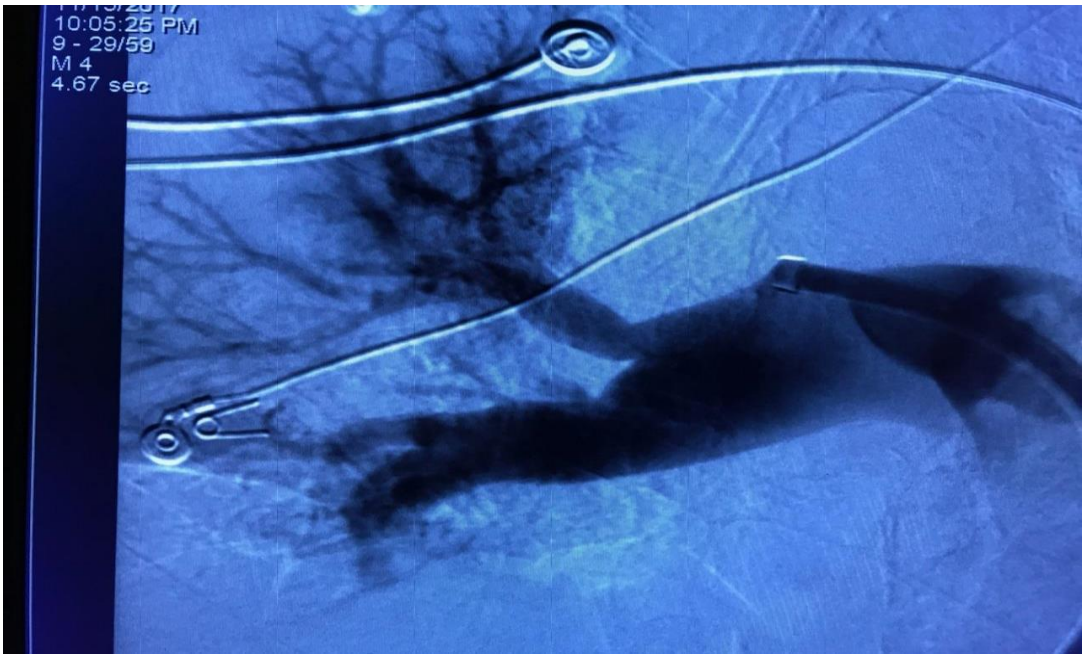

Figure 1. Thrombectomy procedure. a) Pulmonary arteriogram demonstrating thrombus within the pulmonary vasculature prior to thrombectomy using Penumbra's Indigo System. b) Clot removed during thrombectomy. c) Post procedure pulmonary arteriogram demonstrating restoration of blood flow through pulmonary arteries.

Long Term Sequela

When treating hemodynamically unstable patients presenting with pulmonary embolism, it's important to consider not only the immediate threat, but also long term sequela like quality of life. The ELOPE (Evaluation of Long-term Outcomes after PE) cohort study, through a comprehensive follow-up of patients diagnosed with pulmonary embolism, measured outcomes to include quality of life surveys, dyspnea-questionnaires and a six minute work walk distance up to 12 months post treatment. This relevant study looked at the outcomes of patients that were diagnosed with pulmonary embolism through a baseline computed tomography pulmonary angiogram and found specific clinical and physiological predictors of reduced improvement over time, providing new information on prognosis following pulmonary embolism (Kahn et al., 2017). Hemodynamically unstable patients may not do well once diagnosed and treated for massive pulmonary embolism (Kahn et al., 2014). This study demonstrated poor prognosis following PE but noted that the clinical significance of residual pulmonary vascular abnormalities in this outcome continues to be poorly understood. The data provided did show chronic thromboembolic pulmonary hypertension was found to range from 1 to 4% with a poor prognosis and a median survival of 12-24 months.

The paper published by Kahn et al. (2017), was reinforced by a meta-analysis looking at the long term effects of pulmonary embolism on right ventricular function, exercise tolerance and quality of life and assessed whether thrombolytic drugs affected these outcomes.

Costs of Systemic Thombolytics versus Catheter Directed Treatment

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects about 900,000 persons in the United States each year.

According to Dasta et al. (2015), patients admitted and receiving anticoagulation for PE had daily hospital costs of 2,981, 2,034 and 1,564 for their first three days of admission and the costs became stable following the third day. This was a retrospective claims analysis of 64,000 patients diagnosed with deep vein thrombosis or PE. The study also suggested that any change in the length of stay could significantly affect hospitalization costs. Another study by LaMori et al. (2015), examined the initial and subsequent length of stay in hospitals and associated charges in US hospitals in 2011and found that subsequent admissions were costlier than the initial admission. Many of the patients were also discharged to specialist nursing facilities incurring post-hospitalization charges. The median charge amounted to $37, 006 for the initial hospitalization with a mean hospital stay of 5.1 days. It was noted by the authors that appropriate anticoagulation and continuity of care may reduce incidence and frequency of hospital readmissions and thromboembolic morbidity and mortality.

Discussion

A review of the literature shows that systemic thrombolytics remains the gold standard for treatment of massive PE for patients without contraindications. The goal of any treatment is to decrease thrombus burden and return the patient to hemodynamic stability, while at the same time minimizing major bleeding risks and mortality. Catheter directed therapies allow for both low dose intraclot thrombolytics and mechanical thrombectomy and may prove beneficial for the long-term sequela related to massive pulmonary thrombus. Chronic thromboembolic pulmonary hypertension can be found in a small percentage of patients post pulmonary embolism which carries a poor prognosis, and although the clinical significance of residual pulmonary vascular abnormalities continues to be poorly understood, the literature review determined that patients

may not do well long term once diagnosed and treated with thrombolytics (Bloomer, et al., 2017).

The goal of any treatment for acute massive pulmonary embolism is to decrease thrombus burden and return the patient to hemodynamic stability, while at the same time minimizing major bleeding risks, mortality and long term sequela. A comprehensive literature review of previous research was conducted focusing on the risks and benefits of both systemic and endovascular therapies for massive pulmonary embolism by analyzing historical data through a search of PubMed, CINALHL and Cochran. Catheter directed therapies allow for both low dose intraclot thrombolytics and mechanical thrombectomy and may prove beneficial for the long-term sequela related to massive thrombus. However, systemic thrombolytics remains the gold standard for treatment of massive PE for patients without contraindications. Chronic thromboembolic pulmonary hypertension can be found in a small percentage of patients post pulmonary embolism which carries a poor prognosis and although the clinical significance of residual pulmonary vascular abnormalities continues to be poorly understood, the literature review determined that patients may not do well long term once diagnosed and treated with thrombolytics (Kahn et al., 2014).

In Patients Presenting With Acute Massive Pulmonary Embolism, How Does the Use of Systemic Thrombolytics Compare in Efficacy and Safety over Catheter Directed Therapies?

As the first line treatment for hemodynamically unstable patients presenting with pulmonary embolism, systemic thrombolysis is well tolerated and efficacious; however, it may be contraindicated in patients with prior intracranial hemorrhage, cerebral vascular lesions, malignancy, active bleeding, bleeding diathesis or in patients older than 65.

Historically, elderly patients receive inadequate treatment with thrombolysis due to concerns of hemorrhagic complications associated with the above conditions. Ipek et al. (2015) found comparable hemorrhage rates between patients >65 that didn't receive thrombolysis to 205 subjects >65 and 158 subjects <65 that were treated with systemic thrombolysis. Regarding long term follow-up, three of 51 (5.9%) elderly patients who were treated with thrombolytic therapy died at 30 days follow-up. One (1.9%) additional death was seen at 1-year follow-up in this group. In contrast, 11 (7.1%) patients died at 30 days and 20 (12.9%) patients died during follow-up among elderly non-thrombolytic group. These results show the effectiveness of thrombolytic therapy, particularly in patients >65. The effects of comorbid conditions on patient outcomes may be a source of potential bias.

In a retrospective, unblinded study investigating clinical outcomes of 221 patients diagnosed with acute pulmonary embolism and treated with thrombolytic therapy, researches from Japan demonstrated favorable outcomes and no significant complications from hemorrhage when compared to anticoagulation alone. Although the differences in death and recurrence of acute pulmonary thromboembolism between thrombolytic and anticoagulation groups didn't show statistical significance, the thrombolytic group tended to demonstrate better outcomes. Furthermore, there was no significant difference in the rate of major bleeding between thrombolytic and anticoagulation groups (Nakamura et al., 2005).

Throughout this research, systemic thrombolytic therapy has continued as first line treatment for PE even though some studies have shown higher bleeding complications as well as multiple contraindications when compared to anticoagulation alone. Alternative treatments with endovascular therapy using catheter directed techniques to mechanically macerate and remove

clots and/or deliver intraclot thrombolytics continues to show promising results and low complication rates.

A meta-analysis of 594 patients from six prospective and 29 retrospective studies was included in a systematic review evaluating the safety and efficacy of catheter directed therapy techniques for massive pulmonary embolism. The study demonstrated a significant reduction in complication rates with the use of catheter directed therapies and a clinical success rate of 86.5% compared to 77% following systemic thrombolysis. The clinical success of this study was defined as stabilization of hemodynamics, resolution of hypoxia and survival at discharge. Treatment included mechanical fragmentation and/or aspiration of clot as well as intraclot thrombolytics. A source of potential bias was found in the fact that only 60% of patients received intraclot lytics during catheter directed thrombectomy and the study didn't compare systemic thrombolytics to one specific catheter directed therapy. This meta-analysis evaluated short-term clinical success, but as with most studies reviewed, long term data looking at patient's quality of life post massive pulmonary embolism was not included.

Is There Improvement in Quality of Life, Dyspnea, and Functional Capacity with use of Catheter Directed Thrombolysis and Thrombectomy Compared to Systemic Thrombolysis?

Kahn et al. (2014) conducted a one year comprehensive follow-up of patients diagnosed with acute pulmonary embolism using measured outcomes to include quality of life surveys, a dyspnea questionnaire and a 6-minute walk distance at baseline and at 1,3,6, and 12 months. This relevant study looked at the outcomes of patients that were diagnosed with pulmonary embolism through a baseline computed tomography pulmonary angiogram. The study found specific clinical and physiological predictors of reduced improvement over time, providing new information on prognosis following pulmonary embolism. Although these patients were treated

with anticoagulants and not with systemic thrombolysis or catheter directed therapy, it did highlight the need to include measurement of one or more functional outcomes in studies of interventions to treat pulmonary embolism (Kahn et al., 2017). The study design was not appropriate to my research question but it did show alternative treatment outcomes and techniques of data acquisition.

Sista et al. (2017) looked at persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life (QoL) impairment following pulmonary embolism and found 4% of survivors develop chronic thromboembolic pulmonary hypertension stemming from residual pulmonary artery obstruction and a mean pulmonary artery pressure greater then 25 mmHg. The study found evidence that many more have poor QoL and exercise intolerance following PE, termed post-PE syndrome. This syndrome may be the result of unresolved thrombus causing increased right heart pressure in the months and years following PE. The data justified the conclusions demonstrating a substantial reduction in quality of life and shorter walking distances of patients post pulmonary embolization compared to population norms. The study excluded patients that were treated exclusively with embolectomy and was unclear regarding thrombolytics and patient outcomes.

The ELOPE (Evaluation of Long-term Outcomes after Pulmonary Embolism) Study is a prospective, observational, multicenter cohort study of patients with a newly diagnosed, first episode pulmonary embolism with specific determinants of poor outcomes. This relevant study, determined that patients may not do well once diagnosed and treated with thrombolytic therapies; however, the clinical significance of residual pulmonary vascular abnormalities in this outcome continues to be poorly understood. Chronic thromboembolic pulmonary hypertension was found to range from 1 to 4% with a poor prognosis and a median survival of 12-24 months.

The data provided in the article justified the conclusion of poor long-term prognosis following pulmonary embolism by researching several prospective and retrospective studies. The authors of this article are attempting to rationalize the need for a prospective, observational, multicenter cohort study of patients with newly diagnosed pulmonary embolism in order to determine potential poor outcomes by identify clinical, anatomic and physiological determinants. The question of what is the best treatment option for patients presenting with hemodynamically unstable massive pulmonary embolism was not definitively answered in my review of the literature and shows that further research, comparing systemic thrombolytic therapy to catheter directed treatments, is indicated.

Applicability to Medical Practice

Diagnosis of PE uses a combination of techniques including a D-dimer, CTA and scoring systems like Geneva, Wells, and Miniati and studies have demonstrated a low probability of pulmonary embolism if the D-dimer is normal and the scoring system used shows a low probability. This is important data for clinicians working in rural areas where access to CTA might not be available. Whether using advanced technologies or clinical judgement and PE scoring systems combined with laboratory values, the question facing clinicians is how to treat. This is often based on how hemodynamically stable the patient is and the contraindications to various treatment options. As the research in the literature demonstrates, there are pros and cons to all therapies and patient selection is critical. Thrombolysis remains the gold standard of treatment for patients presenting with hemodynamically unstable pulmonary embolism but the data demonstrates similar short-term outcomes in most studies when compared to CDT. The use of systemic thrombolytics increases the risk of hemorrhage when compared to heparin alone or

when combined with placebo but no consensus was found for increased hemorrhage when compared to catheter directed therapies. A Cochran review meta-analysis did find reduction in recurrence rates with systemic thrombolysis but also found an increase risk in hemorrhage when compared to anticoagulation (Hao, Dong, Yue, & Liu, 2015). As with most trials the authors agreed that more randomized studies are needed to assess safety and efficacy of thrombolytics.

Catheter directed therapy affords the opportunity to mechanically remove thrombus and at the same time infuse or bolus low dose thrombolytics directly into clot. This has the potential to reduce the hemorrhage seen with high dose thrombolytics. Several new technologies are being used today showing great efficacy and low complication rates. The Indigo Mechanical Thrombectomy Catheter uses continuous aspiration mechanical thrombectomy with high level suction to remove clots and can be used as a first line therapy. This is just one device of many showing promising results. Chechi et al. (2009) conducted a retrospective study of 51 consecutive patients that presented with acute submassive or massive pulmonary embolism over a seven year period, that were subsequently treated with AngioJet rheolytic therapy, to appraise the impact of this therapy both clinically and angiographically. The data demonstrated safety and efficacy in treating patients with massive pulmonary embolism and concluded that large-scale randomized clinical trials comparing systemic thrombolytic to rheolytic thrombectomy are warranted. This study highlights again the need for further trials comparing systemic therapy to endovascular intraclot thrombolysis and thrombectomy.

The efficacy and safety of both systemic and catheter directed therapies appears comparable depending on which study you read, especially looking at short term outcomes. Several studies have looked at long-term sequela post pulmonary embolism and the role residual thrombus plays in quality of life measures. The clinical significance of residual pulmonary

vascular abnormalities continues to be poorly understood but there is agreement that these patients may not do well long-term due to chronic thromboembolic pulmonary hypertension.

In conclusion, there is a need for prospective, observational, multicenter cohort studies comparing patients treated with systemic thrombolytics to catheter directed therapies in order to determine potential poor outcomes by identifying clinical, anatomic and physiological determinants. In addition, further research is needed in functional capacity limitation, exercise intolerance and quality of life impairment post hemodynamically unstable patients treated with both systemic thrombolysis and catheter directed therapy for a head to head comparison.

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