Journal of Cardiology and Cardiovascular Sciences

Commentary Article Open Access

Commentary: Early Versus Delayed Use of Ultrasound-Assisted Catheter-Directed Thrombolysis in Patients with Acute Submassive Pulmonary Embolism

Karim Saleb*

Department of Internal Medicine, Ascension St. John Hospital, USA

Article Info

Article Notes
Received: July 12, 2018
Accepted: August 11, 2018

***Correspondence:**
Dr. Karim Saleb, Internal Medicine Administration, 19251 Mack Ave, Suite 335, Grosse Pointe Woods, MI 48236, USA; Email: kderias89@gmail.com.

Abstract

Pulmonary embolism remains one of the major causes of morbidity and mortality in the United States. For patients with an intermediate-risk pulmonary embolism, Ultrasound-Assisted Catheter-Directed Thrombolysis (USAT) is a contemporary treatment modality that has emerged as a potential alternative to systemic thrombolysis and surgical embolectomy. Multiple studies have demonstrated the efficacy of USAT in reducing the thrombus burden and reversing right ventricular dysfunction in patients with an intermediate-risk pulmonary embolism. However, literature addressing the potential impact of an early catheter directed revascularization is lacking. A recent retrospective study carried out by *Edla et al* suggests that, compared to a delayed intervention, early USAT can improve recovery of pulmonary hemodynamics in patients with submassive pulmonary embolism and also reduce the overall in-hospital length of stay. This commentary provides a thorough analysis of the results of this study and revisits the existing information on ultrasound-assisted thrombolysis for acute pulmonary embolism.

Introduction

Acute Pulmonary Embolism (PE) is one of the most common causes of hospitalization and mortality in the United States. The mortality rate for acute PE exceeds 15% within 90 days, and 58% in the first hour, in patients with hemodynamic compromise[1,2,3]. Survivors of acute PE remain at risk for chronic thromboembolic pulmonary hypertension[4]. PE can present with a variety of clinical syndromes, depending on hemodynamic stability and the extent of occlusion. Patients that are hemodynamically stable, with no evidence of RV compromise, have been classified as low risk. Such patients generally have an excellent prognosis with anticoagulation alone[5]. High risk/Massive PE has been defined as Acute PE with sustained hypotension, pulselessness, or persistent profound bradycardia[6]. Due to the high risk of in-hospital mortality in those patients, systemic thrombolysis remains the treatment of choice[7]. However, in patients with Intermediate-Risk/Submassive Acute PE —defined as Acute PE without systemic hypotension, but with either RV dysfunction or myocardial necrosis— Systemic thrombolysis and surgical embolectomy carry a higher risk of complications[6,7]; with systemic thrombolysis accounting for 20% risk of major hemorrhage and 3-5% risk of hemorrhagic stroke[8], and surgical embolectomy accounting for 27.2% inpatient mortality rate[9]. Due to the above-mentioned risks that equal to the overall mortality of the disease alone, USAT has emerged as an innovative method, which

aims towards a more targeted thrombolytic approach, thus reducing the risk of major hemorrhagic complications.

USAT is a catheter-based technique that uses a Pharmaco-Mechanical system to break down the clot. The catheter is used to deploy sound waves that break down fibrin crosslinks and separate the fibers to promote penetration of the thrombolytic agent, commonly recombinant, tissue plasminogen activator (rt-PA), injected directly into the clot[10,11]. Thus, both mechanisms act synergistically to break down the fibrin complex within the clot.

Major randomized controlled trials (RCTs), including the ULTIMA[12] and the SEATTLE II[13] trials, have demonstrated the efficacy and safety of USAT in submassive PE. The main findings were the significant improvement in right ventricular systolic function, reduction of the clot burden and hemorrhagic outcomes, in comparison to systemic thrombolysis and anticoagulation alone. While most studies evaluated patients with acute submassive PE within 14 days of symptom onset, there are no studies that have addressed the timing of USAT and comparing outcomes of an early intervention versus a delayed one, and here is where *Edla et al* stands out[14].

Review

Edla et al retrospectively evaluated 41 patients with submassive/intermediate risk PE that were treated with USAT, 21 of which were treated within 24 hours of diagnosis (mean time interval of 13.3 ± 5.6 hours) compared to 20 patients treated after 24 hours (mean time interval of 46.4 ± 10.1 hours). Their hypothesis was that an earlier intervention could theoretically have more impact in reducing the clot burden, improving right ventricular function and improving pulmonary hemodynamics. They analyzed six outcome parameters, one echocardiographic (right ventricular–to–left ventricular (RV/LV) ratio) and five invasive (mean pulmonary artery pressure (MPAP), cardiac index (CI), pulmonary vascular resistance, right ventricular stroke work index (RVSWI), and pulmonary artery pulsatility index (PAPi)). They also assessed several clinical outcomes, including the post-procedural length of stay, in-hospital all-cause mortality, recurrent PE, bleeding, and procedure-related complications.

The study results showed improvement of all six outcome parameters in all 41 patients who underwent USAT. Patients who underwent an early intervention had a statistically significant improvement in CI, pulmonary vascular resistance, and RVSWI, when compared with the late intervention group. *Edla et al* also reported that there was no statistically significant improvement in the RV/LV ratio, MPAP, and PAPi when comparing both groups. However, there was a notable trend favoring the early treatment group.

Discussion

This investigation was the first of its kind in exploring the potential impact of an early USAT intervention. It is worth to point out that this study did not demonstrate a statistically significant reduction in the RV/LV ratio between the two intervention groups. The importance of the RV/LV ratio lies, not only in that it is the most commonly studied parameter to guide treatment, but also in its validity to predict short-term mortality in patient with PE[18,19]. With that said, the trend demonstrated that favoring the early treatment group is a good indicator for future investigations, and it can be hypothesized that this trend can also be magnified with larger studies and a bigger sample size.

The use of pulmonary hemodynamic parameters, such as the RV/LV ratio, MPAP, and CI, in USAT has been investigated in prior studies[12,13]. The improvement of such parameters post-intervention has been reproducible again in this investigation, serving to further validate the efficacy of USAT. In attempt to explore further, *Edla et al* included additional parameters in their study that have not been explored in prior investigations; pulmonary vascular resistance has been studied extensively in systemic thrombolysis trials[15], RVSWI is commonly used to evaluate RV contractility and is routinely used to predict RV failure in patients receiving LV assist devices or heart transplants[16]; PAPi is used to predict RV failure, following inferior wall myocardial infarction[17]. The improvement demonstrated in these additional parameters, in all 41 patients post USAT, strongly validates impact of this intervention on the recovery of pulmonary hemodynamics and reduction in clot burden. However, it remains to be seen whether these benefits can be sustained with long-term follow up. The suggestion that early systemic thrombolysis decreases the risk of chronic pulmonary artery hypertension[21] warrants further randomized controlled trials to understand the implications of USAT timing on long-term clinical outcomes.

In regards to the safety outcomes, *Edla et al* reported neither deaths nor severe life-threatening bleeding in the post-procedural period. These results are consistent with the safety profile established with previous investigations[12,13,20]. One notable finding was the statistically significant reduction in the length of stay in the early intervention group versus the delayed group (6.0 ± 2.6 days versus 10.1 ± 6.9 days, respectively). This clinical outcome is important to highlight considering the limited data in the current literature assessing the post procedural length of stay after USAT in patients with submassive PE. In one trial, the ULTIMA trial, the mean hospital stay following USAT was reported as 8.9±3.4 days compared to 8.6±3.9 days in patients treated with unfractionated heparin[12]. It will be interesting to see if this significant finding can be

reproduced again in future studies, especially in comparison with other modalities of treatment of submassive PE.

Study Limitations

Despite the promising results of this study, its impact remains limited by its sample size and the single-center population. Such results require further validation with larger randomized trials. Furthermore, an element of selection bias cannot be ruled out considering that the timing of USAT intervention was dependent on the subjective decision of the cardiologist. Finally, there is no established data to suggests that the improvement of the newly studied pulmonary hemodynamic parameters, such as the RVSWI and PAPi, correlates with a reduction in the development of chronic pulmonary hypertension. Thus, the long-term utility of such parameters remains unclear.

Conclusion

The findings of *Edla et al* serve to emphasize the relative safety and efficacy of USAT as a treatment modality for patients with the sub-massive pulmonary embolism. They also bring to attention the short-term impact of early catheter-directed therapy in improving pulmonary hemodynamics and possibly reducing the development of chronic pulmonary hypertension. Finally, this single-center study also lays the groundwork for future investigators, and shows that larger, multi-center trials are needed to explore the potential long-term benefit with the early use of USAT.

References

1. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International cooperative pulmonary embolism registry (ICOPER). Lancet. 1999; 353: 1386-1389.
2. Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. Circulation. 2010; 122: 1124-9.
3. Wood KE. Major pulmonary embolism: Review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002; 121: 877-905.
4. Klok FA, Delcroix M, Bogaard HJ. Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism. J Thromb Haemost 2018; 16: 1040-1051.
5. Bova C, Pesavento R, Marchiori A, et al. Risk stratification and outcomes in hemodynamically stable patients with acute pulmonary embolism: a prospective, multicentre, cohort study with 3 months of follow-up. J Thromb Haemost. 2009; 7: 938-944.
6. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association. Circulation. 2011; 123: 1788-1830.
7. Martin C, Sobolewski K, Bridgeman P, et al. Systemic Thrombolysis for Pulmonary Embolism: A Review. Pharmacy and Therapeutics. 2016; 41(12): 770-775.
8. Fiumara K, Kucher N, Fanikos J, et al. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol 2006; 97: 127-9.
9. Kilic A, Shah AS, Conte JV, et al. Nationwide outcomes of surgical embolectomy for acute pulmonary embolism. J Thorac Cardiovasc Surg. 2013; 145: 373-377.
10. Engelberger R, Moschovitis A, Fahrni J et al. Fixed low-dose ultrasound-assisted catheter-directed thrombolysis for intermediate and high-risk pulmonary embolism. Eur Heart J. 2013; 36(10): 597-604.
11. Francis CW, Blinc A, Lee S, et al. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. Ultrasound Med Biol. 1995; 21(3): 419-424.
12. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014; 129: 479-486.
13. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. JACC Cardiovasc Interv. 2015; 8: 1382-1392.
14. Edla S, Rosman H, Neupane S, et al. Early Versus Delayed Use of Ultrasound-Assisted Catheter-Directed Thrombolysis in Patients With Acute Submassive Pulmonary Embolism. J Invasive Cardiol. 2018; 30(5): 157-162
15. Meyer G, Sors H, Charbonnier B, et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blind trial. The European Cooperative Study Group for Pulmonary Embolism. J Am Coll Cardiol. 1992; 19: 239-245.
16. Ochiai Y, McCarthy PM, Smedira NG, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. Circulation. 2002; 106: I198-202.
17. Korabathina R, Heffernan KS, Paruchuri V, et al. The pulmonary artery pulsatility index identifies severe right ventricular dysfunction in acute inferior myocardial infarction. Catheter Cardiovasc Interv. 2012; 80: 593-600.
18. Doğan H, de Roos A, Geleijins J, et al. The role of computed tomography in the diagnosis of acute and chronic pulmonary embolism. Diagn Interv Radiol. 2015; 21(4): 307-316.
19. Schoepf UJ, Kucher N, Kipfmueller F, et al. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation. 2004; 110: 3276-80.
20. Engelhardt TC, Taylor AJ, Simprini LA, et al. Catheter-directed ultrasound-accelerated thrombolysis for the treatment of acute pulmonary embolism. Thromb Res. 2011; 128(2): 149-54.
21. Sharma GV, Folland ED, McIntyre KM, et al. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. Vasc Med. 2000; 5: 91-95.