

Special Article - Trauma

Early Versus Late Post-Traumatic Venous Thromboembolism; An Elapsed Time Controversy and Risk Factors

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Received: October 11, 2019; Accepted: October 14, 2019; Published: October 21, 2019

Editorial

Unfortunately, after reviewing literatures over the past twelve years, the author found that there was no fixed definition for either “early” or “late” post-traumatic Pulmonary Embolism (PE). Indeed, post-traumatic Venous Thromboembolism (VTE) that includes both PE and Deep Venous Thrombosis (DVT) remains a major problem and a large challenge in cardio-pulmonary diseases. PE remains relatively common after trauma [1]. PE is a well-recognized potentially fatal complication after trauma [1]. Despite compliance with prophylactic measures, PE remains a threat to post-injury recovery [2]. Post-traumatic pulmonary embolic events are associated with significant morbidity [3]. The reported incidence of PE after trauma has more than doubled in recent years. But, the PE-accompanied mortality has remarkably decreased, suggesting that we are identifying a different disease entity or stage [2]. PE is also well-known to cause significant morbidity and mortality after injury [4]. There are higher frequency of DVT in post-traumatic critically ill patients [5]. Despite the high frequency of DVT in post-traumatic critically ill patients, symptomatic PE remains, although not frequently observed, because systematic screening is not performed [5].

Currently, an early PE after trauma may occur with variant underlying pathophysiology than previously thought [6]. In fact, the inflammatory process that is initiated by a chest trauma may be forced by a coexisting tissue hypoxia and systemic inflammation (usually associated with severe injury) leading to pulmonary endothelial damages and in situ thrombosis of pulmonary arteries [7]. In addition, severe trauma increases the levels of pro-inflammatory pro-coagulant cytokines, leading to an inflammatory reaction [7]. Although early acute traumatic coagulopathy has received much recent attention, the procoagulopathy that often follows appears less appreciated [8]. In the more advanced studies using thromboelastography indicate that patients are at risk for hypercoagulability early after injury⁴. Hypoxia early after injury is often ascribed to other causes [1]. Indeed, Knudson et al. [2], had postulated the ability of a major chest trauma in stimulating inflammation which lead to the direct formation of PE by direct inflammation of pulmonary vessels. This theory may explain why chest injury is associated with PE, but not significantly with DVT. In fact, only 20% of the patients with PE had an associated

DVT event [2]. Knudson et al. [2] agree with this interpretation and their hypothesis [7].

PE is generally thought to occur days after the acute injury [1]. In 2007, Menaker et al. [1] hypothesized that PE often occurs early after injury. They sought to elucidate the timing of PE after trauma. From 2007 to 2018 literature publications, there were five large post-traumatic venous thromboembolism studies [3,4,6,9,10]. (Table 1). All the five studies signify the difference between early and late pulmonary embolism [3,4,6,9,10]. Otherwise, Kazemi et al. [9] study that conducted in the Intensive Care Unit (ICU), all studies were done in Level I trauma center [3,4,6,10].

Bahloul et al. [7]. So, according to the above studies, the definition for an early PE varies from less than two days (Gelbard et al. [3]), to less than three days (Bennis et al. [6], Coleman et al. [4], and Kazemi et al. [9]), to less than four days (Brakenridge et al. [10]) for occurrence of pulmonary embolism after trauma (Table 2). And, the definition for the late PE actually will be the larger values than the previous for early PE [3,4,6,9,10]. Thus, the range of elapsed time for occurrence of pulmonary embolism after injury is 2-4 days [3,4,6,9,10].

However, these studies considered multiple risk factors for evaluation and assessment the cases of post-traumatic venous thromboembolism. Indeed, the risk factors for posttraumatic PE might be different from those for Deep Venous Thrombosis (DVT) [2]. Trauma produces from time-dependent responses from the haemostatic system can increase the risk of bleeding of an injury which needs blood transfusion⁷. However, it has been well-established that the cases with hemorrhagic shock and/or those which required blood transfusion are highly associated with the development of an early PE [8]. Worthily, there are numerous risk factors implicated in these studies. The following risk factors linked to timing of early versus late post-traumatic PE [3,4,6,9,10]:

- Age
- Long bone fracture
- Brain injury
- Spinal cord injury
- Severe Injury severity score (ISS)
- Chest AIS more than 3
- RV dysfunction
- Hospital length of stay (LOS)
- Transfusions
- DVT Prophylaxis.

Table 1: Showing the major post-traumatic venous thromboembolism studies.

Issue	Brakenridge et al. [10]	Benns et al. [6]	Coleman et al. [4]	Gelbard et al. [3]	Kazemi et al. [9]
• Informative data					
• Year of study	2011	2014 (2005-2010)	2015 (2007-2013)	2016 (2008-2013)	2018
• Site of study	Level I trauma center	Level I trauma center	Level I trauma center	Level I trauma center	ICU
• No. of total patients	17,736 (108 PE)	6,483 (54 PE)	54,964 (144 PE)	NA (50 PE)	240
• Risk factors:					
• Age	-	-	-	-	More early PE
• Long bone fracture	More early PE	More early PE	More early PE	-	More early PE
• Brain injury	More late PE	More late PE	More late PE	-	-
• Spinal cord injury	-	-	More late PE	-	-
• Severe ISS	More late PE	More late PE	More late PE	-	More early PE
• Chest AIS >3	More late PE	-	-	-	-
• RV dysfunction	-	-	-	More early PE	-
• Hospital LOS	-	More early PE	-	-	-
• Transfusions	-	-	More late PE	-	-
• DVT Prophylaxis	More late PE	More late PE	-	-	-
• Results					
• % of early PE	50%	35%	42.9%	28%	40.4%
• % of Late PE	50%	65%	57.1%	72%	59.6%

AIS: Abbreviated Injury Score; DVT: Deep Venous Thrombosis; ISS: Injury Severity Score; LOS: Length Of Stay; PE: Pulmonary Embolism; RV: Right Ventricle

Table 2: Showing the timing for major post-traumatic PE studies.

Study	Year of study	Timing for early PE	Timing for late PE
1. Brakenridge et al. [10]	2011	within four days	More than four days
2. Benns et al. [6]	2005-2010	within three days	More than three days
3. Coleman et al. [4]	2007-2013	within three days	More than three days
4. Gelbard et al. [3]	2008-2013	within two days	More than two days
4. Kazemi et al. [9]	2018	within three days	More than three days

PE: Pulmonary Embolism

In 2011

Brakenridge et al. [10] study was the first to clear risk factors which were accompanied to the timing of a post-traumatic PE. The only independent and highest risk factor for early PE was the long bone extremity fractures. But, the late PE groups had a higher ISS, severe head injury, severe chest injury, and a delay in the chemical prophylaxis initiation around 24 hours. The benefits of immediate prophylaxis may outweigh risks. Patients with severe head injuries appear to have later PE events¹⁰.

In 2014

Benns et al. [6] reported that the occurrence of early PE more suggested than late PE. This despite larger difference of clinical entity in the early PE than the late PE. They found that the early PE patients were more likely to have; lower extremity injuries, ISS, less likely to undergo the operative interventions, less likely for femoral vein cannulation, and shorter average LOS. In contrast, late PE patients who had suffered from a traumatic brain injury had more delay in initiating chemical prophylaxis [6].

In 2015

Coleman et al. [4] showed that there were specific injury patterns, such as an extremity abbreviated injury score (AIS) >3, were predictive of early PE. Whereas, a severe head injury and spinal cord injury were linked to a higher risk of late PE, as well as, blood transfusions and high ISS.

The study used thromboelastography as an indicator for the patients that are at risk for hypercoagulability early after injury⁴. Despite this risk, prophylactic anticoagulation is often delayed in patients with certain injuries due to concerns about bleeding. Unfortunately, the timing of prophylactic anticoagulation had no

impact on early PE [4].

In 2016

Gelbard et al. [3] retrospective study, reported that the Computed Tomographic (CT) effects for all patient of traumatic injury with possible PE. CT measurement can be predictive for Right Ventricular (RV) dysfunction. The primary targets for the study were PE-related mortality and its relation with RV dysfunction. They found RV pathophysiological changes with post-traumatic PE. But the early post-traumatic PE appears to be associated with fewer RV changes than the late post-traumatic PE and may be representative of primary pulmonary thrombosis. Whatever, patient sustaining a late PE had a higher PE-related mortality rate (16.7% vs. 0%), larger RV diameters, RV/LV volume ratio, RV volumes, and RV/LV diameters ratio [3]. Yet, they set out to demonstrate that early PE is not accompanied to a RV dysfunction when using a CT measurement, and suggested that early PE may have a different underlying pathophysiology. Indeed, there was controversy in the outcome for both early and late PE and in embolic management of CT findings for early PE. However, it remains unclear whether these physiologic effects or clinical outcomes differ between early (<48 hours) vs late (≥48 hours) post-traumatic PE. Thus, there were no significant differences in the baseline characteristics nor in injury patterns between the early and late PE groups [3].

In 2018

Kazemi et al. [9] study identified the factors linked to traumatic PE in the Emergency Ward. They concluded that the occurrence of early PE can be predicted in a majority of the trauma-patients who were requiring ICU admission especially older patients, patients with long bone fractures and those with severe injury. This study has confirmed that the patients in early PE group were older than those who suffered

late PE (45.9 ± 7.49 vs. 42.6 ± 8.81 years; $P=0.002$). In addition, the prevalence rate of long bone fractures in lower extremities was significantly higher in those with early PE when compared with the other patients (26.8% vs. 7.0%, $P<0.001$). Finally, they found that the group with early stage PE had more severe injuries when compared to those with late PE ($P=0.007$) [9].

Conclusion and Recommendations

The author think that if the further studies confirm the presence of unsuspected early PE, all admitted trauma patients should be re-evaluated for a hypercoagulability after trauma. Further studies are indicated as this has implications concerning the prevention of PE in trauma patients. Unfortunately, the timing of early VTE versus late VTE is still controversial issue for further decisive study.

Acknowledgement

The author wishes to thank Editor-in-chief and editorial board to give me the chance for submission of an editorial article.

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