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Association between aspirin use and deep venous thrombosis in mechanically ventilated ICU patients

Ena Gupta[1] · Furqan S. Siddiqi[2] · Ryan Kunjal[3] · Muhammad Faisal[2] · Farah Al-Saffar[4] · Abubakr A. Bajwa[2] · Lisa M. Jones[2] · Vandana Seeram[2] · James D. Cury[2] · Adil Shujaat[5]

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Abstract Deep venous thrombosis (DVT) is common in intensive care unit (ICU) patients. It is often silent and may be complicated by pulmonary embolism and death. Thromboprophylaxis with heparin does not always prevent venous thromboembolism (VTE). Aspirin (ASA) reduces the risk of VTE in surgical and high-risk medical patients but it is unknown if ASA may prevent DVT in mechanically ventilated ICU patients. We performed a retrospective chart review of critically ill patients who received mechanical ventilation for >72 h and underwent venous ultrasonography for suspected DVT between Jan 2012 and Dec 2013. We excluded patients who were on therapeutic doses of anticoagulation or had coagulopathy. We used multivariable logistic regression to evaluate association between aspirin use and DVT during hospitalization. There were 193 patients. The mean ± SD age was 58 ± 15.7 years. Half were male. DVT was found in 49 (25.4%). DVT was found in the first 15 days of hospitalization in 67.3% of the patients. The majority (82.8%) received thromboprophylaxis with unfractionated or low molecular weight heparin. Fifty-six (29%) were on ASA. On multivariable regression analysis, ASA use was associated with a significant reduction in the odds of finding DVT (OR 0.39, 95% CI 0.16–0.94; p = 0.036). DVT is common in mechanically ventilated ICU patients despite the use of thromboprophylaxis. Aspirin may prevent DVT in such patients.

Keywords Deep venous thrombosis · Venous thromboembolism · Aspirin · Thromboprophylaxis · Heparin · Intensive care unit

Introduction

Deep venous thrombosis (DVT) is common in critically ill patients [1–3]. Such patients are especially vulnerable due to multiple risk factors: mechanical ventilation, immobilization, use of sedatives and paralytics, use of central venous catheters (CVC) [4], prior history of venous thromboembolism (VTE), end-stage renal disease, use of vasopressors, platelet transfusion [3], malignancy [2], morbid obesity [5], and congestive heart failure [6, 7]. Deep venous thrombosis may be complicated by pulmonary embolism (PE) and death. Deep venous thrombosis in critically ill patients is often clinically silent [8] and pharmacologic thromboprophylaxis with subcutaneous heparin is not always effective in preventing VTE in such patient [2, 3, 5]. Dalteparin was not found to be any better than unfractionated heparin in reducing DVT in critically ill patients in the PROphylaxis for ThromboEmbolism in Critical care Trial (PROTECT) [9]. Consequently, there is a need for a more effective method of pharmacologic thromboprophylaxis. Aspirin (ASA) has been shown to reduce the risk of VTE in surgical and high-risk medical patients [10]. However, it is

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✉ Ena Gupta
enagupta8@gmail.com

[1] Division of Pulmonary, Critical Care and Sleep Medicine, Thomas Jefferson Medical College, 834 Walnut Street, Suite 650, Philadelphia, PA 19107, USA

[2] Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, Jacksonville, FL, USA

[3] Department of Medicine, University of Florida, Jacksonville, FL, USA

[4] Division of Cardiology, Mayo Clinic, Scottsdale, AZ, USA

[5] Division of Pulmonary, Critical Care and Sleep Medicine, University at Buffalo, SUNY, Buffalo, USA

unknown if ASA may prevent DVT in mechanically ventilated intensive care unit (ICU) patients, who remain at risk of VTE despite pharmacologic thromboprophylaxis. We hypothesized that rate of DVT would be lower in mechanically ventilated ICU patients who are on ASA compared to those who are not on it.

Materials and methods

We performed a case control study of adult patients who were in an ICU between Jan 2012 and Dec 2013 and met the following inclusion criteria: received mechanical ventilation for >72 h and underwent venous ultrasonography for suspected DVT. We excluded patients who were on therapeutic anticoagulation. We retrospectively reviewed the electronic medical charts of the patients who met the inclusion criteria. The study (UFJ 2014-025) was approved by the Institutional Review Board of the University of Florida at Jacksonville.

We collected the following data: demographic characteristics including age, gender, body mass index (BMI); risk factors for DVT like CVC or peripherally inserted central venous catheters (PICC), active malignancy, prior history of VTE, sepsis; use of ASA; use of other anti-platelet agents; use of thromboprophylaxis; ventilator days; and hospital length of stay (LOS). ASA was administered either orally in patients who could tolerate or crushed and delivered via oro-gastric/nasogastric feeding tube in intubated patients.The diagnosis of DVT was based on the visualization of an intravascular thrombus, incompressibility of the vein by probe pressure, absence of spontaneous flow by Doppler, and absence of variation in flow with respiration. The diagnosis of DVT required direct visualization of the thrombus and one or more of the other signs in the deep veins of either upper or lower extremity. The CVCs used at our institution are made of oligon material and are heparin-coated. Catheter-related DVT was defined as DVT in an extremity vein in which CVC or PICC was in place at the time of diagnosis or within the preceding 72 h.

We reported categorical variables as numbers (percentages) for and continuous variables as means (standard deviation). Univariable regression analysis was performed for all the collected variables. Variables from univariable analysis were then used in a stepwise approach to perform multivariable logistic regression to evaluate association between ASA use and DVT. The model with the lowest Akaike's Information Criterion was selected and used to estimate the odds ratio (OR) for the association. We defined statistical significance as p value <0.05. We also performed sensitivity analysis by excluding patients with catheter related DVT or history of VTE. We used Stata, version 12.1 (Stat Corp, College Station, Texas) to perform statistical analysis.

Results

There were a total of 193 patients. The mean ± SD age was 58 ± 15.7 years and 50% were male. Deep vein thrombosis was found in 49 (25.4%) patients. The characteristics of patients with and without DVT are compared in Table 1.

Deep venous thrombosis was catheter related in 17 (34.6%) patients. There were only six patients with active malignancy but DVT was found in half of them. There were only six patients with a prior history of VTE and DVT was found in only one of them.

All received mechanical thromboprophylaxis with an intermittent pneumatic compression device. The majority (n = 159, 82.8%) of patients received pharmacologic thromboprophylaxis in addition to mechanical thromboprophylaxis. All patients on pharmacological thromboprophylaxis received unfractionated heparin. Dose adjustment based on body weight was performed in morbidly obese patients (BMI > 40) as per the ICU protocol. There were 56 (29%) patients on ASA. Of the patients on pharmacological thromboprophylaxis, 48 (30.19%) were on aspirin and 39 (24.53%) experienced DVT (Table 2). The majority (n = 47, 83.9%) of those on ASA received 81 mg daily and the rest (n = 12, 17%) 325 mg daily. There were only 11 (5.7%) patients on dual antiplatelet therapy with ASA and Clopidogrel. Deep venous thrombosis was found in the first 15 days of hospitalization in the majority (67.3%) of the patients.

Deep venous thrombosis involved the upper extremity in 28 (57%) patients and the lower extremity in 21 (42.9%). The characteristics of patients with upper and lower extremity DVTs are compared in Table 3.

Patients with upper extremity DVT were older in age (60 vs. 56 years) and had a higher mean BMI (32 vs. 28) compared to patients with lower extremity DVT but statistical significance was not seen in any of these associations (Table 3).

On multivariable analysis, we found a statistically significant decrease in the odds of finding DVT in patients on ASA after adjusting for age, male gender, CVC (or PICC), sepsis and use of pharmacologic thromboprophylaxis (OR 0.39, 95%CI 0.16–0.95; p = 0.039) (Table 4).

This association remained even after excluding catheter related DVTs. Deep venous thrombosis was not found in any of the 11 patient who were on both ASA and Clopidogrel.

Table 1 Characteristics of patients with and without DVT

	DVT N (%) or mean ± SD	No DVT N (%) or mean ± SD	Total N (%) or mean ± SD	P value
Number	49 (25.39)	144 (74.61)	193	
Age (years)	56.98 ± 16.60	58.24 ± 15.43	57.92 ± 15.71	0.63
Male gender	28 (57.14)	68 (47.22)	96 (49.74)	0.230
BMI (kg/m^2)	30.55 ± 11.16	30.90 ± 11.94	30.81 ± 11.70	0.868
Active malignancy	3 (6.12)	6 (4.17)	9 (4.66)	0.575
Prior VTE	1 (2.04)	5 (3.50)	6 (3.12)	0.613
Sepsis	32 (68.09)	89 (64.96)	121 (65.76)	0.697
Pharmacologic thromboprophylaxis	39 (79.59)	120 (83.92)	159 (82.81)	0.479
Aspirin	8 (16.33)	48 (33.33)	56 (29.02)	0.023
Aspirin and Clopidogrel	0	11 (7.80)	11 (5.79)	0.044
Ventilator days	22.59 ± 23.41	21.07 ± 20.08	21.46 ± 20.92	0.661
Total hospital LOS	50.75 ± 80.23	46.64 ± 46.41	47.68 ± 56.79	0.662
Days when DVT tested	16.79 ± 17.38	33.80 ± 79.93	26.69 ± 69.82	0.163
IV catheters				0.098
CVC	41 (83.67)	96 (67.61)	137 (71.73)	
PICC	5 (10.2)	28 (19.72)	33 (17.28)	
IV catheter Site				0.033
Upper extremity	35 (77.78)	104 (90.43)	139 (86.88)	
Lower extremity	10 (22.22)	11 (9.57)	21 (13.12)	
Service				0.254
Medical ICU	39 (79.59)	121 (84.03)	160 (82.90)	
Surgical ICU	6 (12.24)	10 (6.94)	16 (8.29)	
Neurological ICU	4 (8.16)	7 (4.86)	11 (5.70)	
Cardiovascular ICU	0	6 (4.17)	6 (3.11)	

BMI body mass index, *CVC* central venous catheter, *DVT* deep vein thrombosis, *ICU* intensive care unit, *IV* intravenous, *LOS* length of stay, *PICC* peripherally inserted central venous catheter, *VTE* venous thromboembolism

Table 2 Distribution of patients with DVT based on thromboprophylaxis and aspirin during hospital stay

		N	DVT N (%)
Pharmacological thromboprophylaxis	Aspirin	48	7 (14.8)
	Not on Aspirin	111	32 (28.83)
	Total	159	39 (24.53)
Only mechanical thromboprophylaxis	Aspirin	8	1 (12.50)
	Not on Aspirin	25	9 (36)
	Total	33	10 (30.30)

Table 3 Characteristics of patients with upper extremity and lower extremity DVT

	Upper extremity DVT N (%) or mean ± SD	Lower extremity DVT N (%) or mean ± SD	P value
Number	28 (57.14)	21 (42.86)	
Age (years)	59.5 ± 16.21	55.52 ± 13.40	0.366
Male gender	12 (42.86)	9 (42.86)	1
BMI (kg/m^2)	32.47 ± 13.47	27.74 ± 5.71	0.181
Catheter-related DVT	13 (46.43)	4 (19.05)	0.046

BMI body mass index, *DVT* deep vein thrombosis

Table 4 Multivariable regression analysis showing adjusted odds of DVT in a critically ill patient

	Odds ratio (95% CI)	P value
Aspirin	0.39 (0.16–0.95)	0.039
Age (years)	1.00 (0.98–1.02)	0.731
Male gender	1.50 (0.74–3.04)	0.262
Pharmacologic thromboprophylaxis	0.74 (0.30–1.81)	0.592
Hospital LOS when tested for DVT	0.91 (0.80–1.04)	0.159
Sepsis	0.87 (0.50–1.86)	0.716
IV catheter		
CVC	3.89 (0.83–18.27)	0.085
PICC	2.35 (0.36–15.15)	0.368

CVC central venous catheter, *DVT* deep vein thrombosis, *IV* intravenous, *LOS* length of stay, *PICC* peripherally inserted central venous catheter

Discussion

Our study confirms that DVT is common in mechanically ventilated ICU patients despite the use of thromboprophylaxis, and suggests that ASA may prevent DVT in such patients. The 25% rate of DVT in our study is similar to the rate found in a study of mechanically ventilated medical ICU patients in whom pharmacologic thromboprophylaxis was universal [2]. Similarly, the majority of DVTs in that study was also found in the first 2 weeks of hospitalization. However, that study did not look into any possible association between use of ASA and DVT.

The use of ASA was associated with a significant reduction in the odds of DVT in mechanically ventilated ICU patients in our study. There is a possibility that this association may not be causal given the retrospective nature of our study. However, reduction in the rate of DVT with the use of ASA is supported by the medical literature. There is growing evidence of the role of platelets in venous thrombosis. The amount of platelets in venous thrombi is relatively low in comparison to that of red cells and leukocytes. However, it has been shown that in platelet-depleted mice venous thrombi are not formed [11]. Platelets play a role in the formation of venous thrombi by releasing polyphosphates and pro-inflammatory mediators, phosphatidylserine and/or tissue factor-exposing microparticles, as well as by stimulating the formation of the neutrophils extracellular traps [12]. The latter provide a scaffold and a stimulus for platelet adhesion and thrombus formation [13]. Increased spontaneous platelet aggregation and circulating platelets aggregates have been shown in patients with idiopathic recurrent DVT [14].

The PE prevention (PEP) trial [15], together with a previous meta-analysis by the Anti-platelet Trialists' Collaboration (ATC) showed that, in orthopedic, general surgical and high-risk medical patients, ASA reduced the risk of DVT and PE by at least a third, largely irrespective of the use of any other thromboprophylaxis (including subcutaneous heparins) [16]. The small number of high-risk medical patients consisted of those who suffered an acute myocardial infarction (MI) or stroke. Aspirin is recommended as an option for thromboprophylaxis after major orthopedic surgery [17, 18]. In another meta-analysis that included only recent studies, the ATC showed that, in high-risk medical patients, ASA reduced the risk of PE by 25%. High-risk medical patients consisted of those at increased risk of occlusive vascular events i.e., those with an acute MI or ischemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation [19]. More recently, a combined analysis of WARFASA and ASPIRE trials showed that ASA reduced the rate of recurrent VTE by one-third in patients with unprovoked VTE who had completed initial treatment with heparin followed by warfarin for a minimum of 6 weeks [20].

Nevertheless, only a placebo-controlled randomized clinical trial can definitively prove if ASA can reduce the risk of DVT and PE in critically ill patients. Such a trial should be feasible since ASA is widely available and inexpensive, and such a trial would be worthwhile for a number of reasons. Deep venous thrombosis in critically ill patients is often clinically silent [8] and may prove fatal. Pharmacologic thromboprophylaxis with subcutaneous heparin is not always effective in preventing VTE in critically ill patients [2, 3, 5]. The subcutaneous route may be unreliable in such patients [21] especially with the use of vasopressors [22]. The PROTECT clinical collaborators also reported that failure of pharmacologic thromboprophylaxis is more likely in obese ICU patients [5]. Critically ill patients who develop VTE have longer ICU and hospital LOS which contribute to hospital costs, morbidity and mortality [23].

Our study is not without limitations. It is retrospective and small. It does not exclude the possibility of prevalent DVTs at the time of admission to ICU since patients were not screened. However, it is unlikely this would have affected the results since only 3% of DVTs were prevalent DVTs in a prospective study of the prevalence, incidence, and risk factors for proximal lower extremity DVT among critically ill medical-surgical patients in whom pharmacologic thromboprophylaxis was universal [3]. Our study did not look into the rate of PE—an outcome that is more important than DVT. Since ICU patients who are found to have DVT may not be evaluated for PE even when suspected PE is the reason for performing venous ultrasonography, the rate of PE would have been low and our study sample would have been too small to find any association between use of ASA and PE. Moreover, a small proportion (17%) of patients in our study were not on any pharmacologic thromboprophylaxis. However, all patients received

mechanical prophylaxis with an intermittent pneumatic compression device. More importantly, our study did not evaluate the possibility of bleeding complications associated with use of ASA in critically ill patients. Anti-platelet agents were found to be a risk factor for major bleeding in critically ill patients receiving pharmacologic thromboprophylaxis in PROTECT [24]. However, the majority of patients in our study was on low dose ASA.

Conclusions

Our study suggests that ASA may potentially reduce the rate of VTE beyond what can be achieved with pharmacologic thromboprophylaxis in mechanically ventilated ICU patients. The use of this widely available and inexpensive drug in critically ill patients to prevent an easily overlooked and potentially fatal disease as VTE should be further evaluated with randomized clinical trials.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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