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Incidence and factors associated with bleeding in critically ill medical patients on pharmacological prophylaxis for deep vein thrombosis in intensive care unit - a single-center observational study from South India

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Abstract

***Objective*: This study was aimed to assess the incidence of bleeding and factors associated with bleeding among critically ill medical patients on anticoagulant prophylaxis in the intensive care unit (ICU).**

***Design*: Observational study conducted over a period of 18 months.**

***Setting*: Multi-disciplinary ICU of a tertiary care center in South India.**

***Patients and participants*: Patients aged >18 years admitted to the ICU satisfying the inclusion and exclusion criteria.**

***Methods*: All critically ill medical patients on pharmacological prophylaxis for deep vein thrombosis (unfractionated heparin [UFH] or low molecular weight heparin) were included in this study. Patients with proven thrombosis, active bleeding, surgical or trauma patients, pregnant, and lactating women were excluded from the study. The outcome was categorized as presence or absence of bleeding. Factors associated with bleeding, the pattern of bleeding among study participants were compared between bleeders and non-bleeders.**

***Results*: A total of 490 patients were studied and the incidence of bleeding observed was 5.9% (n=29). Among those who had bleeding (n=29), 8 patients had major bleeding and 21 patients had minor bleeding. Use of enoxaparin or UFH was not significantly associated with bleeding risk (p-value=0.692). The presence of coronary artery disease (CAD) and baseline prolongation in activated partial thromboplastin time (aPTT) were significantly associated with risk for bleeding among medically ill patients on pharmacological prophylaxis in ICU (p-value=0.023, p-value=0.002, respectively). The most common site of bleeding noted was from the urinary tract (n=11) followed by endotracheal tube bleed (n=4). Four patients died in the group who had major bleeding.**

***Conclusion*: The use of anticoagulants for thromboprophylaxis was associated with bleeding and bleeding rates were similar between UFH and low molecular weight heparin (enoxaparin). Underlying comorbid illnesses like CAD and baseline elevated aPTT were associated with a significant risk of bleeding in ICU patients on pharmacological prophylaxis for DVT.**

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Key words: Bleeding, heparin, enoxaparin, critically ill, medical.

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Introduction

Deep vein thrombosis (DVT) is a frequent cause of morbidity and mortality in hospitalized patients. About 25% of all cases of DVT are associated with hospitalization and 50% to 75% of cases of DVT occur in hospitalized medically ill patients. (1-3) Majority of patients have at least one risk factor for DVT, and this risk persists for several weeks after discharge. (4) Twenty-six percent of patients with undiagnosed and untreated DVT had a subsequent fatal embolic event, whereas another 26% had a non-fatal recurrent embolic event. (5) About two-thirds of venous thromboembolism (VTE) cases are associated with hospitalization in the prior 90 days, emphasizing the importance of medical illness, major surgery, or immobilization as risk factors for DVT and pulmonary embolism (PE). Intensive care unit (ICU) patients represent a heterogeneous population, and most information about the incidence of VTE is from studies in trauma or surgical patients. Studies in which patients were prospectively screened for deep vein thrombosis (DVT), and the diagnosis confirmed by objective testing, suggest that in the absence of thromboprophylaxis the incidence of DVT ranges from 7% to 33%, depending on the patient population and setting. (6,7) In trauma patients approximately 60% have DVT within the first two weeks after admission. In medical ICU patients, despite varying degrees of prophylaxis for DVT, the incidence of DVT remains high.

The decision to initiate DVT prophylaxis among medical patients should be based on an individualized assessment of the risk for DVT and bleeding, as well as potential harm against modest or even no benefit. Because no standard formula for risk assessment exists to identify which medical patients are likely to benefit from DVT prophylaxis, the decision is best left to the physician's judgment. Prophylaxis is generally considered reasonable for critically ill patients who are bedridden for >2 days and have at least one risk factor. Heparin and related drugs are associated with an increased risk for both major and minor bleeding. Risk factors for bleeding with anticoagulant therapy include older age, female sex, diabetes, hypertension, presence of cancer, acute or chronic alcoholism, liver disease, severe chronic kidney disease, peptic ulcer disease, anaemia, prior stroke or intracerebral haemorrhage, presence of aneurysms, bleeding disorder and concomitant use of drugs like aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and antiplatelet agents. (8)

American College of Physicians (ACP) recommends pharmacological prophylaxis with heparin or a related drug for DVT in medical patients including those who have stroke unless the assessed risk for bleeding outweighs the likely benefit. (8) Validated models for evaluating the risk of bleeding in hospitalized medical patients are lacking. Our study was done to assess the incidence and factors associated with bleeding in critically ill medical patients on pharmacological prophylaxis for DVT.

Objectives

1. To assess the incidence of bleeding in critically ill medical patients receiving pharmacological prophylaxis for DVT.
2. To study the factors associated with bleeding and the pattern of bleeding (major or minor) among study participants.

Materials and methods

This was an observational study done over a period of 18 months. The study was done in a multidisciplinary ICU of a tertiary care teaching hospital in South India. Study participants were patients aged >18 years admitted to the ICU who satisfied the inclusion and exclusion criteria. All critically ill medical patients on pharmacological prophylaxis for deep vein thrombosis (unfractionated heparin [UFH] or low molecular weight heparin [LMWH]) were included in this study. Exclusion criteria included:

1. All patients requiring a therapeutic dose of heparin for any cause like acute coronary syndrome and acute venous thrombosis (proven or suspected)
2. Patients already on UFH or oral anti-coagulant prior to hospitalisation
3. Patients having active bleeding on admission
4. Pregnant or lactating women
5. Patients with surgical and orthopaedic illness

All medical patients admitted to multi-disciplinary ICU, who were started on pharmacological prophylaxis for deep vein thrombosis were studied and evaluated as per the study inclusion and exclusion criteria. Informed consent from either the patient (alert participants) or closest family member (in less alert or confused participants) was obtained prior to inclusion in the study. Institutional Ethics Committee (IEC) approval was obtained (IEC: CSP-MED/15/JAN/21/08) and the study followed the ethical standards laid down in the 1964 Declaration of Helsinki. Totally 490 patients were included in the study. Details of presenting history, past and personal history followed by clinical examination and findings were recorded in a structured data collection sheet along with details of initial investigations and treatment. Patients were followed up through-

out the course of hospital stay and details of the investigation, treatment, and clinical course including complications were noted.

The outcome was categorized as presence or absence of bleeding. The incidence of bleeding among study patients receiving pharmacological prophylaxis for deep vein thrombosis was assessed and a pattern of bleeding among them (major bleeding or minor bleeding) was noted. Those with bleeding were further classified as patients with major bleeding and those with minor bleeding.

Bleeding was defined as major if the patient had any one or more of the following:

1. Decrease in haemoglobin level of 2 g/dl or greater
2. Transfusion of two or more units of packed red blood cells
3. Life-threatening bleeding at a critical site (intracranial, intra-abdominal) (8)

Minor bleeding was defined as any bleeding that occurred in these patients that did not satisfy the definition of major bleeding. Between them (bleeders and non-bleeders), factors such as age, gender, comorbidities, substance abuse, platelet count, anti-platelet agent use, baseline coagulation profile before the onset of bleeding, the severity of bleeding, need for blood product administration or intervention, and duration of anti-coagulant received were compared and analyzed.

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) and categorical variables were expressed as numbers (%). Descriptive variables included age, gender, prior medical comorbidities, admission laboratory parameters, anti-platelet agent use, anti-coagulant received, duration of anti-coagulant received, and outcome which was categorized as patients who had bleeding and patients who had no bleeding. The collected data were analyzed with IBM SPSS statistics software version 23.0. To analyze the descriptive data, frequency analysis and percentage analysis were used for categorical variables and mean±SD was used for continuous variables. To find the significant difference between the bivariate samples in paired groups, the paired sample t-test was used and for independent groups, the unpaired sample t-test was used. The chi-square test and Fisher's exact test were used to find the significance in categorical data. A p-value <0.05 was considered statistically significant.

Results

Totally 490 patients were included in the final analysis in this study, males were predominant (n=282, 57.6%). The study patients comprised of all age groups, ranging from 19 years to 93 years, with the mean age being 61.15 years. The most observed underlying medical comorbid illnesses were diabetes (n=255, 52%) followed by hypertension (n=232, 47%). Baseline characteristics of study participants are shown in **Table 1**. Anticoagulant drugs used for thromboprophylaxis were enoxaparin (LMWH) 1 mg/kg/day subcutaneous (SC) once daily in 91.6% patients (n=449) and UFH 5000 units SC twice daily in 8.36% patients (n=41). The LMWH, enoxaparin, dose was adjusted for estimated creatinine clearance in patients who had kidney injuries. Bleeding (including major and minor) occurred in 29 patients which accounted for 6% incidence of bleeding among critically ill medical patients receiving thromboprophylaxis in our study. Non-bleeders were 94% (n=461). Among those who had bleeding, eight had major bleeding (1.6%) and 21 had minor bleeding (4.3%). On comparison between bleeders and non-bleeders, the presence of coronary artery disease (CAD) was associated with bleeding which was statistically significant (p-value 0.023) whereas factors such as age, gender, presence of underlying comorbidities except CAD did not have any significant association with outcome. **Table 2** shows the variables compared between those who had bleeding and those who had no bleeding.

Though we observed bleeding to be more commonly associated with enoxaparin use rather than UFH, it was not statistically significant (p-value 0.692). Among bleeders (n=29), majority were on enoxaparin (n=26, 89.6%) and UFH use was observed in 10.3% (n=3). All eight patients who had major bleeding were on enoxaparin. The three patients who had bleeding with UFH use were minor type. **Table 3** shows the coagulation profile, duration of anticoagulant used, and choice of anticoagulant among bleeders and non-bleeders. Baseline prolongation in prothrombin time (PT) of more than 20 seconds was noted in only 10% (n=3) of those who had bleeding. Elevated international normalized ratio (INR) in the range of 1.30 to 1.99 was observed in 81 patients (16.5%) among whom bleeding was present in six patients (1.2%). Prolongation of baseline activated partial thromboplastin time (aPTT) was significantly associated with bleeding (p-value 0.002). Among those who had bleeding (n=29), six patients (20.6%) had prolonged aPTT in the range of 40-60 seconds. Baseline platelet count and duration of anticoagulant use did not have a significant association with bleeding (p-value 0.73 and 0.389, respectively).

Among the bleeders, the most frequent site of bleeding was the urinary tract (n=11) followed by endotracheal (ET) bleed in four patients. The other sites of bleeding included oral mucosa (n=4), gastrointestinal (n=3), psoas muscle (n=1), abdominal wall (n=1), nasal cavity (n=1), intrarenal (n=1), uterine (n=1), hemorrhagic transformation of cerebral infarct (n=1), and dialysis catheter insertion site bleed (n=1). Anticoagulation was stopped in all patients who had bleeding and four patients were transfused with two units of packed red cells each. In this study, among those who had bleeding, mortality occurred in four patients. All four deaths were among those who had major bleeding. It can be stated that bleeding along with other significant causes which included sepsis, shock, and multi-organ dysfunction syndrome (MODS) were major contributors to death in these patients.

Discussion

In our study, the incidence of bleeding was found to be 5.9%. This translates to a bleeding incidence of 59 per thousand persons exposed to heparin for DVT prophylaxis among hospitalized critically ill medical patients in ICU. In the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) trial, reported bleeding incidence was 3.2%, of which 1.2% had major bleeding and 2.1% had non-major but clinically relevant bleeding. (9) The incidence of major bleeding reported in IMPROVE trial correlated with our study, though the minor bleeding in our study was found to be higher in comparison. In the Diabetes Remission Clinical Trial (DIRECT), the incidence of major bleeding was found to be 7.2%. (10) F. Lauzier et al observed major bleeding of 5.6% and minor bleeding of 7.6%. (11) In our study, major bleeding was not observed with the use of UFH. Contrastingly, Arnold D. et al in his single-center observational study reported major bleeding of 5.2% among those who received prophylactic UFH in ICU, and in the PROphylaxis for ThromboEmbolism in Critical Care Trial (PROTECT), major bleeding occurred in 5.6% of patients who received UFH. (12,13) These observations were in contrast to our findings, possibly due to the low event rate and relatively lesser sample size in our study. Major bleeding rates were similar between UFH and LMWH in a meta-analysis by Alhazzani et al. (14) A study done by Fraisse et al showed the frequency of bleeding in patients receiving LMWH ranged from 7.2% to 23.1% compared to 15.9% in patients receiving placebo. (6)

UFH for thromboprophylaxis is usually given in a dosing frequency of twice daily or thrice daily. A meta-analysis by Phung OJ on comparison between twice-daily UFH and thrice-daily UFH showed both regimens of UFH had similar effects on the rates of DVT, PE, major bleeding, and death. (15) We did not observe age and gender as risk factors for bleeding in our study. Though concurrent use of antiplatelets was not associated with bleeding, the presence of underlying CAD was a significant risk factor for bleeding in our study. Retrospective analysis of data from the IMPROVE identified 11 factors at admission to be independently associated with in-hospital bleeding which included active gastroduodenal ulcer, bleeding during the 3 months prior to admission, low platelet count at admission, advanced age, hepatic failure, renal failure, ICU/coronary care unit (CCU) stay, central venous catheter, rheumatic disease, current cancer, and male sex. (9) F. Lauzier et al noted treatment with antiplatelet agents as an independent predictor of bleeding. (11) PT, INR, and aPTT are the commonly tested coagulation tests in the event of bleeding. We observed a significant correlation with an increase in aPTT (in seconds) with bleeding risk. Anand SS et al reported a relationship between aPTT and bleeding risk in his study among patients with acute coronary syndrome and he observed that every 10 seconds increase in aPTT was associated with a 7% increase in major bleeding among patients receiving heparin. (16) Patients with platelet count less than 100,000/mm^3 were not started on pharmacological prophylaxis for DVT in our study as per the hospital norms, hence observed baseline mean platelet count among patients who had bleeding while on thromboprophylaxis was 260,000/mm^3. Data from previous studies shows platelet count <50,000/mm^3 was significantly associated with bleeding risk for patients on anticoagulants for thromboprophylaxis. (9,11) The most common bleeding site reported in IMPROVE trial was gastrointestinal whereas we observed hematuria from the urinary tract as a common source of bleeding.

Conclusion

We observed an incidence of 5.9% bleeding in critically ill medical patients on pharmacological prophylaxis for DVT, the incidence of major bleeding being 1.6% and that of minor bleeding was found to be 4.3%. Comparison of bleeding rates between UFH and LMWH was not significant in our study. The presence of CAD and baseline prolongation in aPTT value were found to be significant risk factors for bleeding among patients receiving thromboprophylaxis.

Limitations of our study

The sample size in our study might be small to assess accurately the risk factors associated with bleeding in patients receiving pharmacological prophylaxis for DVT. This was due to the low bleeding event rate. Our study did not assess the incidence of DVT in the study population on pharmacological prophylaxis as an outcome.

Table 1. Baseline characteristics of the study participants

Variable	Number	Percentage
Age (years), mean±SD	61.15±15.65	-
Male	282	57.6%
Female	208	42.4%
Presence of type II diabetes mellitus	255	52%
Presence of systemic hypertension	232	47.3%
Presence of coronary artery disease	91	18.6%
Presence of chronic kidney disease	56	11.4%
Presence of stroke in past	45	9.2%
Dyslipidemia	13	2.7%
Others*	156	31.8%

Legend: SD=standard deviation.
*Include presence of hypothyroidism, seizure disorder, chronic obstructive pulmonary disease, tuberculosis in past.

Table 2. Comparison of factors between bleeders and non-bleeders

Variable	Non-bleeders (n)	Presence of bleeding (n)	p-value
Age (years), mean±SD	61±15.56	60±17.21	0.63
Gender - Male (n=282) - Female (n=208)	 267 194	 15 14	0.513
Diabetes mellitus (n=255)	235	20	0.06
Systemic hypertension (n=232)	218	14	0.918
Coronary artery disease (n=91)	81	10	0.023
Chronic kidney disease (n=56)	51	5	0.31
Cerebrovascular accident (n=45)	42	3	0.823
Dyslipidemia (n=13)	13	0	-
Concurrent anti-platelet use (n=236)	222	14	0.99
Alcoholism (n=44)	41	3	0.791
Smoking history (n=37)	36	1	0.389

Legend: SD=standard deviation.

Table 3. Comparison of coagulation profile, duration, and use of anticoagulant between bleeders and non-bleeders

Parameter	Non-bleeders (n)	Presence of bleeding (n)	p-value
Baseline platelet count (x100,000/mm^3), mean±SD	2.71±1.17	2.63±0.93	0.738
Prothrombin time - <20 seconds - 20-40 seconds	 337 30	 26 3	0.684
International normalised ratio - <1.30 - 1.30-1.99	 291 30	 23 6	0.98
Activated partial thromboplastin time (aPTT) - <40 seconds - 40-60 seconds	 337 20	 23 6	0.002
Anticoagulant used - Enoxaparin - Unfractionated heparin	 423 38	 26 3	0.692
Duration of anticoagulant used (days), mean±SD	5.37±5.16	6.21±3.82	0.389

Legend: SD=standard deviation.

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