Original Article

Prevalence of Deep Vein Thrombosis and Associated Factors in Adult Medical Patients Admitted to the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Background: Deep vein thrombosis (DVT) and pulmonary embolism (PE) collectively referred to as venous thromboembolism (VTE) are associated with significant morbidity and mortality worldwide.

DVT is common in hospitalized patients with acute medical illness. Routine use of thromboprophylaxis has been shown to reduce prevalence of DVT in hospitalized patients with acute medical illness. Thromboprophylaxis is not routinely given to hospitalized medical patients in most hospitals in Zambia.

Objectives: The objectives of this study were: to determine the prevalence and anatomical distribution of DVT in medical patients admitted to the UTH for at least 7 days; establish demographic and clinical characteristics of medical patients with DVT and finally determine the accuracy of the Well's score for DVT.

Methods: This was a descriptive, cross sectional analytical study. The sample size comprised 296 medical patients admitted for at least 7 days. A questionnaire was used to obtain demographic characteristics and relevant clinical history. A focused detailed physical examination was conducted to screen for DVT of the lower limbs and Well's score for DVT computed. Laboratory tests including HIV test and full blood count were done. Biochemical and genetic studies to evaluate for inherited and acquired thrombophilias could not be done due limited financial resources. Compression ultrasound scans (USS) were done on lower limbs of recruited patients to determine the presence of DVT. Variables of interest were compared by chi-square, Kruskal-wallis and t-tests. Multivariate and univariate logistic regression analysis were used to assess for associations between DVT and independent variables of interest.

Results: The Prevalence of DVT of the lower limbs was 11.1 % (33/296). Prevalence of proximal lower limb DVT was 9.1%. Eighty two percent (27/33) of all patients with DVT had proximal lower limb DVT. Asymptomatic lower limb DVT was noted in 85 % (28/33) of all patients with DVT.

The Mean age of patients with DVT was 42.12 years (SD 12.71).The mean duration of hospital admission was 11.91 (SD 7.77) days. Seventy six percent (25/33) of all patients with DVT had an infectious disease as a primary diagnosis. Tuberculosis was the most common infectious disease among patients with DVT accounting for 60.6 % (20/33) of all infections. Up to 70 % (23/33) of all patients with DVT were HIV positive.

The specificity for the Wells score specificity for DVT was 73.4% while the sensitivity was 100%. The accuracy was 76.3%.The positive and negative predictive values were 32% and 100% respectively.

Conclusion: Proximal Lower limb DVT is common among HIV positive medical patients admitted for at least 7 days at the UTH. In our study, lower extremity proximal DVT was more common in patients with *Tuberculosis* and a low BMI. Up to 85% of lower limb DVT was asymptomatic. Without a high index of suspicion, lower limb DVT is likely to be missed. The pretest Wells score correlated well with the USS findings and could be used as a rule out test for those with

suspected DVT.A follow up study to evaluate for genetic and biochemical factors that predispose to DVT need to be undertaken in the near future. There is need to advocate for thromboprophylaxis in medical patients with acute illness and prolonged hospital stay.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) collectively referred to as venous thromboembolism (VTE) are a global concern with significant morbidity and mortality.[1,2,3,4] Fortunately both DVT and PE are preventable in hospitalized medical patients with acute illness by routine thromboprophylaxis.[5]

Approximately 10 million cases of VTE occur every year across low, middle and high income countries worldwide.[29] Global and regional statistics on VTE related deaths and disabilities are not readily available but predominantly confined to the United States of America (USA) and Europe.[29] Over 2 million people develop DVT in the USA alone every year.[6] Furthermore, over 300 000 patients die from complications of VTE in the USA annually.[1] In Europe, more than 500 000 deaths occur annually as a complication of VTE.7

Three major multi-centre double blind randomized controlled studies have given an insight to the global prevalence of VTE.[2,3,4] The Medical patients on Enoxaparin (MEDENOX) study found prevalence of VTE in the placebo group of 14.9%.[2] The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized patients Trial (PREVENT) found prevalence of VTE in placebo group of 4.96 % compared to 2.77% in the Dalteparin arm.[4] The ARTEMIS (Arixtra for ThromboEmbolism Prevention in a Medical Indication) study found prevalence of VTE in placebo group of 10.5% compared to 4.96 % in the fondaparinux arm.[3]

A retrospective autopsy study conducted in Nigeria by Sotunmbi *et al* found prevalence of VTE of 2.9%, with increased risk in male patients older than 40 and in those with cancer.[8]

Risk factors for DVT are multifactorial and can be classified as modifiable or non-modifiable.[9] Modifiable risk factors include immobility, HIV infection, sepsis, malignancy, heart failure, renal failure, diabetes mellitus, obesity, long travel, trauma and surgery.[9] Non modifiable risks include gender, age, race and hereditary risk factors such as factor V Leiden, antithrombin, Prothrombin gene mutation G20210A, protein S and protein C deficiency.[9]

The associations between a number of medical conditions and VTE are well documented. These associations are now outlined below.

Sepsis is characterized by an overall shift in the balance between procoagulant and anticoagulant factors towards a prothrombotic state.[1°] Epidemiological studies have revealed that HIV infected patients have a 2-10 fold risk of developing VTE compared to the general population.[11]

Heart failure (HF) is associated with a 2-3-fold risk of DVT and PE.[15] This increases further by 38.3 fold in patients with Ejection Fractions [EF] of less than 20%.[16] Patients with nephrotic syndrome have a 39% estimated risk of developing DVT and a 72% risk of having pulmonary embolism compared to those without nephrotic syndrome.[17]

Obesity is a recognized proinflammatory and hypercoagulable state with haemostatic alterations that predispose to venous thromboembolism.[18] DVT of the lower limbs is the most common manifestation of the antiphospholipid syndrome occurring in 29% to 55% of patients.[12] Thromboembolic events are a major cause of morbidity and mortality in cancer patients.[13] It is estimated that approximately one third of individuals with VTE have an identifiable inherited thrombophilia.[14]

Thromboembolism has been noted to be common among individuals taking the combined oral contraceptives (OCs).[19] Pregnancy is associated with up to a 5 fold risk of VTE and 60-84 fold risk three months after delivery.[20]

The MEDENOX study revealed a 20.3% incidence of VTE among patients with restricted mobility.[2] A study conducted by Warlow *et a*l involving stroke patients with paralyzed limbs, found the prevalence of asymptomatic DVT of 60% in paralyzed limbs compared with 7% in the non-paralyzed limbs.[21] Up to 75% of air travel related VTE has been linked to immobility during long-distance flights.[22]

Pulmonary embolism is the most serious potentially life threatening complication of DVT.[23] In addition, PE associated with DVT is the leading cause of hospital

related preventable death.[23] A study by Kakkar *et al*, revealed that 4 out of 9 patients who had proximal DVT detected by ultrasound scan subsequently developed PE diagnosed clinically.[24] Another study by Cogo *et a*l revealed that up to 99% of patients with proximal DVT also had calf vein thrombosis suggesting that most thrombi originated in the calf.[25]

Compression B mode ultrasound scan is now the preferred choice of diagnosing lower limb proximal DVT with a sensitivity of 95% and a specificity of 96%.[26] The major diagnostic criterion for venous thrombosis by compression ultrasound scan is demonstration of venous non compressibility.[27]

The Well's score for DVT, based on clinical signs and symptoms can be used to screen for DVT in patients with prolonged hospital admission.[28] Patients with a score of ≥ 3 are classified as high risk, those with a score of 1 or 2 as moderate risk and those with a score of ≤ 0 as low risk. Well's score is further used to stratified patients into categories of DVT likely if the clinical score is more than 1 and DVT unlikely if the score is 1 or less.[28] Table 1 below shows the components of the Wells score for DVT.

Table 1. Wells Score for DVT[28]

Clinical Findings	Points
Paralysis, paresis or recent orthopedic casting of lower extremity	1
Recently bedridden (> 3 days) or major surgery within past 4 weeks	1
Localized tenderness in the deep veins	1
Swelling of entire leg	1
Calf swelling 3 cm greater than other leg (measured 10 cm below the Tibial tuberosity	1
Pitting edema greater in the symptomatic leg	1
Collateral non-varicose superficial veins	1
Active cancer or cancer treated within 6 months	1
Alternative diagnosis more likely than DVT (Inguinal lymphadenopathy, Cellulitis, external venous compression, muscle damage, post-phlebitic Syndrome, superficial venous thrombosis, Baker's cyst)	-2

The prevalence of DVT and associated risk factors in medical patients in Zambia are not well documented. Additionally, thromboprophylaxis for DVT is not routinely given to hospitalized medical patients despite the documented morbidity and mortality.

Anecdotally, sudden deaths of stable acutely ill medical patients from suspected PE have been reported for some time but only occasionally confirmed by postmortems. The purpose of this study was to determine the prevalence of DVT and associated risk factors in medical patients admitted to the UTH with aim of advocating and instituting appropriate interventions.

MATERIALS AND METHODS

We carried out a descriptive, cross sectional analytical study. The study was conducted in all medical wards at the UTH from 1st July to 30th November 2015. A total of 296 patients admitted for at least 7 days were consented and recruited to the study. Demographic characteristics and relevant clinical history were obtained using a questionnaire.

A focused physical examination was conducted to screen for DVT of the lower limbs and elicit associated clinical signs. The Well's score for DVT was computed using relevant information obtained from medical history and physical examination.

Baseline investigations including full blood count, HIV test, CD4 count, renal function and liver function tests were done. Serum levels of protein C, protein S, homocysteine, antithrombin, anticardiolipin, anti-â2 glycoprotein I, lupus anticoagulant antibodies, specific mutations for factor V Leiden (Arg506Gln) and prothrombin gene (G20210A) associated with inherited thrombophilias could not be done due to financial constraints.

Compression ultrasound scans (USS) of the lower limbs were done to screen for DVT of the lower limbs. All variables collected were entered in Microsoft excel spread sheets 2013 version. Data analysis was done using SSPS version 16.0. Categorical and continuous variables were compared by chi-square, Kruskal-wallis and t-tests. Multivariate and univariate logistic regression was used to assess for associations between DVT and independent variables of interest.

RESULTS

Table 2. Baseline clinical characteristics of recruited patients

Variable	Total recruited patients (n=296)	Patients with DVT (n=33)
Male	140	15
HIV Positive	173	23
Patients on ART	128	19

A total number of 332 patients were screened and identified for possible recruitment to the study. Thirty six (11%) declined to give consent for provider initiated counselling and testing (PICT) for HIV. Female patients made up 52.7 % (156/296) of all subjects recruited to the study. Fifty two percent (154/296) of all recruited patients were aged 40 years or more. Only 3.7 % (11/296) of all recruited patients were obese.

Infectious diseases were the most common primary diagnosis in patients recruited making 53% (156/296) of all diagnoses. Tuberculosis accounted for 66 % (103/156) of all infectious diseases. Other common primary diagnoses included, heart failure accounting for 17.2 % (51/296), renal failure 7.8 % (23/296) and active malignancy 6.8 % (20/296).

Anaemia was present in 210 (70.9%) of all the patients in the study. Of all male patients, 110 (79.7%) had a haemoglobin below 15g/ml. A total of 100 (64.5%) of all female patients had a haemoglobin of less than 13g/ml. Thrombocytosis was noted in 11.8 % (35/296) of all patients in this study. Leukocytosis was present in 23.6 % (70/296) of all patients recruited to this study.

The prevalence of lower limb DVT in our study population was 11.1% (33/296). Compressible, hyperechoic, very sluggish venous blood flow was noted in 25 (9%) patients recruited to our study. The prevalence of proximal lower limb DVT was 9 % (27/296).Symptomatic lower DVT was noted in only 5 (16%) of all patients with DVT. Bilateral lower limb DVT was observed in 9 (27%) of all patients with DVT

Table 3.Comparison of clinical characteristics of hospitalized patients with and without DVT

Variable	DVT (n = 33)	No DVT (n=263)	P
Age, years, mean (SD)	42.1 (12.7)	42.0 (16.8)	0.98
Male, n (%)	15 (45.5)	125 (47.5)	0.82
BMI, mean (SD)	18.73 (4.0)	20.6 (4.7)	0.03
Total days of immobility, mean (SD)	24.0 (12.8)	21.8 (11.9)	0.33
HIV+, n (%)	23 (69.7)	150 (57.0)	0.16
Haemoglobin, g/dL, mean (SD)	8.6 (8.1)	9.4 (3.5)	0.44
Platelet count, mean (SD)	197 (17)	231 (137)	0.17
Primary Diagnosis	20 (60.6)	83 (31.6)	0.002
Tuberculosis	6 (18.1)	45 (17.1)	0.88
Heart failure	2 (6.0)	21 (8.0)	0.70
Renal failure			

The mean period of hospital admission was 11.91 (SD 7.77) days. The Mean age of patients with DVT was 42.12 years (SD 12.71) while mean BMI was 18.73(SD 3.98).Tuberculosis was the most common primary diagnosis among patients with DVT accounting for 60.6 % (20/33) of all diagnoses. The means for BMI between patients with and without DVT differed significantly (p = 0.03). Patients with DVT had a lower BMI compared to those without DVT. The means of the rest of the variables representing demographic and clinical characteristics of patients with and without DVT did not differ significantly.

The multivariate and univariate logistic regression for independent variables of interest namely, age, sex, HIV status, CD4 count, duration of hospital admission, haemoglobin, white cell and platelet count did not show association with DVT.

The specificity of the Wells score for DVT was 73.4% while the sensitivity was 100%. Accuracy was 76.3%. The positive and negative predictive values were 32% and 100% respectively.

DISCUSSION

The prevalence of lower limb DVT among medical patients admitted for at least 7 days was 11.1%.Patients with DVT had a lower mean BMI and were more likely to be admitted with a diagnosis of Tuberculosis. A low likelihood Wells score (0 or 1) had 100% negative predictive value for excluding DVT.

The prevalence of DVT falls within the range of 4.96 to 14.9% found in the MEDENOX, PREVENT and ARTEMIS trials conducted in high income countries in Europe and North America.

The definition of VTE in our study differed from that in the three studies. In the three studies, VTE was defined as asymptomatic DVT, symptomatic DVT, symptomatic PE, and fatal PE. In our study VTE referred to asymptomatic or symptomatic proximal and distal lower limb DVT diagnosed by compression USS.

Diagnostic techniques employed in the diagnosis of VTE in the three studies differed from that used in our study. Venography was used to diagnose VTE in the ARTEMIS and MEDENOX studies .The PREVENT study employed compression USS as in our study.[2,3,4]

The prevalence of proximal lower limb DVT of 9.1% in our study was higher than that found in the ARTEMIS, MEDENOX and PREVENT studies. In the ARTEMIS study prevalence of proximal lower DVT was 3.4%.In the MEDENOX and PREVENT studies it was 6.6% and 5.0% respectively.[2,3,4]

The compressible, hyperechoic, very sluggish venous blood flow that was observed in 25(9%) patients could indicate developing or resolving DVT. The follow up of the patients with this finding was beyond the scope of this study.

The clinical and demographic characteristics of patients in our study differed in a number of aspects from those recruited in the ARTEMIS, MEDENOX and ARTEMIS studies. Patients with DVT in our study were relatively younger.

The patients recruited to our study had lower Body Mass Indices (BMI) compared to those recruited in the 3 major VTE studies. The mean BMI in our study was 20.4.The mean BMIs in the ARTEMIS, MEDENOX and PREVENT studies were all between 25 and 27.4.In our study mean BMI was lower among the patients with DVT .It is possible that low BMI was a marker of chronic debilitating illness that predisposed to DVT formation.

The major primary diagnoses in our study differed compared to in the ARTEMIS, MEDENOX and PREVENT studies in terms of hierarchy and proportion. Acute infectious disease was the most reason for hospital admission in patients recruited to our study followed by heart failure and renal failure.

Acute congestive heart failure made up 51.4% (1905/3706) of the primary diagnoses in the PREVENT study. [4] Infectious disease and respiratory failure accounted for 36.7% (1360/3706) and 30.2 % (1121/3706) respectively. [4]

In the ARTEMIS study, the most common primary diagnosis was acute infectious or inflammatory disease making up 25.2 % (214/849).Congestive heart failure and acute respiratory disease accounted for 24.9 % (212/849) and 19.7 % (167/849) respectively.[3]

Acute respiratory failure was the most common primary diagnosis making up 53.4 % (589/1102) of all primary diagnoses in the MEDENOX study.[2] Acute infectious disease and congestive heart failure made up 53 % (584/1102) and 34.1% (376/1102) of primary diagnoses respectively.[2]

In our study, 66.7 % of all patients with DVT had acute infectious disease as the primary diagnosis. This was followed by heart failure accounting for 18.2 % and renal failure 6 %.Tuberculosis was the most common infectious disease among patients with DVT accounting for 80 % of all infections.

Over half of the patients in our study were HIV infected, but HIV was not significantly associated with DVT. In contrast, the MEDENOX study excluded patients who were HIV infected. HIV status was not described in the ARTEMIS and PREVENT studies.

Proximal lower limb DVT was present in 82 %(27/33) of all patients with DVT. This finding implies that without thromboprophylaxis for DVT, majority of our patients are prone to pulmonary embolism. Unlike the above-referenced clinical trials, we did not routinely perform

any imaging tests to rule out pulmonary embolism. Thus, the real prevalence of combined lower extremity DVT plus pulmonary embolism may have been much higher.

The ARTEMIS, MEDENOX and PREVENT studies have provided overwhelming evidence that thromboprophylaxis can reduce prevalence of VTE in medical patients with acute illness by between 45% to 63%.[2,3,4]

A once daily dose of 2.5mg of Fondaparinux for 14days reduced risk of VTE by 47% in the ARTEMIS study.[3] A 63% reduction in the risk for VTE was observed in the group that took enoxaparin at a dose 40mg once daily for 14days in the MEDENOX study.[2] In the PREVENT study, VTE and sudden death were reduced by 45% in the group taking a once daily dose of 5000 IU of Dalteparin for 14 days.[4]

Our data provides valuable information in the Zambian setting regarding risk stratification for thromboprophylaxis decision making at the start of hospital admission. Among patients with expected duration of stay greater that 7 days, those with low BMI and primary diagnosis of tuberculosis appear to be at the highest risk of DVT. We do note, however that it is not always easy to predict hospital length of stay.

For patients admitted for over 7 days and in whom the diagnosis of DVT is being considered, negative Wells score appears to perform very well for ruling out DVT, with 100% negative predictive value. However, a positive Wells score of 2 or more points does not perform as well as a rule-in test and would need to be followed up with an ultrasound. The Wells pretest score for DVT does not require sophisticated equipment and can be done in any setting

CONCLUSION

Proximal lower limb DVT is common among HIV positive medical patients admitted for at least 7 days at UTH. Tuberculosis and a low BMI were statistically associated with a high likelihood of developing DVT in our patients. In our study up to 85% of lower limb DVT was asymptomatic. Without a high index of suspicion, lower limb DVT is likely to be missed. The pretest Wells score correlated well with the USS findings and could be used as a rule out test for those with suspected DVT.There is need to advocate for thromboprophylaxis in medical patients with acute illness and expected prolonged hospital stay. Low BMI and diagnosis of tuberculosis could be used to identify patients at higher risk of DVT.

ACKNOWLEDGEMENTS

I pay special gratitude to the following individuals for their immense support and valuable advice: Dr Victoria Sunkutu-Sichizya, Dr Mushota Kabaso and Mrs. Janet Tembo.

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