DEEP VEIN THROMBOSIS IN THE ERA OF HIGH HIV AND TB PREVALENCE: A PROSPECTIVE REVIEW OF ITS DIAGNOSIS AND TREATMENT IN A QUATERNARY CARE CENTRE

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I, Katherine Elizabeth Hodkinson declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine (Haematology) at the University of the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature of the Student: 

06th day of November 2017 in Johannesburg

Declaration: Students contribution the article and agreement of the co-author

I, Katherine Elizabeth Hodkinson, 0202211F (student number), declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my Research Report.

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Agreement by the co-author:
By signing this declaration, the co-author listed below agrees to the use of the article by the student and part of her Research Report.
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Abstract

Background

Venous thromboembolic disease (VTE) is a leading cause of morbidity and mortality worldwide. Human immunodeficiency virus (HIV) and tuberculosis (TB) infections have an aetiological association with VTE. Implementation of national HIV and TB programs in South Africa have changed the burden of these two conditions with resultant effects on VTE prevalence. Furthermore, with the increased use of direct oral anticoagulants (DOACs), baseline thrombosis data is needed in order to evaluate the impact of these new agents.

Objectives

To determine the real-life baseline VTE characteristics in a pre-DOAC era and to document the association of HIV and TB infections with VTE.

Methods

This is a single centre prospective cohort study performed in a quaternary care centre at the Charlotte Maxeke Johannesburg Academic Hospital (CMAJH), Gauteng, South Africa. Key inclusion criteria included a signed informed consent by adults (≥ 18 years) with a new episode of thrombosis. Procedures included physical examination, thrombosis risk factor assessment, duplex doppler examination, thrombotic screen tests, inpatient treatment and outpatient follow-up.

Results

Ninety-nine participants with confirmed thrombosis met the inclusion criteria. Participants were predominantly black (80%) and female (65%) with a median age of 46 (38-57) years. The HIV and TB prevalence were 53% and 21% respectively. The most common thrombosis risk factors were TB infection (17%) and malignancies (14%). The thrombotic screen assays had a low diagnostic yield. The median time to target international normalized ratio (INR) during hospitalization was 5.5 (4.0-7.0) days and the median duration of hospitalization was 9 (7-11) days. The overall mortality in the cohort at three months post hospitalization was 12%.

Conclusion

This prospective study provides real-life data of thrombosis diagnosis and management at a quaternary public healthcare facility. This data provides a valuable baseline against which the impact of new DOAC anticoagulants can be assessed.

Introduction

Venous thromboembolic disease (VTE), comprising of deep vein thrombosis (DVT) and pulmonary embolism, is a worldwide leading cause of morbidity and mortality.[1-2] The prevalence of VTE within the South African population is currently poorly characterized and largely unknown.

In South Africa, there is a high dual burden of human immunodeficiency virus (HIV) and tuberculosis (TB), both of which have well established associations with the development of VTE. There are several plausible explanations for the pro-thrombotic effect of these infections. These include induction of TNF-alpha and IL-6 production by chronic infections, which renders the vascular endothelium thrombogenic, interference with the normal production of coagulation factors within the liver, increase in the level of factor VIII, fibrinogen, and PAI-1, and a reduction in anti-thrombin and protein C.[3-5] The causal relationship between TB and VTE is demonstrated in part by an improvement in the hypercoagulable state within one month of initiating anti-tuberculosis therapy.[4]

Recently implemented national diagnostic and treatment programs in South Africa are rapidly changing the landscape of both HIV and TB.[6-7] Examples of which include an improvement in TB cure rates to around 80%, a ~20% reduction in the number of new HIV cases and an increase in antiretroviral (ARV) therapy coverage.[6]

Direct oral anticoagulants (DOACs) are intended to be introduced into quaternary care institutions for the treatment of DVT. This is due to the more predictable pharmacokinetics which allows for standardized dosing and less frequent follow-up, all of which may improve long-term anticoagulation and compliance rates.[8] The current treatment of VTE with warfarin anticoagulation is challenging in the setting of comorbid HIV and/ or TB. This is due to the many drug interactions, particularly in patients on TB treatment, where therapeutic international normalized ratio (INR) values can be difficult to achieve.[9] With the introduction of new DOACs, it will be important to obtain baseline data on the VTE prevalence, diagnosis, and treatment in order to evaluate the benefit of these anticoagulants in an era of high HIV and TB prevalence and incidence.

On this premise, the study aims to characterize thrombosis with regard to its clinical presentation, diagnosis, treatment and follow-up with specific consideration of HIV and TB in a quaternary public sector healthcare setting in South Africa.

Methods

Study design and study population

This was a single centre, prospective, cohort study performed at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a quaternary healthcare facility. This study, conducted from November 2015 to January 2017, was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (HREC Clearance certificate number: M150938) as well as the CMJAH management.

Study participants were unselected patients presenting at the Haematology Unit of the CMJAH. Key inclusion criteria included a signed informed consent by adults (≥ 18 years) with a new episode of DVT. These patients were consecutively sourced from the CMJAH emergency unit, through referrals from other centres, or were inpatients where the Haematology Unit was consulted to manage the DVT.

Physical examination and thrombosis pretest probability assessments (Wells' score) were performed and thrombosis was confirmed using a duplex doppler examination (DDE). HIV status was established as per institutional procedure. Where indicated, a thrombotic screen was performed as part of the routine diagnostic workup. Data collected included a past medical history, concurrent diseases and treatment history, and routine bloods for haematology, coagulation and chemistry testing as per standard of care. This data was captured together with the results of routine testing on a data collection sheet and anonymised prior to analysis.

Statistical analysis

Data analysis was performed using STATA (Stata Corp 2015. Release 14. College Station, TX: USA) with the help of a statistician. Quantitative data was summarized in tables and figures and described using medians with interquartile ranges, counts with percentages (%), the Fischer's exact test and the Mann-Whitney U test. A p-value of <0.05 was considered statistically significant.

Results

Demographics and clinical presentation

During the 15-month study period, 126 individuals were referred to the CMJAH with clinical symptoms of DVT. Thrombosis was confirmed in 99 of these and their pertinent demographic data is summarized in Table 1.

Table 1: Demographic data and baseline characteristics of participants (N=99)

Demographic parameter	Result
Median age, years (range)	46 (38-57)
Sex	
Male, n (%)	35 (35)
Female, n (%)	64 (65)
Race*	
Black, n (%)	79 (80)
White, n (%)	13 (13)
Coloured, n (%)	4 (4)
Indian, n (%)	3 (3)
Thrombosis investigation	
Duplex doppler confirmation, n (%)	99 (100)
CTPA, n (%)	5 (5)
Ventilation perfusion scan, n (%)	1 (1)
HIV† diagnosis and treatment	
Positive, n (%)	44 (53)
Negative, n (%)	39 (47)
On treatment, n (%)	34 (77)
Not on treatment, n (%)	10 (23)
Tuberculosis‡ diagnosis and treatment	21 (21)
On active treatment, n (%)	17 (81)
Not on treatment, n (%)	4 (19)

* race was determined by self-identification; † through objective laboratory testing;
‡ both pulmonary and extra-pulmonary tuberculosis; CTPA, Computerized Tomography Pulmonary Angiogram

The clinical presentation was that of both pain and swelling of the limb in 60 (61%) participants with the remainder reporting either limb pain (5) or swelling (34). None of the participants were admitted specifically for symptoms of HIV or TB.

Diagnostic workup

The thrombosis risk profile of the study population stratified by HIV and TB status is shown in table 2.

Table 2: Risk factors for DVT by HIV and TB infection (N=99)

Risk factors, n	HIV + (n=24)	HIV + and TB + (n=20)	HIV- (n=39)	HIV unknown* (n=16)
Major general surgery	0	0	3	2
Orthopaedic surgery	0	0	0	1
Hospitalized for ≥3 days	1	0	1	0
Malignancy	5	0	7	2
Paralysis/ stroke	2	0	1	2
Tuberculosis treatment	0	16	1	0
Lower limb cast	0	0	0	2
Oral contraceptive	0	2	5	0
Pregnancy	1	0	1	0
Postpartum	0	0	2	0
Central line	0	1	2	0
Long journey of 4-6 hours	0	0	1	3

HIV, human immunodeficiency virus; TB, tuberculosis infection; * these participants either refused testing or there was no indication to do the HIV test.

The median Wells' score was 3 (2-4). In the majority of participants, the thrombosis occurred in the lower limb (97) with only two participants having upper limb thromboses.

The median D-dimer value in 93 participants tested was 1.71 (1-3.67) mg/L. Four participants had a negative D-dimer result despite demonstrable thrombosis on DDE. The median waiting period for a DDE in 88 evaluable participants was 30 (24-36) hours and 20 participants waited longer than 48 hours. DDE of 11 participants was done by the referring hospital or at the CMJAH during admission, for another reason, prior to admission to the Haematology Unit.

Assays to investigate the aetiology of thrombosis were performed in 64 participants on admission. All 64 had clotting assays done whilst only 40 had molecular tests performed. The summary of the thrombotic screen results are shown in Table 3. The 64 thrombosis assays performed revealed a total of 6 abnormal screens, none of these patients were on Warfarin at the time of testing. There were no abnormal molecular results.

Table 3: Assays for thrombosis aetiology investigation

Thrombosis assay	Number of assays with abnormal results
Clotting assays (n=64)	
Protein C	5
Protein S	4
Antithrombin	2
APCR*	0
Molecular assays (n=40)	
Factor V Leiden	0
Prothrombin gene (G2021A)	0

*APCR-activated protein C resistance

Management of thrombosis

Table 4 shows the follow-up and outcomes of participants during the study.

Table 4: Patient follow-up during study

Phases of follow-up	**Number**
Screening phase	
Screened for thrombosis	126
Confirmed thrombosis	99
Deaths	0
In hospital follow- up	
Treated with VKA* + LMWH†	91
Treated with LMWH only	5
Deaths‡	3
Post hospitalization follow-up	
Follow-up at 1 month	79
≥3 months follow-up	57
Lost to follow-up	11
Deaths‡	9

*Vitamin K antagonist; †Low molecular weight heparin;
‡Possible causes of death included malignancy (8), sepsis (3) and stroke (1)

Of the 99 evaluable participants, 91 were initiated on a low molecular weight anti-coagulant, enoxaparin sodium and then given simultaneous enoxaparin sodium and a vitamin K antagonist, warfarin, once the diagnosis of thrombosis was made. The starting dose of warfarin was 5 mg with no loading dose. Enoxaparin sodium was given subcutaneously at 1 mg/kg twice daily on admission. Once a thrombosis was confirmed, enoxaparin sodium was continued for at least 5 days following the initiation of concomitant warfarin anticoagulation. Five participants were on enoxaparin sodium alone without warfarin which included patients with malignancy (3) and those

who were pregnant (2). Enoxaparin was stopped as soon as the INR was in the therapeutic range (2-3). Enoxaparin sodium was discontinued after a minimum of 5 days and once a therapeutic INR was achieved in 38% of the participants. The median warfarin dose per week required to obtain a therapeutic INR was 30 (20-43) mg and the median time to therapeutic INR was 5.5 (4.0-7.0) days. Of the 14 participants with cancer associated thrombosis only 3 (21%) were treated with enoxaparin sodium which is the preferred treatment modality.[10-13] The median duration of hospitalization in the cohort was 9 (7-11) days.

All participants were referred to the CMJAH INR clinic upon discharge for long-term follow-up. Of the 91 participants on warfarin, 79 returned for follow-up at one month. During this period, adequate duration and consistency of anticoagulation therapy was achieved by 57 (72%) participants. Eleven participants were lost to follow-up. Twelve out of 99 (12%) participants demised during the study period.

Comorbid HIV and TB infections

In 83 of the 99 participants, an HIV status was established. Forty-four (53%) were HIV positive with a median CD4 count of 152 (85-493) $x10^6$/L and median viral load of 482 (23–221 250) copies/mL. Thirty-four of the 44 (77%) participants who were on (ARV) therapy, 3 started treatment during the hospitalization. Of the 10 participants who were not initiated on ARV therapy in hospital, 2 were not eligible as TB therapy had just been started.

A diagnosis of TB infection was present in 21 of 99 (21%) participants, 4 of whom were diagnosed during the hospitalization. Seventeen participants were receiving TB treatment at the time of DVT diagnosis. HIV and TB co-infection was present in 20 participants. This group had a lower median CD4 count of 118 (60-191) $x10^6$/L versus 321 (92-545) $x10^6$/L (p value <0.05) compared with their HIV positive, TB negative counterparts.

Discussion

In this prospective cohort study, baseline data is provided on the clinical presentation, diagnostic workup and management of 99 participants with DVT with or without HIV and/or TB infections in a quaternary public healthcare facility.

The median age of the patient cohort was 46 years, which reflects the adult haematology practice where the study was performed. This age is higher than the peak HIV prevalence age at the CMJAH, which is in the second and third decades. The racial distribution of the cohort mirrors that of the users of public healthcare facilities in South Africa. These figures would therefore be different in the private healthcare sector and therefore do not reflect the true prevalence of thrombosis in the South African general population.

The clinical presentation of thrombosis in our patient cohort is similar to that seen globally.[14] Fifty-three percent of participants with thrombosis were also HIV positive. This figure is similar to HIV positive rates seen in many public healthcare facilities in South Africa.[15-16]

Tuberculosis was the most common risk factor for thrombosis in participants who were also HIV positive. The burden of HIV and TB has begun to change in South Africa with the implementation of national diagnostic and treatment programs. It remains to be seen whether this will in turn have an impact upon the prevalence of thrombosis.

The work-up of participants with a suspected DVT included the use of a clinical scoring system (the Wells' score), a quantitative D-dimer test with confirmation on DDE. Studies have shown that a DVT can be safely excluded in patients with the combination of a low Wells' score and a negative quantitative D-dimer.[17-19] In our cohort, all participants with a negative D-dimer (4) had an intermediate Wells' score and thus went on to have a DDE to confirm thrombosis. The value of routinely using such an approach would be to limit the number of unnecessary DDE.

Thrombotic aetiology tests were performed in 64 participants and 6 screens were abnormal. This result is low relative to published studies and may reflect less discriminate testing practices.[20] Factor V Leiden and Prothrombin G20210A mutations molecular tests were negative in all 35 Black participants in our study a finding in keeping with previous studies confirming the absence of the Factor V Leiden mutation in this population.[21-23]

Warfarin and enoxaparin sodium are currently the most widely used anticoagulants for the treatment of DVT in South African public hospitals. Their use at the CMJAH were comparable to published national and international guidelines.[24-28] Enoxaparin sodium discontinuation procedures were adhered to in only 38% of participants. This low adherence is explained by both hospital and patient related factors which included delays in initiating warfarin, constant bed shortages at the CMJAH and the inability of participants to be absent from work for extended periods. A more achievable target was therefore to obtain a single therapeutic INR prior to discontinuation of at least 5 days of enoxaparin sodium. The use of enoxaparin sodium in cancer associated thrombosis was low (21%) in our cohort. Plausible explanations include cost, a lack of awareness of the current guidelines, clinician habit, safety concerns and the burden of daily injections for the cancer patients.[29]

In the current study, the average duration of hospitalization required to achieve a therapeutic INR was between 1-2 weeks. Approximately 70% of the cohort achieved adequate and consistent long-term anticoagulation therapy as shown in Table 4. Possible reasons for inadequate and inconsistent anticoagulation in the 30% may include an inability for participants to take time off work for follow-up visits and unaffordable transport costs.[30]

The introduction of DOAC therapy has the potential to reduce or eliminate the need for hospitalization and testing thus providing substantial cost savings to both the hospital and patient. However, in patients with HIV and/ or TB, studies predict that significant drug interactions will be present between DOACs and certain HIV and TB medications. There are known interactions with strong CYP3A4 inducers and inhibitors, namely rifampicin (standard of care) and protease inhibitors.[31-33] Based on these predictions, anticoagulation of patients with TB will likely remain a challenge as is currently experienced with warfarin anticoagulation. Therefore, it is anticipated that the benefits of DOACs may not be fully realized in patients with TB and are yet to be determined in HIV.

The HIV prevalence rate of 52% in our cohort was notably higher than the Sub-Saharan African prevalence of 19.2%.[34] This finding probably reflects the pro-thrombotic risk associated with HIV. In addition to the direct effect of HIV on DVT development, opportunistic infections and their treatments with associated prolonged bed rest and malignancies are possible contributing factors in this subgroup. A significant proportion of the participants were on ARV therapy at the time of DVT diagnosis (77%) which indicates the efficiency of the national ARV rollout program in South Africa. ARV therapy has been shown to reduce markers of coagulation however, abnormalities persist despite viral suppression. Twenty-one participants had comorbid HIV and TB which reflects the scenario in the general population in this region. As expected, the CD4 counts were significantly lower when compared to their TB negative counterparts. Satisfactory anticoagulation therapy is a huge challenge in patients with TB infection. This is due to the unpredictable effects of rifampicin and isoniazid on the cytochrome P450 system, which is involved in warfarin metabolism.

There were 12 (12%) participants who died at different time points during the study as shown in Table 4. The majority of the deaths occurred during the post hospitalization follow-up. The possible causes of death in these participants included malignancies (8), sepsis (3) and recent stroke (1). The malignancies included signet ring cell adenocarcinoma; mesothelioma; breast, cervical, prostatic and bronchoalveolar carcinoma; and a carcinoma of unknown primary. Whilst no deaths were documented due to thrombosis or bleeding complications in the study, these remain possibilities for the 11 participants who were lost to follow-up.

The small patient population of 99 participants is an obvious limitation of this study. Therefore, our study figures cannot be extrapolated to the general hospital population and might not reflect the total thrombosis picture in a quaternary care setting. The majority of the participants included in this study were those with lower limb thromboses. Other sites of thrombosis such as intra-abdominal and pulmonary sites might have been missed in this study as they were managed by other disciplines of medicine. Finally, the study cohort follow-up of three months was short and might not reflect the true outcome of management of thrombosis in a quaternary care setting in the long term.

Conclusion

This prospective study provides real-life data on the prevalence of DVT in the pre-DOAC era. This data set will serve as a baseline reference for measuring the effectiveness and impact of the DOACs new anticoagulants when used routinely outside clinical trials. This is of particular interest in patients with comorbid HIV and TB where conventional anticoagulation treatment is challenging. The prevalence of HIV and TB observed in this study provides an important reference point for assessing the aetiological association between thrombosis and these infections, especially as their prevalence changes due to the current national interventions.

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R14/49 Dr Katherine Hodkinson

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150938

NAME: (Principal Investigator)	Dr Katherine Hodkinson
DEPARTMENT:	Molecular Medicine and Haematology Charlortte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Deep Vein Thrombosis at a Quaternary Academic Hospital : A Prospective Review of Its Management
DATE CONSIDERED:	02/10/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Johnny Mahlangu
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/11/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 31·10·2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES