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ORIGINAL RESEARCH

Coagulation in the HIV-positive pregnant patient: a thromboelastography study

S Mayeza, MJ Arcache, L Loo, RA Dyer

Department of Anaesthesia and Perioperative Medicine, University of Cape Town, South Africa
Corresponding author, email: *sleemayeza@gmail.com*

Background: HIV infection is associated with haematological changes, including thrombocytopaenia. Pregnancy induces a hypercoagulable state. There are limited data on the coagulation status of women with term pregnancy and HIV receiving anti-retroviral medication. Regional anaesthesia is the technique of choice for caesarean section (CS), and is contraindicated in a hypo-coagulable state. We therefore investigated the coagulation status of term pregnant women with HIV, presenting for elective CS.
Methods: This was a single-centre cross-sectional observational study, using thromboelastography, comparing the coagulation status of HIV-negative and -positive women with no other comorbidities, in pregnancy at term. A blood sample was taken immediately prior to spinal anaesthesia, and thromboelastography was performed within four minutes. In addition, platelet count, haemoglobin, and fibrinogen level were measured.
Results: Blood samples were obtained from 75 patients. There were no between-group differences in obstetric and demographic data, and no difference in platelet count. The mean (standard deviation [SD]) fibrinogen level was higher in HIV-positive women (3.9 [1.5] vs 3.5 [0.7] g/L) respectively, $p = 0.04$. There were no significant differences in the r time, alpha angle, k time, maximum amplitude (MA), or LY-30.
Conclusions: The results of this thromboelastography study show that in asymptomatic HIV-positive pregnant patients on anti-retroviral treatment, there are no significant differences in coagulation parameters when compared with HIV-negative patients. This suggests that routine assessment of coagulation is unnecessary before spinal anaesthesia in patients without further comorbidities. Further studies could demonstrate the incidence of abnormalities in coagulation or platelet function in patients with AIDS-defining disease or HIV-positive patients with other comorbidities.

Keywords: HIV, coagulation, pregnancy, thromboelastography, anaesthesia

Introduction

In 2017, South Africa was estimated to have a prevalence of human immunodeficiency virus (HIV) infection in adults aged 15–49 years, of 18.8%.[1] The 2015 National Antenatal Sentinel HIV and Syphilis Survey in South Africa estimated a prevalence of 30.8% amongst women presenting for antenatal care, the lowest being in the Western Cape Province (18.9%).[2]

HIV infection is known to be associated with haematological changes. The most common is anaemia, found in 95% of patients in the course of their disease. Thrombocytopaenia is also a feature, the most common cause of which is immune thrombocytopaenia.[3] The changes in the coagulation system could collectively represent a hypocoagulable state. Pregnancy is well known to induce a hypercoagulable state; other haematological features include a dilutional anaemia and relative thrombocytopaenia.[4]

Regional anaesthesia is the technique of choice for CS in the parturient in the absence of contraindications, and has been shown to decrease morbidity and mortality in HIV-positive patients undergoing elective CS.[5,6] Thromboelastography (TEG) has been extensively utilised in previous studies to demonstrate the coagulation status of pregnant patients,[7,8] and the measured parameters influence the decision to perform regional or general anaesthesia for CS.

There are limited studies examining the effect of HIV infection and anti-retroviral medication on coagulation in pregnancy.[6,9] We therefore performed a cross-sectional study comparing the coagulation profile (as assessed by TEG) of HIV-positive versus -negative patients at term. Secondary outcomes included a comparison of TEG variables in patients in whom anti-retroviral therapy (ART) had been commenced before or during pregnancy. In addition, between-group comparisons were performed of platelet count, fibrinogen level, and blood loss during CS.

Methods

This was a single centre observational study, which was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (HREC Ref: 241/2013). Patients were recruited prior to elective CS at Mowbray Maternity Hospital, Cape Town, South Africa, from August 2013 to April 2014. Informed consent was obtained from all patients by the principal investigator at least 12 hours prior to CS. The standard of care at this hospital is for all patients to be screened for HIV infection as part of the antenatal assessment. Patients with any other comorbidities were excluded. All blood specimens drawn during the study were labelled with study-specific labels, rendering patients anonymous. The results of the study had no effect on the quality of care received by the participants.

Immediately prior to spinal anaesthesia, a 16- or 18-gauge intravenous cannula was inserted. A blood sample of 10 mL was taken from the cannula. The initial 8 mL was placed in an EDTA tube (BD Vacutainer® K3E 7.2 mg) for measurement of platelet count, haemoglobin (Hb) level and CD4 count, if the latter had not

been performed within six months of participation in the study. The remaining 2 mL of the specimen was placed in a citrated tube (VACUETTE® 9NC Coagulation Sodium Citrate 3.2%) for the assessment of the fibrinogen level. A separate syringe was used to withdraw a further 2 mL of blood for TEG measurements after the initial sampling, thus eliminating contamination by tissue factors that could affect the results. An aseptic venipuncture was performed if there was difficulty in obtaining a satisfactory blood sample from the cannula.

All TEGs were performed on site within four minutes of sampling by a qualified technologist using the TEG® 5000 Haemostasis Analyzer System (Haemonetics® Corp, Braintree, MA, USA; Software version 4.2). Regular quality control and calibrations was performed according to manufacturer's recommendations. One mL of native blood was activated using kaolin, and 360 µL pipetted into a cup that had been pre-warmed to 37 degrees Celsius. The same technologist performed all the TEGs, thus eliminating inter-individual variability in performing the test. The samples ran for a period of 60 minutes. The mean (SD) r time (time taken for clot formation to start), k time (time from end of r time until the clot reaches 20 mm), α angle (the tangent of the curve when the k time is reached), maximum amplitude (MA) (indicative of platelet function and fibrinogen level, and a marker of clot strength), and LY-30 (percentage decrease in MA after 30 minutes)[10] were recorded and compared between HIV-positive and -negative patients. With respect to the TEG parameters, the primary outcome was the r time; k time, α angle, MA and LY-30 were secondary outcomes.

The platelet count, Hb level, CD4 count and fibrinogen levels were all performed by the National Health Laboratory Service (NHLS) at Groote Schuur Hospital. Reference ranges were applied as per NHLS standards. Estimated blood loss was recorded by the attending senior anaesthetist, using observation of swabs, measurement in suction bottles, and assessment of surgical field losses.

Statistical methods

Demographic data is presented as mean ± SD. TEG data was analysed using the paired *t* test and Wilcoxon signed-rank test. The required sample size was estimated for this comparison of TEG parameters between HIV-positive and -negative women, using similar methodology to that of Butwick et al.[11] A 20% difference in TEG parameters was regarded as a clinically relevant endpoint for the study. Assuming an r time estimate for the normal pregnant population of 6.5 minutes, with an SD of 2.5 minutes, 32 patients would be required in each group to detect a 1.5 minute difference in the HIV-positive group greater or less than the r time in the control group, with 80% power and alpha error 0.05. Seventy five patients were recruited, to account for possible errors in the processing of samples. The statistical programme used was Statistica Version 11 (StatSoft Inc, Tulsa, USA).

Results

Patients were recruited sequentially upon presentation for CS. Blood samples were obtained from 75 patients, of whom 38 were HIV-positive and 37 HIV-negative. Obstetric and demographic data are presented in Table I.

Table I: Obstetric and demographic data presented as mean (standard deviation)

	HIV-positive (*n* = 38)	HIV-negative (*n* = 37)	*p*-value
Age (years)	32.2 (4.6)	30.4 (5.2)	
Weight (kg)	88.0 (14.2)	88.2 (16.9)	
Gestational age (weeks)	38.9 (0.9)	39.3 (0.9)	
CD4 count	546 (239)	N/A	
Estimated blood loss (mL)	516 (255)	469 (280)	0.45

HIV – human immunodeficiency virus

There were no significant between-group differences.

Laboratory data is presented in Table II.

Table II: Laboratory data

	HIV-positive	HIV-negative	*p*-value
Haemoglobin (g/dL)	11.7 (1.3)	11.8 (1.4)	0.62
Platelet count (x10^9/L)	246.8 (59.0)	261.7 (64.4)	0.29
Fibrinogen (g/L)	3.9 (1.5)	3.5 (0.7)	0.04

Four specimens were discarded by the laboratory due to inadequate volume for analysis. The fibrinogen level in the HIV-positive patients was higher than in the control group ($p = 0.04$).

The TEG values for the two groups are presented in Table III. There was no significant difference in the r time, alpha angle, k time, MA, or LY-30. The results were not influenced by the timing of commencement of ART, before or during pregnancy.

Table III: The TEG values for both groups

	HIV-positive	HIV-negative	*p*-value
r time (minutes)	4.8 (1.7)	4.2 (1.5)	0.09
k time (minutes)	1.5 (0.4)	1.4 (0.7)	0.49
α angle	67.7 (1.7)	69.5 (7.0)	0.23
MA (mm)	72.7 (3.8)	74.1 (6.6)	0.25
LY-30 (%)	0.86 (1.2)	2.21 (7.9)	0.29

r time – reaction time, k time – clot formation time, α angle – clot formation rate, MA – maximum amplitude, LY-30 – percentage decrease in MA at 30 minutes

Discussion

This cross-sectional comparison of TEG parameters in pregnant women close to term, showed no significant differences between HIV-positive and -negative patients, except for a clinically insignificantly higher fibrinogen level in HIV-positive women. Clot strength as evidenced by the MA was also not significantly different. The LY-30 in both groups showed no evidence of fibrinolysis. As all of the patients in the HIV cohort were on ART during the time of this study, no conclusions can be drawn as to

the effect of ART on coagulation parameters. There were also no between-group differences in platelet count, fibrinogen level, or blood loss at caesarean delivery.

Regional anaesthesia is the preferred method in pregnancy, where epidural anaesthesia is the gold standard for labour analgesia, and spinal anaesthesia predominates for CS, avoiding the risks of general anaesthesia, such as failed tracheal intubation. The presence of coagulation abnormalities influences the decision to perform regional anaesthesia in pregnancy. The high prevalence of HIV infection in the South African population and the increasing rate of CS necessitates the understanding of haematological changes and the implications for regional anaesthesia.

HIV causes endothelial dysfunction with activation of the coagulation system. This is evidenced by the finding of elevated D-dimer- and thrombin-antithrombin complex levels,[9,12] a progressive increase of Factor VIII levels, and a decline in functional Protein S and Protein C levels. These changes are more pronounced with advancing disease.[3,13] The presence of lupus anticoagulant and antiphospholipid antibodies, which are associated with a prothrombotic state, may also contribute to HIV infection-associated thrombosis,[3,13] although this is controversial.[13,14]

Pregnancy is associated with an increase in pro-coagulant factors (II, VII, VIII, X and XI) and a decrease in anti-coagulant factors (Protein C and S, and Antithrombin III).[4,9] Fibrinogen levels rise from 28 weeks gestation, and D-dimer levels are raised throughout pregnancy. These haematological occurrences are thought to be a physiological adaptation to minimise blood loss during childbirth.[4] Karlsson et al. showed increased coagulation in Scandinavian women,[15] as did Gorton et al. in the United Kingdom.[16]

The MA on the TEG tracing is a measure of clot strength, and is a direct indication of fibrinogen and platelet interaction.[17] The MA has therefore been found to correlate well with platelet count.[18] The increased fibrinogen level in pregnancy may reduce the effect of thrombocytopaenia on the TEG tracing, as both contribute to the MA.[19] Thrombocytopaenia is one of the earliest manifestations of HIV infection[20] and immune thrombocytopaenia is the most common cause.[3] Two previous studies in healthy patients found mean MA values of 66.4[7] and 75.4 mm.[21] The latter study found fibrinogen levels of 5.0 g/L (3.7–6.4). These values are similar to those found in our study (MA 74.1 in the HIV-negative and 72.7 mm in HIV-positive patients), although fibrinogen levels in our population were lower. These results indicate that asymptomatic HIV-positive parturients remain within normal limits for this parameter, as suggested by previous studies. The findings in one study in HIV-positive patients in the non-obstetric population, have suggested defects in platelet function. There was reduced aggregation in response to thrombin receptor-activating peptide, adenosine phosphate and collagen. In addition, an increased response to epinephrine was shown using a platelet aggregation assay, when comparing HIV-positive, 80% of whom were on ART, and -negative patients.[22]

A study by Arildsen et al., which compared haematological changes in HIV-positive patients before and after highly active anti-retroviral therapy (HAART), found endothelial dysfunction, higher fibrinogen and D-dimer levels prior to treatment. The raised fibrinogen and D-dimers did not fully correct following a treatment period of six months.[12] Haugaard et al. also found increased D-dimer levels in untreated HIV-positive patients, but still found that these patients were relatively hypercoagulable as assessed by TEG.[23] A further study found that HIV patients on ART had increased levels of tissue plasminogen activator antigen and plasminogen activator inhibitor type 1, which suggests increased fibrinolysis.[9] Our study found no between-group difference in fibrinolysis as assessed by the LY-30, despite the fact that our patients were receiving ARV therapy.[12]

The findings of our study, comparing the coagulation status using TEG of HIV-positive and -negative patients, suggests that in asymptomatic HIV-positive patients, routine laboratory or point of care coagulation studies are not indicated before regional anaesthesia. Our results are in keeping with a recent study on predictors of thrombocytopaenia in asymptomatic patients scheduled for caesarean delivery, which found that only preeclampsia was predictive of mild thrombocytopaenia. A sub-analysis in that study showed that HIV status was not independently associated with moderate thrombocytopaenia, and that all asymptomatic patients had a platelet count > 70.000/μL. The authors concluded that on this basis a routine full blood count is indicated in preeclampsia, but not in patients who are HIV-positive, unless there are other comorbidities.[24]

Davies et al. evaluated differences in healthy pregnant versus preeclamptic women using the Platelet Function Analyzer (PFA-100) and TEG. This study found a mean MA of 73 mm, and that despite an abnormal clotting time in the preeclampsia cohort, the MA remained within the normal range. This indicates that TEG may not detect abnormalities in primary haemostatic function.[19]

A limitation of our study was that we did not study platelet function, or the effect of ART, since most of our patients were receiving this medication at the time of the study.

In conclusion, the results of this thromboelastography study show that in asymptomatic HIV-positive pregnant patients on ART, there are no significant differences in coagulation parameters when compared with HIV-negative patients. This suggests that routine assessment of coagulation is unnecessary before spinal anaesthesia in patients without further comorbidities. Further studies could demonstrate the incidence of abnormalities in coagulation or platelet function in patients with AIDS-defining disease or HIV-positive patients with other comorbidities.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval

Ethics Committee approval was received from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (HREC Ref: 241/2013).

ORCID

S Mayeza https://orcid.org/0000-0002-2562-4202

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