ORIGINAL ARTICLE

Detection of Coagulopathy in Chronic Renal Disease using Thromboelastography and its comparison with Conventional Tests

Chandra Kant Pandey[1*], Kelika Prakash[2], Sunaina Tejpal Karna[3], Suman Lata Nayak[3], Manish Tandon[3], Priyanka Jain[4]

Abstract

Purpose of the Study: Thromboelastography provides a holistic picture of blood coagulation including fibrin formation, cross, linking and fibrinolysis. Coagulaopathy in end stage renal disease (ESRD) is multifactorial. The present evaluated the thromboelastographic profile of ESRD patients and compared it to conventional tests of coagulation.

Study Design: In this observational case control study, fifty ESRD patients and 50 controls were recruited. Venous samples were withdrawn and platelet count, International Normalization Ratio and fibrinogen levels were measure. Simultaneously a thromboelastography (TEG) was performed. All samples were drawn prior to initiation of dialysis.

Results: The fibrinogen concentration was higher in the ESRD group compared to control (455.51±83.39 vs. 233.84±71.71 mg/dl, P<0.05). The maximum amplitude in ESRD group was 76.94 ± 15.11 mm, which was significantly higher than control group 65.10±10.31 mm (P<0.05).Out of 50 ESRD patients,39 had maximum amplitude (MA) >73mm, 3 had MA <55 mm while 8 patients had normal MA. Further, it was seen that in four out if the five patients whose INR was greater than 1.5. TEG was hypercoaguable. Also, three patients whose platelet count was less than x10^5/dl had normal thromboelastographs. Two patients with normal platelet count, fibrinogen and INR had hypercoaguable thromboelastographs. Thromboelastography could detect fibrinolysis in 5 patients of end stage renal disease.

Conclusion: The present study demonstrated that INR, platelet count and fibrinogen levels do not reflect the actual coagulation status in patients of ESRD. Thromboelastography is a better tool to detect coagulopathy in this group of patients.

Introduction

Coagulopathy in End stage renal disease(ESRD) is multifactorial.[1] Some patients have bleeding tendencies while others are prothrombotic.[2-5] Conventional coagulation tests do not evaluate the interaction between various components involved in coagulation nor provide a real time assessment of clot kinetics, clot strength, fibrinolysis and overall quality of clot. Thromboelastography overcomes the above deficiencies and provides a holistic picture of coagulation in a short period of time using only 0.36 ml of blood. Thromboelastography is superior to conventional tests during liver transplantation,[6] cardiopulmonary bypass,[7] trauma[8] and Disseminated Intravascular Coagulopathy (DIC).[9] However, its utility in ESRD has not been explored. Therefore, this observational study is designed to detect coagulopathy in patients suffering from ESRD using thromboelastography and to compare the findings with conventional tests.

Material and Methods

This single centre observational study was conducted over a period of 1 year duration from April 2015 to March 2016 in a tertiary health care centre. Institutional ethical committee approval was obtained (No.F/25/5/81/ILBS/AC2015/820-25, dated 22/12/2015) and written informed consent was taken from all participating patients. This study was performed in keeping with the Declaration of Helsinki and Strobe guidelines. Fifty diagnosed end stage renal disease (ESRD) patients defined by Kidney Disease: Improving Global Outcomes 2012[10] (KDIGO) who never received renal replacement therapy (RRT) and 50 healthy voluntary donors were recruited for the study. Patients with known bleeding disorders, coexisting liver diseases, malignancies, those who were on antiplatelet or anticoagulant therapy and patients who had received red blood cells, fresh frozen plasma or platelet transfusions in the past three months were excluded from the study. Pregnant patients and patients less than 18 years of age were also excluded from the study.

In all 100 participants, venous blood samples was analysed for serum urea, serum creatinine, serum electrolytes, complete blood count, and conventional tests of coagulation i.e. platelet count, Activated Partial Thromboplastin time (aPTT), Prothrombin Time (PT) with INR, and Fibrinogen.(The normal laboratory range of fibrinogen was 150 to 300mg/dl and platelet count

[1]Senior Professor and Head, [2]Assistant Professor, [3]Associate Professor, [4]Statistican, Institute of Liver and biliary Sciences, New Delhi; *Corresponding Author
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Table 1: Normal kaolin TEG parameters

R	4-8 minutes	Clot initiation
K	0 to 4 minutes	Speed of fibrin build up
α angle	47 to 74	Speed of fibrin build up
MA	55 to 73 mm	Clot strength
LY30	0 to 8	Fibrinolysis

R (Reaction Time); K (kinetics); MA (Maximum Amplitude); LY30 (Lysis at 30 minutes)

Table 2: Demographic data in healthy controls and ESRD patients

Parameter	Controls	ESRD patients
Age (years)	44.98 ± 11.70	47.78 ± 16.30
Male: Female	26:24	22:28
Patient distribution according to etiology of ESRD		
Hypertension- n(%)	-	20(40%)
Diabetes- n(%)	-	11(22%)
CTID- n(%)	-	10(20%)
CGD- n(%)	-	7(14%)
Amyloidosis- n(%)	-	1(2%)
TMA- n(%)	-	1(2%)

All values are represented as Mean ± standard deviation or median (minimum, maximum), *P < 0.05 is statistically significant; CTID: chronic tubulointerstitial disease, CGD: chronic glomerular disease, TMA: Thrombotic Microangiopathy

was 1.0 to 4x10^5/dl). A standard kaolin thromboelastography was performed along with above mentioned tests before institution of any medical treatment. All samples were collected from a peripheral vein using a vacutainer. For TEG analysis 1cc of whole blood was transferred into a company provided kaolin coated vial and mixed. Following this 0.36 ml of blood was pipetted into the TEG cup. The R time, K, $\bar{\alpha}$ angle, Maximum Amplitude (MA), Clot Lysis 30 (CL30) was noted. A summary of the normal values of TEG parameters[11] is given in Table 1.

From CKD patients all blood samples were taken prior to initiation of RRT. Coagulation abnormality was defined as: hypercoaguable, when MA > 73mm and hypocoaguable when MA was< 55 mm.[12,13] In addition, in the CKD group, following enrolment, the duration of disease, the presence of comorbid conditions like hypertension, diabetes mellitus, Coronary Artery Disease (CAD) or Cerebrovascular Accidents (CVA) was noted. A history of deep vein thrombosis or pulmonary embolism or any clinical manifestation of bleeding like petechiae, mucosal bleed, bleeding per rectum was noted.

Statistical Analysis

Sample size calculation was based on a previous study by for a power of 0.80 to detect two sided α error of 0.05.[14] All continuous variables were expressed in mean ± SD. For discrete variables median was used. For non-parametric test, Mann-Whitney U test was used to test significant difference among continuous variables. For the data that followed normality, independent t test was used. Chi-Square or Fisher's Exact test was used for categorical variables, to test the association between two variables. All data was analysed by SPSS version 21.

Table 3: Laboratory investigations in healthy controls and ESRD patients

Laboratory tests	Control	ESRD	P value
Hb(g/dl)	13.18 ±1.67	8.12 ± 1.67	<0.001*
Blood urea (mg/dl)	22.9 (11.0,37.90)	174.4 (54.0, 517.3)	<0.001*
Serum creatinine (mg/dl)	0.67 ± 0.17	10.24 ± 4.99	<0.001*
Platelet count (*10^5/ dl)	2.42. ± 0.79	1.98 ± 0.95	0.01*
INR	1.05 ± 0.10	1.23 ± 0.24	<0.001*
Fibrinogen (mg/dl)	233.84 ± 71.71	455.52 ± 83.39	<0.001*

All values are represented as Mean ± standard deviation or median (minimum, maximum), *P < 0.05 is significant

Results

The demographic data is depicted in Table2. The mean age and male to female ratio in the two groups was comparable. The aetiology of CKD is shown in Table 2.

Hypertension was the causative factor for CKD in most patients. Twenty two patients had hypertension related CKD of whom 3 also had diabetes mellitus. One patient had diabetes mellitus alone. No patient had a history suggestive of thrombotic or bleeding tendencies.

Laboratory parameters

The mean haemoglobin, platelet count, INR, Kidney Function Tests and serum fibrinogen levels are given in Table 3.

All values were within normal range in all the healthy donors. In the ESRD group, the median blood urea level was 174mg/dl (range 54.0-517.0) which was significantly higher than the control group {median 11.0 (range 11.0-37.9), P<0.01}. Similarly serum creatinine level in the ESRD group (10.2 ±0.67 mg/dl) was significantly higher than the healthy controls (P<0.01).ESRD patients had significantly lower haemoglobin levels than their healthy counterparts (P<0.01). On analysis of platelet count, it was noted that while the platelet count was within the normal range for all healthy volunteers, in the ESRD group, three patients had a platelet count of less than 1x10^5/mm^3 while two patients had a platelet count of more than 5x10^5/mm^3. The platelet count was within the normal range for the rest of the 45 ESRD patients. Five patients in the ESRD group had INR >1.5. The average fibrinogen level in the control group was 233.83±65.36mg/dl, the fibrinogen concentration was 455.51±83.39 mg/dl in the ESRD group which was greater than the upper limit of the normal fibrinogen level. The difference in the fibrinogen concentration between the two groups was statistically significant (P<0.01). On further analysis, it was noted that the fibrinogen levels were high in 47 out of 50 patients suffering from ESRD. In the remaining three patients, fibrinogen level was low (168 mg/dl) in one and normal in two patients (Table 3).

Table 4: TEG parameters in healthy controls and ESRD patients

Parameter	Controls	ESRD
R (minutes)	5.05 (1.20, 7.40)	4.00(0.20,21.20)
K(minutes)	2.00 (0.80, 5.90)	1.65(0.80,7.00)
alpha	57.69 ± 14.91	65.37 ± 13.57
MA(mm)	65.10 ± 10.31	76.94 ± 15.11*
CL 30(%)	1.77 ± 2.29	1.80 (0.0, 45.4)

All values are represented as Mean ± standard deviation or median (minimum, maximum), *P < 0.05 is significant

Thromboelastography findings

R time, K time, $\bar{\alpha}$ angle, MA and CL 30 were within the normal range in control group (Table 4).

The median R and K time were within the normal range in ESRD patients. One patient had R time of 21.2 which was beyond the normal range. The mean α angle was 57.70 ± 14.77 in the ESRD group which was within the normal range. Thirty nine out of 50 ESRD patients had a MA greater than 73mm. MA was less than 55 mm in 3 ESRD patients while it was normal in the remaining 8 patients. The average MA of ESRD patients (65.10 ± 10.21 mm) was significantly higher than control group (65.10 ± 10.31 mm, P<0.01). Five ESRD patients had a fibrinolytic picture on TEG with CL 30 > 8%.

TEG vs conventional coagulation Parameters

The thromboelastography profile

was also evaluated with respect to conventional coagulation tests. It was observed that of the five patients whose INR was greater than 1.5, MA was greater than 73mm (indicating a hypercoaguable state) in four patients while in one patient TEG was hypocoaguable. The three patients who had low platelet counts had normal thromboelastograph. Also, it was observed that in two ESRD patients with normal platelet count, fibrinogen and INR, TEG was hypocoaguable.

Discussion

In the present study group 78% of ESRD patients were hypercoaguable and only 6% were hypocoaguable. Further, 94% of patients in the ESRD group had higher than normal fibrinogen levels. As MA depends on fibrinogen levels the hypercoaguable TEG can be expected. The interesting findings in the present study were (1) the presence of a hypercoaguable TEG in 4 out of 5 patients with INR >1.5. and (2) a hypocoaguable TEG seen in ESRD patients with normal conventional coagulation tests (3). hyperfibrinolysis in 5 patients, a factor which have gone unnoticed by conventional tests (fibrinogen level, INR and platelet levels).These findings can be explained by looking into the pathophysiology of coagulopathy in CKD.

Coagulopathy in CKD is multifactorial. Apart from an alteration in the number/function of platelets and amount of coagulation factors, accumulated uremic toxins, metabolic compounds and inflammatory proteins play an important role. Other factors attributed include alterations in the level and activity of protein C complex, antithrombin, thrombin–antithrombin complexes, D-dimers and prothrombin fragments 1 + 2 (F1 + 2).[15] Ultimately the state of coagulation is determined by a complex interaction between platelets, coagulation and fibrinolytic factors as well as accumulated uremic and inflammatory molecules.

Conventional coagulation tests provide information till formation of initial fibrin strands. Moreover, CCTs measure levels of a given parameter and do not take into account interaction between different components. TEG is a viscoelastic assay which provides a holistic picture of blood coagulation including the rate of clot formation, clot strength, thrombolysis. A TEG picture depends on interaction between various blood components and other molecules present in whole blood which may affect coagulation. It is a faster assay utilising only 0.36 ml of blood.[16]

Darlington et al studied the TEG profile of ESRD patients on maintenance haemodialysis and compared it with the TEG profile of patients suffering from coronary artery disease.[14] They reported that 42.9% ESRD patients were hypocoaguable unlike the present study where 6 % (3/50) patients were found to be hypocoaguable on thromboelastograph. A plausible explanation is that the patients in our study group had not been started on maintenance haemodialysis.

TEG has wide clinical applications. TEG based management of coagulopathy in patients undergoing cardiopulmonary bypass surgeries has been found to be associated with decreased use of transfusions[17]. TEG has also been used to guide anticoagulant therapy in patients undergoing kidney pancreas transplantation.[18,19] Given the benefits of thromboelastography, TEG has become a standard of care for diagnosis and management of coagulopathy in trauma[20] and liver diseases.[21] Particularly in the latter, where coagulation is dependent on interaction between various components, it is recommended that TEG and other point of care tests rather than INR or platelet count should be used. As mentioned previously, coagulopathy in CKD is complex and multifactorial. The present study studied TEG profile as well as CCT in ESRD patients. However a potential limitation of the study was that the change in coagulopathy with dialysis over a course of time was not studied. We found that TEG is a better assay than CCTs to detect coagulopathy in ESRD patients. The utility of TEG to monitor anticoagulant therapy in ESRD patients as well as to guide management of heparin administration during dialysis needs to be explored. The effect of hemodialysis on TEG can also be explored further.

Conclusion

We conclude from the present study that thromboelastography provides a holistic picture of coagulation and is a better assay than CCTs to detect coagulopathy in ESRD patients. The INR, platelet count and fibrinogen level do not reflect the actual coagulation status in ESRD patients.

Author contributions

Concept or design: KP, CKP, SLN. Acquisition of data:. KP, CKP, SLN, SK, MT, PJ. Analysis or interpretation of data: KP, CKP, SLN, PJ.

Drafting of the article: KP, CKP, SLN, SK, MT, PJ. Critical revision for important intellectual content: KP, CKP, SLN, SK, MT, PJ.

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Declaration

All authors have no conflicts of interest to disclose. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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