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RESEARCH

Thromboelastography in mild, chronic liver disease: challenging conventional coagulation tests preceding liver biopsy

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Patients presenting for liver biopsy may have a deficiency of the synthetic function of the liver. They commonly undergo testing of their INR, which is used to decide if there may be a bleeding risk and if that needs to be mitigated by the administration of clotting factors. This study aimed to observe the coagulation profile of these patients via a thromboelastogram (TEG), and to search for a relationship between the traditionally used INR and the R-time of the TEG.

A prospective observational pilot study was conducted over a seven-month period. An FBC, INR and kaolin activated thromboelastogram were performed on each patient. Spearman's correlation coefficient was used to determine the relationship between the INR and the R-time of the TEG.

The TEG was performed on 28 participants. Two were excluded from analysis as they had received Vitamin K. Twenty-three patients (88%) had abnormal liver function tests. Drug or toxins were responsible for liver injury in 15 (58%) participants. Twenty-two (85%) had normal platelet counts. Three (12%) were found to be hypocoagulable, four (15%) were hypercoagulable, and the remaining 19 (73%) had normal thromboelastography. The three (12%) participants who were hypocoagulable had a normal platelet count. No association was found between INR and the R-time of TEG (Spearman's rho −0.20, $p = 0.34$). In the two participants (8%) with a raised INR (1.26 and 1.7 respectively), the TEG suggested a normal or hypercoagulable status.

This study revealed that most patients with mild, chronic liver disease presenting for liver biopsy have a normal TEG. There was no association between INR and the R-time of the TEG. This suggests that INR may not be a reliable test of coagulation status in these patients with mild chronic liver disease, which is contrary to the traditional practice of using INR to infer coagulation status. Further larger studies looking specifically at patients with drug and toxin induced liver injury are warranted.

Keywords: international normalised ratio, liver biopsy, liver disease, thromboelastography, viscoelastic coagulation testing

Introduction

One of the main functions of the liver is to regulate coagulation. Patients with liver disease have been shown to experience coagulation deficits according to conventional coagulation tests (CCT). Liver biopsies are frequently performed to determine the definitive diagnosis in patients with deranged liver enzymes. A complication of the procedure is bleeding[1] and the most common contraindication to liver biopsy is a suspected bleeding diathesis.[2] Clinicians have traditionally used CCT to determine the coagulation status of these patients to decide on bleeding risk, and the need for correction of coagulation abnormalities. Many institutions have protocols consisting of measuring the international normalised ratio (INR) and platelet count[3] and delaying the biopsy to correct significant abnormalities. In our institution, if the INR is over 1.4, fresh frozen plasma (FFP) is given, and if the platelet count is below 100×10^9/l, platelets are administered.

Viscoelastic testing (VET), consisting of thromboelastography or rotational thromboelastometry (ROTEM), is another option in evaluating coagulation in patients undergoing liver biopsy.[4] The advantage of VET over CCT is the ability to achieve a more composite picture of coagulation, as it takes platelets, fibrinogen, clotting factors, fibrinolysis and the interaction of the components into account.[5] The clotting index (CI) is a number that reflects the overall coagulability by using an algorithm from the manufacturer, which takes into account the R-time, K-time, α angle and maximum amplitude (MA). The more negative the CI, the more hypocoagulable the sample, and vice versa.[6] All the measured values can be compared with the reference ranges to identify coagulation deficits, and to guide correction or replacement of components with blood products. The R-time of the TEG is the parameter that most closely reflects the clotting factors, thus in liver disease it is a parameter one could postulate may be the most likely to have a relationship with the INR.

Most of the research that has been done on VET in mild chronic liver disease (CLD) shows a surprisingly high trend towards hypercoagulability,[4] which is not diagnosed using conventional tests of clotting.[2] In the current South African context, the majority of patients presenting for liver biopsy are those with drug or toxin induced liver injury which has not, to date, been a focus in the international literature with regard to coagulation deficits.

The primary aim of this study was to describe the coagulation profile of patients with mild chronic liver disease who were admitted to the liver unit for liver biopsy. Our hypothesis was that they would have normal thromboelastography. Our secondary aim was to determine whether there was an association between the INR and the R-time of the TEG in this group of participants. Our hypothesis was that there would be no association between INR and R-time.

Methods

A prospective observational study design was used to investigate the coagulation profile of patients presenting for liver

biopsy. The research was approved by the University of Cape Town Human Research Ethics Committee (ref no. 376/2015). A convenience sampling method was used to recruit participants. Patients who presented to the hepatology unit at Groote Schuur hospital for liver biopsy between August 2015 and February 2016 were approached, consented and included in the study. Blood samples were taken by venepuncture by the hepatology team. Four and a half millilitres (ml) of blood were taken into a citrated tube, mixed properly to avoid clotting and taken to the laboratory immediately. Samples were left to de-calcify for 30 minutes, then checked for clots and one millilitre of blood was activated with kaolin. The sample was re-calcified with 20 microlitres of calcium chloride. All of our samples were run within 60 minutes (within 4 hours is the acceptable time-frame to perform a TEG on a citrated sample).

Data were transcribed from the patient's notes into a Microsoft Excel® spreadsheet (Microsoft Corp, Redmond, WA USA) by the researcher. An additional 10 ml of blood was collected from each participant at the time of routine blood testing, to perform the TEG. Additional data collected from the patient included patient characteristics (age and sex), co-morbidities, blood results (full blood count, liver enzymes, INR), the working diagnosis for deranged liver enzymes and medication. The TEG was performed by a single investigator within 60 minutes of drawing the sample, which was activated by kaolin. The TEG instrument (Thrombelastograph Hemostasis Analyzer Model 5000, Haemonetics Corp, Braintree, MA, USA) is regularly calibrated. All TEG values were recorded and the CI was used to detect the overall coagulation status of each sample. Liver biopsy results were recorded once the biopsy was performed.

All data were kept in a secure file to ensure confidentiality and anonymity of the participants. Patients' names were replaced by unique identification codes known only by the researcher. Descriptive statistics were used to describe demographic variables of all blood results. Numerical data were summarised using medians and interquartile range (IQR), or means and standard deviations (SD) as appropriate. Categorical data were summarised using frequencies and percentages. Spearman's correlation and simple linear regression analysis was used to determine whether there was an association between INR and the R-time on the TEG. Statistical significance was defined as $p < 0.05$. Statistica (TIBCO Software Inc, Palo Alto, CA, USA) was used for statistical analysis.

Table 1: Demographics and laboratory results of study participants (n = 26)

Demographics:		
Male	12	(46)
Age	41	± 17
Haematology:		
Mean Hb (SD)	12.7	± 2.3
Median platelet count (IQR)	272	(225–320)
Median INR (IQR)	1.0	(1.0–1.1)
Liver function tests:		
Median bili tot (IQR)	32	(12–76)
Median bili conj (IQR)	17	(6–72)
Median AST (IQR)	94	(28–156)
Median ALT (IQR)	131	(36–216)
Median GGT (IQR)	203	(42–806)
Median ALP (IQR)	159	(75–251)

Hb = haemoglobin, g/dL; INR = international normalised ratio; bili tot = total bilirubin, mmol/L; bili conj = conjugated bilirubin, mmol/L; AST = aspartate transaminase, units/l; ALT = alanine transaminase, units/l; GGT = gamma glutamyl transferase, units/l; ALP = alkaline phosphatase, units/l.
Data are presented as n (%) unless otherwise specified.

Results

Data were collected from 28 participants over a seven-month period. Two patients were excluded from analysis due to recent Vitamin K administration. Table 1 represents the demographics and laboratory results of the study participants. Of the 26 included participants, 23 (88%) had abnormal liver function tests. The three who had normal liver function tests were known to have Hepatitis B infection. Twenty-two patients (85%) had normal platelet counts (reference range [RR] 150–450 × 109/l18), one (4%) had thrombocytopaenia, and the remaining three (12%) had thrombocytosis. The one participant with thrombocytopaenia was observed to have a normal TEG. Of those with thrombocytosis, two had hypercoagulability and one had a normal TEG.

The median value of INR among our participants was 1.0 (IQR 1–1.1), which is considered normal. Two (8%) of participants had INR values of 1.26 and 1.79, which exceeded the normal reference range (0.8–1.2). Liver biopsy results are illustrated in Figure 1. Drug or toxins were responsible for liver injury in 15 (58%) of the participants.

Thromboelastography was conducted on all participants and the TEG parameters are illustrated in Table 2. Overall, (n = 19, 73%) the TEG results in the cohort were normal. In one participant the K-time could not be measured due to their state of hypocoagulability (the TEG tracing did not reach the 20 mm amplitude required). The CI could also not be measured for this reason, as K-time is required in the CI algorithm.

The coagulability profile according to the Clotting Index is represented in Figure 2. The severely hypocoagulable patient with unmeasurable K-time is also included. Nineteen (73%) participants had normal coagulation, three (12%) were hypocoagulable and four (15%) were hypercoagulable.

The three (12%) participants who were hypocoagulable had a normal platelet count. In one of these patients, the K-time could not be measured due to the extent of the hypocoagulable state, whereas the INR was 1.0. The other two participants who were also hypocoagulable (CI −4.4 and −8.3) had INR values of 0.95.

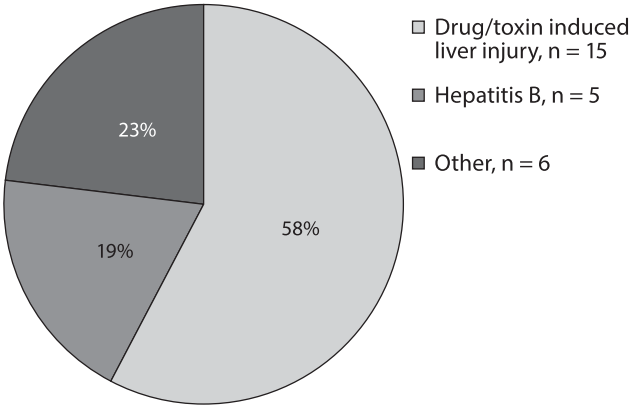

Figure 1: Liver biopsy results (n = 26).

Table 2: Coagulation profile from TEG

Factor	R-Time (2–8)	K (1–3)	Angle (55–78)	MA (51–69)	Lys30 (0–8)	CI (−3–3)
n valid	26	25	26	26	26	25
n missing	0	1	0	0	0	1
Median	5.5	1.2	71.5	65.5	0.95	1.9
IQR	(4.75–6.35)	(1.0–1.9)	(62.0–74.9)	(57.2–69.6)	(0.1–2.1)	(−0.9–2.8)

R-time = reaction time in minutes; K = kinetics time in minutes; Angle = alpha angle in degrees; MA = maximum amplitude in millimetres; LYS30 = % lysis at 30 min; CI = clotting index in number; reference ranges for each entity in brackets under column headings.

Among the four (15%) hypercoagulable participants, all were jaundiced with elevated transaminases, and two had thrombocytosis (platelet counts were 652 and 534×10^9/l). In terms of their TEG parameters: all had normal R-times, three (11%) had an increased α angle and three (11%) had an increased maximum amplitude (MA). The INR was found to have variation among these participants: one result was moderately raised (1.26); and three were normal (two were 1.0 and one was 1.2).

Figure 3 represents the relationship between R-time of the TEG and INR in the entire cohort using Spearman's correlation. There was no association between R-time of the TEG and INR (rho −0.20, $p = 0.34$).

Discussion

We investigated the coagulation profile of patients presenting for liver biopsy and found that most patients had a normal thromboelastogram. Statistical analysis also revealed that, in this cohort of 26 patients, there was no association between INR and the R-time on the TEG.

Many patients presenting for liver biopsy have a disorder of the synthetic function of the liver. This may result in the liver no longer adequately producing factors that are pro-coagulant as well as anti-coagulant.[4,6] This may cause the homeostatic balance of their coagulation to shift towards clot formation or towards bleeding.[4,7] As a result, it becomes very difficult to predict the coagulation status in any individual.[8]

The findings of this study are similar to those in previous studies, which show that most patients with mild, chronic liver disease display a normal pattern on TEG or a trend towards hypercoagulability.[3,7,9–11] Recent studies of patients with liver disease who are acutely ill or encephalopathic do not have the same coagulation profile as shown in the population we studied, and may display severe hypocoagulability.[12] Another recent study using the TEG showed hypocoagulability in patients with cirrhotic liver disease.[13] This contrasts with previous studies and highlights the complexity of liver disease, and the fact that different liver pathologies may have a significant impact on the coagulation profile. The majority of our patients had drug/toxin and Hepatitis B-induced liver injury, which may have resulted in a differing coagulation profile from those with alcoholic liver cirrhosis or biliary cirrhosis, which have been more extensively researched internationally. South Africa has a high incidence of tuberculosis and human immunodeficiency virus (HIV) infection, which results in many patients taking antiretroviral drugs and tuberculosis treatment. These drugs can cause either a direct toxic or an immune-allergic liver injury, and this is an increasing indication for liver biopsy. More than one-third of the patients in our sample were receiving anti-retrovirals or drugs used to treat tuberculosis. We believe that future studies using thromboelastography and specifically examining drug-induced liver damage will provide more insight into this population. In these patients, the coagulation profile may differ depending on the nature of the drug/toxin induced liver injury, and may also differ from the coagulation status in cirrhotic liver disease.

There have been only two previous studies examining the association between R-time and INR.[13,14] These investigators did not find a significant association between these variables, which is congruent with our results. The INR was originally introduced to monitor the effect of warfarin on the vitamin K-dependent clotting factor.s[3,6] Over the years, this test has evolved to be used as an assessment of the synthetic function of the liver, and it has been assumed that this also correlates with the coagulation status.[9] There is a growing body of evidence showing that the INR does not reliably determine coagulation status in patients with LD.[6,15] The reason for this is that it does not provide an assessment of coagulation parameters in an

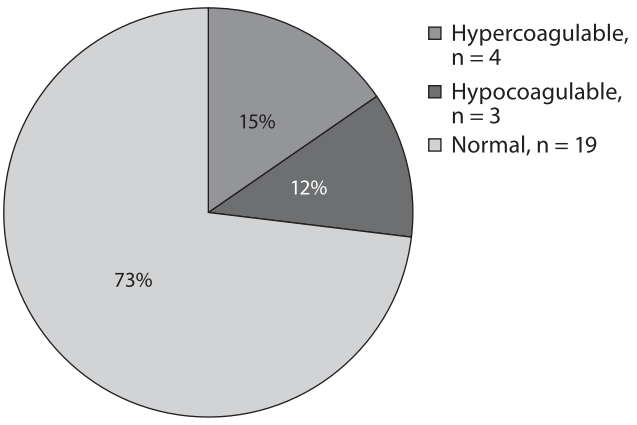

Figure 2: Coagulability profile of participants ($n = 26$).

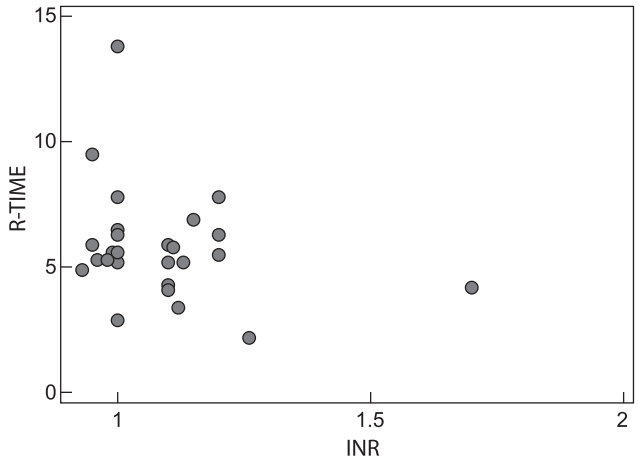

Figure 3: R-time versus INR ($n = 26$).

integrated manner, as it takes only fibrinogen and the procoagulant vitamin K-dependent clotting factors into account. In addition to this, there is evidence that INR is a poor prognosticator of bleeding risk;[6,15–17] nonetheless it is still used in many major centres both locally and internationally.[2] There is also little evidence to suggest that correction of the INR by administration of FFP has any beneficial clinical effect.[18–20]

Also noteworthy from our study was that in the three patients who were hypocoagulable on TEG, the INR results were normal. Anaesthesiologists may use the INR to decide if the patient is fit for surgery, to plan blood conservation strategies and to order blood products. These decisions become compromised when they are based on a test that has the potential to incorrectly reflect the coagulation status.

In 2016, the Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine released a report of a consensus conference entitled, 'Haemostatic balance in patients with liver cirrhosis'.[21] They state that 'current evidence does not support the use of prothrombin time values as predictors of bleeding or to monitor the effectiveness of haemostasis-modifying therapy in patients with cirrhosis'.[21] They recommend that 'the use of algorithms based on thromboelastometry/thromboelastography may facilitate targeted transfusions with haemostatic agents, such as fresh frozen plasma, in patients undergoing liver transplantation or in those with severe bleeding. However, the threshold values of these tests to target transfusion requirement need to be established in appropriate clinical trials.'[21] It is well illustrated by this consensus statement that the research community is moving away from using prothrombin time/INR to infer coagulation status in patients with LD, and is favouring the use of TEG.

There were limitations to our study. The sample size was based on available resources and time constraints, and this should therefore be regarded as a pilot study. Future studies should endeavour to include a larger cohort. The fibrinogen levels may have been raised in the hypercoagulable participants and contributed towards these results, but fibrinogen was not measured. The study was not powered to compare INR between the hypocoagulable, hypercoagulable and normal sub-groups as determined by CI.

Conclusion

Thromboelastography in liver disease is increasingly being used to assess coagulation status before liver biopsy, and to provide guidance for blood product administration. This study was congruent with other studies, showing that in patients with mild, chronic liver disease thromboelastography usually reveals a normal coagulation status. A growing body of evidence suggests that the INR is an inappropriate test to determine the coagulation status in mild liver disease. This is likely due to the fact that INR does not reflect the complexity of the coagulation system. Our pilot study also showed no association between INR and R-time and further research should be performed on a larger sample. Further research in patients with drug-induced liver injury will be of benefit in this current era of large-scale use of hepatotoxic drugs.

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Conflict of interest – None.

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