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

LR Veronese*, M Miller* and WC Spearman*

*Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa
Division of Hepatology, Department of Medicine, University of Cape Town, Cape Town, South Africa
*Corresponding author, email: lara.veronese7@gmail.com

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 and the most common contraindication to liver biopsy is a suspected bleeding diathesis. 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 risk, and the need for correction of coagulation abnormalities. 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 = 0.034). In the two participants (7%) with a raised INR (1.26 and 1.7 respectively), the TEG suggested a normal or hypocoagulable 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

Viscoelastic testing (VET), consisting of thromboelastography or rotational thromboelastometry (ROTEM), is another option in evaluating coagulation in patients undergoing liver biopsy. 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. 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, an angle and maximum amplitude (MA). The more negative the CI, the more hypocoagulable the sample, and vice versa. 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. Clinical practice is to use INR to guide correction or replacement of components with blood products. In our institution, if the INR is over 1.4, fresh frozen plasma (FFP) is given, and if the platelet count is below 100 x 10⁹/l, platelets are administered.

Most of the research that has been done on VET in mild chronic liver disease (CLD) shows a surprisingly high trend towards hypercoagulability, which is not diagnosed using conventional tests of clotting. In the current South African context, the majority of patients being considered 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
Thromboelastography in mild, chronic liver disease

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-calculated 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.

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/l, one (4%) had thrombocytopenia, and the remaining three (12%) had thrombocytosis. The one participant with thrombocytopenia 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.

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

<table>
<thead>
<tr>
<th>Demographics:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Age</td>
<td>41 ± 17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematology:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hb (SD)</td>
<td>12.7 ± 2.3</td>
</tr>
<tr>
<td>Median platelet count (IQR)</td>
<td>272 (225–320)</td>
</tr>
<tr>
<td>Median INR (IQR)</td>
<td>1.0 (1.0–1.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver function tests:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median bili tot (IQR)</td>
<td>32 (12–76)</td>
</tr>
<tr>
<td>Median bili conj (IQR)</td>
<td>17 (6–72)</td>
</tr>
<tr>
<td>Median AST (IQR)</td>
<td>94 (28–156)</td>
</tr>
<tr>
<td>Median ALT (IQR)</td>
<td>131 (36–216)</td>
</tr>
<tr>
<td>Median GGT (IQR)</td>
<td>203 (42–806)</td>
</tr>
<tr>
<td>Median ALP (IQR)</td>
<td>159 (75–251)</td>
</tr>
</tbody>
</table>

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.
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. As a result, this 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.3,9–11 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 antiretrovirals 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 factors.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

Table 2: Coagulation profile from TEG

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

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; Cl = clotting index in number; reference ranges for each entity in brackets under column headings.
integrated manner, as it takes only fibrinogen and the pro-
coagulant vitamin K-dependent clotting factors into account.
In addition to this, there is evidence that INR is a poor prognos-
ticator of bleeding risk.\textsuperscript{15–17} Nonetheless it is still used in many
major centres both locally and internationally.\textsuperscript{2} There is also little
evidence to suggest that correction of the INR by administration
of FFP has any beneficial clinical effect.\textsuperscript{18–20}

Also noteworthy from our study was that in the three patients
who were hypercoagulable 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 compro-
mised 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.’\textsuperscript{21} They state that ‘current evidence
does not support the use of prothrombin time values as predic-
tors of bleeding or to monitor the effectiveness of haemostasis-
modifying therapy in patients with cirrhosis.’\textsuperscript{22} 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 bleed-
ing. However, the threshold values of these tests to target trans-
fusion requirement need to be established in appropriate clinical
trials.’\textsuperscript{23} 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 hypercoagulable, 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 con-
gruent 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 coagu-
lation 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.

Acknowledgements – The authors would like to thank Bruce
Biccard and Michael James for assistance with statistical analysis,
and Margot Flint and Lizel Loo for assistance with data collec-
tion. We also thank Nelliswa Gogela and the Liver Unit for their
exceptional effort with data collection.

Funding – No funding was received for this study.

Conflict of interest – None.

Financial statement – Funding was made possible through the
University of Cape Town Anaesthetic Department Research
Fund.

Author contributions – L Veronese: substantial contributions to
conception and design, acquisition of data, interpretation of
data, drafting and revising article. M Miller: substantial con-
tributions to conception and design, revising of article, final
approval. W Spearman: revising of article for important intellec-
tual content and language, final approval

References
1. Caldwell S, Northup PG. Bleeding complication with liver biopsy: is it
doi.org/10.1016/j.cgh.2010.06.010
2. Ewe K. Bleeding after liver biopsy does not correlate with indices of
org/10.1007/BF01313579
3. Caldwell SH, Hoffman M, Lismam T, et al. Coagulation disorders and
hemostasis in liver disease: pathophysiology and critical assessment
doi.org/10.1002/hep.21303
thrombosis in end-stage liver disease and liver transplantation.
5. Karon BS. Why is everyone so excited about thromboelastography
ccaa.2014.05.013
6. Tripodi A, Caldwell SH, Hoffman M, et al. Review article: the pro-
thrombin time test as a measure of bleeding risk and prognosis in
org/10.1111/j.1365-2036.2007.03369.x
7. Krzanicki D, Sugavanam A, Mallett S. Intraoperative hypercoagulabil-
ity during liver transplantation as demonstrated by thromboelasto-
23668
8. Lismam T, Porte RJ. Rebalanced hemostasis in patients with liver
disease: evidence and clinical consequences. Blood. 2010;116
(6):878–85. https://doi.org/10.1182/blood-2010-02-261891
9. Mallett SV, Chowdry P, Burroughs AK. Clinical utility of viscoelastic
tests of coagulation in patients with liver disease. Liver Int. 2013;33
with primary biliary cirrhosis and primary sclerosing cholangitis evalu-
doi.org/10.1016/S0168-8278(97)80420-5
11. Tripodi A, Primignani M, Chantarangkul V, et al. The coagulopathy of
cirrhosis assessed by thromboelastometry and its correlation with
conventional coagulation parameters. Thromb Res. 2009;124
patients with severe chronic liver disease: insights from thromboelas-
2016.10.030
liver transplantation: a comparison of the thromboelastometry analy-
zer, the thromboelastogram, and conventional coagulation tests. J
1053/j.jvca.2006.01.016
15. Townsend JC, Heard R, Powers ER, et al. Usefulness of international
normalized ratio to predict bleeding complications in patients with
end-stage liver disease who undergo cardiac catheterization. Am J


Received: 2-01-2018 Accepted: 3-08-2018