Platelet function as measured by the Thromboelastrogram in End Stage Renal Failure patients presenting for surgery – a pilot study.

David Peter Wels

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine

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DECLARATION

I, David Peter Wels declare that this thesis is my own work. It is submitted for the admission to the degree of Master of Medicine by the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____________________
7th day of October, 2011
PRESENTATIONS ARISING FROM THIS STUDY

Poster presentation at annual South African Society of Anaesthesiologists congress

February 27 – 2 March 2011

Awarded the Discovery Prize for best Poster exhibited at the Congress.
ABSTRACT

Chronic renal failure patients develop a coagulopathy primarily due to reversible platelet dysfunction. This coagulopathy makes certain anaesthetic techniques and procedures such as neuraxial anaesthesia and invasive line placement possibly contra-indicated or risky. There is no evidence to suggest that the degree of platelet dysfunction is proportional to the degree of renal dysfunction. In this research project the platelet function of 39 end stage renal failure patients, who received regular dialysis and who presented to theatre for vascular access, was assessed using the thromboelastogram. A bleeding time was also performed pre-operatively. A linear regression model was used to determine if the bleeding time, plasma urea, plasma creatinine or creatinine clearance could predict maximum amplitude (and therefore clot strength) on the thromboelastogram. No such regression could be found. The clinical implication of this result is that there exists no "safe" plasma urea or creatinine, below which it is safe to perform procedures which are contra-indicated in coagulopathies. The degree of renal dysfunction did not predict the degree of platelet dysfunction. Since dialysis reverses the platelet dysfunction, the question that should be asked before performing such a procedure is not "how severe is the renal dysfunction?" but rather "has the patient been receiving regular dialysis?"
ACKNOWLEDGEMENTS

I would like to acknowledge Anne Barker from Haemoscope, who spent many Saturdays training me to use the TEG® and always went the extra mile to provide me with reagents. Your willingness and friendliness will be remembered.

The Donald Gordon Medical centre very generously paid for all reagents and consumables.

I was fortunate enough to have Prof. Christina Lundgren as my supervisor, whose insight into research is invaluable. Thank you for supervising my study despite your already impossible schedule.

Lastly I would like to thank my partner and best friend for his support and encouragement.
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1.1 Introduction

Chronic renal failure patients are at greater risk for bleeding. The cause of the bleeding is multifactorial and includes platelet dysfunction\textsuperscript{1}, alterations in the fibrinolytic system, and vascular abnormalities\textsuperscript{2}.

This problem is further compounded by the fact that many of these patients receive haemodialysis, which by itself can activate platelets, coagulation and fibrinolysis\textsuperscript{3-4}. The process of haemodialysis affects haemostasis due to the nature of the composition of the circuit, contact with the dialysis membrane, altered rheology of blood in the circuit as well as any additional anticoagulants\textsuperscript{5}.

The major contributing factor to the bleeding diathesis in chronic renal failure patients remains platelet dysfunction\textsuperscript{6-8}. There are many methods to measure platelet function. Similarly they all measure the same end point, i.e. clot formation. Older techniques such as bleeding times and absolute platelet counts are no longer utilized alone due to poor specificity and sensitivity\textsuperscript{9}. Newer technologies for measuring platelet aggregation have become available. One of these is the thromboelastogram (TEG®). The thromboelastogram provides information about the entire coagulation system in a graphic format, which not only gives information about clot formation but also about clot
lysis. Information about the different components of coagulation can be extrapolated from the graphic data including platelets, fibrin, thrombin and other clotting factors. The maximal amplitude (MA) of the graph is an indication of platelet and fibrin function, i.e. clot integrity\textsuperscript{10}.

In anaesthesia certain procedures are contra-indicated if the patient has a coagulopathy. This includes the platelet dysfunction associated with chronic renal failure. These procedures include neuraxial anaesthesia such as spinals and epidurals, certain nerve plexus blocks and placement of invasive lines such as central venous catheters. Chronic renal failure patients are also at higher risk for post-operative bleeding complications\textsuperscript{11}.

1.2 Background to the study

Patients with renal dysfunction pose an interesting dilemma to the anaesthetist. It is well known that their platelets are dysfunctional, but what is not known is at which point during the renal failure the platelet dysfunction becomes clinically significant. Traditionally anaesthetists have used arbitrary “cut-off” values for plasma urea, above which it is deemed unsafe to perform invasive anaesthetic techniques such as neuraxial anaesthesia. This arbitrary value varies greatly between anaesthetists and has no scientific evidence to support it.
1.3 Problem Statement

Anaesthetic interventions may be contra-indicated in chronic renal failure patients due to the presence of a coagulopathy. There is no evidence to suggest that this dysfunction can be quantified by using the TEG®, or that this dysfunction is proportional to the renal failure.

1.4 Purpose of the study

1.4.1 Aim

The aim of this study was to investigate whether patients with end stage renal failure, presenting for surgery, had a coagulopathy in the form of platelet dysfunction.

1.4.2 Objectives

1.4.2.1 Primary Objective

The primary objective of this study was to confirm and quantify the presence of platelet dysfunction in patients with chronic renal failure presenting for surgery.

1.4.2.2 Secondary Objective

The secondary objective of this study was to describe a correlation, if any, between the severity of the renal dysfunction and the platelet dysfunction.
1.5 Research Assumptions

The following definitions were used within the scope of this study:

- **Chronic Renal Failure**: “Kidney damage for more than three months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) manifest by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging testing OR GFR less than 60 ml/min/1.73m² for more than three months, with or without kidney damage.”

- **End stage renal disease**: “GFR of less than 15 ml/min/1.73m² or patients requiring chronic dialysis (also termed stage five chronic renal disease).”

- **Uraemic bleeding**: Any bleeding due to the coagulopathy of chronic renal disease.

- **Coagulopathy**: a disease affecting the coagulability of blood; that is the ability of blood to clot.

- **Thromboelastography**: A laboratory investigation where a small whole blood sample is allowed to clot in a cup. A pin, suspended and rotated in the cup, interacts with the clot formed. The interaction with the clot is transduced to an electrical signal which is analysed. The data is presented in a graphic format, the thromboelastogram.

- **Glomerular Filtration Rate (GFR)**: Amount of fluid filtered at the glomerulus in the kidney measured in ml/min. GFR is an indication of kidney function. It is calculated using the Cockcroft-Gault formula which is as follows:
\[ eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}} \]

\[ \text{(Constant} = 1.23 \text{ in males and } 1.04 \text{ in females)} \]

1.6 Demarcation of the study

1.6.1 Chris Hani Baragwanath Hospital

The study was conducted in the JD Allen theatre complex of the Chris Hani Baragwanath hospital.

1.6.2 Charlotte Maxeke Johannesburg Academic Hospital

The study was conducted in the main theatre complex of the Charlotte Maxeke Johannesburg Academic Hospital.

1.7 Ethics

1.7.1 Approval was obtained from the University of the Witwatersrand Human Research Ethics Committee on 29 August 2008, Ref R14/49 Wels (Appendix B)

1.7.2 Permission was granted from management of the Chris Hani Baraqwanath Hospital and Charlotte Maxeke Johannesburg Academic Hospital respectively.
1.7.3 Informed consent was obtained from all patients after explaining the study to them. This consent was recorded on a consent form (Appendix C).

1.7.4 Approval of the study was granted by the Post Graduate Committee (Appendix D).

The research was conducted in keeping with the principles of the Declaration of Helsinki (2009)\textsuperscript{14}.

1.8 Summary of Methodology

This study is a contextual, prospective, descriptive study. As no other research has been conducted on this topic it is a small pilot study.

A Sample size of at least thirty was needed. The sampling was done according to a consecutive sampling method\textsuperscript{15}.

To be included in the study the patients had to be adults, 18 years and older, in a capacity to give informed consent. They were all end stage renal failure patients classified as grade five chronic kidney disease and enrolled on the chronic haemodialysis program at CMJAH or Chris Hani Baragwanath Hospital. Patients were booked for theatre for vascular access and were dialysed in the 48 hour period prior to surgery. Patients had a full blood count, plasma urea and creatinine performed prior to surgery.
Any patient with a diagnosed and confirmed bleeding disorder not related to renal failure or on any anticoagulation therapy was excluded from the study.

Patients were recruited from the Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Hospital.

Once anaesthetised and before the commencement of surgery the principal investigator sampled venous blood from the patient and performed a TEG® on the blood sample. The principal investigator also performed a bleeding time. The patient’s name, blood investigation results, TEG®, and the bleeding time were recorded on a data sheet.

Data was summarized using descriptive statistics. This includes mean, standard deviation and 95% confidence interval. Regression modeling was explored along ordinary least squares multiple linear regression.

1.8 Clinical importance of the Study

The study aimed to confirm the presence of platelet dysfunction in chronic renal failure patients. If this platelet dysfunction could be predicted, guidelines and precautions can be put into place to limit risk from bleeding or blood loss in renal failure patients coming to theatre.
1.9 Validity and Reliability

It was not necessary to standardize the general anaesthetics used in this study as none of the anaesthetic techniques affected coagulation. The principal investigator received training on calibration and test running of the TEG® by a certified Laboratory Technician from the manufacturer. The TEG® at both hospitals were calibrated daily by the principal investigator with control tests provided by the manufacturer. All TEG® tests were performed by the principal investigator as per manufacturer instructions. All reagents were new and not expired and stored as per manufacturer requirements. The principal investigator personally performed all bleeding times as per standard protocol.

1.10 Limitations of the Study

Patient numbers were a limiting factor as only two or three patients received surgery per vascular access list, and the lists were not regular. This study is contextual and there was no randomization of patients. This is a pilot study but was deemed necessary to determine if further investigation is warranted.

1.11 Research Report Outline

This research report will comprise the following chapters:

Chapter One: In this chapter an introduction and overview of the research project is discussed, including the problem statement and a summary of the research methodology.
Chapter Two: This chapter looks at currently available literature which deals with this research topic.

Chapter Three: In this chapter the research methodology is discussed in more detail.

Chapter Four: The data is presented and described.

Chapter Five: In the final chapter the analysed data is discussed. Conclusions are drawn and recommendations made.
2.1 Introduction

Chronic renal failure patients are at greater risk for bleeding. The cause of the bleeding is multi-factorial and includes platelet dysfunction\(^1\), alterations in the fibrinolytic system and vascular abnormalities\(^2\).

2.2 Normal Coagulation

2.2.1 Initiation of Coagulation

The major stimulus to trigger coagulation is blood vessel wall damage. Any damage, whether mechanical, chemical or electrical results in the activation of the endothelium and the expression of P-selectin on the cell surface\(^16\). This vessel damage also activates platelets, which also express P-selectin on their surfaces. These P-selectin molecules bind to to P-selectin glycoprotein ligands-1 (PSGL-1), which occur on monocytes and neutrophils\(^17\). Once bound this promotes the “rolling” of platelets and leukocytes against the wall of the damaged vessel\(^18\).

Von Willebrand factor (vWF) is a protein contained in the Weibel-Palade bodies of endothelial cells, as well as in the alpha granules of platelets. When released after
vessel damage it binds to glycoprotein Ib (GPIb) on the surface of platelets and exposed subendothelial connective tissue. It promotes the adhesion of platelets at the site of injury\textsuperscript{19}. Von Willebrand factor also binds to the Glycoprotein IIbIIIa (GPIIbIIIa) receptor on platelets enhancing platelet aggregation.

Tissue factor is a glycoprotein present in endothelial cells. When vessel damage occurs, this tissue factor is exposed. Tissue factor has a very strong affinity for factor VII. Once bound, tissue factor and factor VII form an activated tissue factor, factor VIIa complex, which has enhanced catalytic properties. The tissue factor-VIIa complex activates factor IX to IXa and X to Xa. Factor Xa activates factor V which has been released from the alpha granules\textsuperscript{20-21}. Prothrombin, which is bound to the GPIIbIIIa receptor on the activated platelet, is converted to thrombin by Xa. Note that only small quantities of thrombin are formed in this fashion. The majority of thrombin is produced during the amplification phase\textsuperscript{22}.

\textbf{Figure 2.1 Platelet Aggregation}
2.2.2 Amplification phase

The small amount of thrombin produced in the initiation phase activates more platelets, factor V and factor XI (Factor XI is bound to the GPIb receptor of activated platelets). Xla activates IX to IXa. Both the IXa produced here and the IXa generated from the tissue factor-VII complex diffuse to the surface of activated platelets and bind to the membrane\textsuperscript{23}. Von Willebrand factor is also bound to GPIb/IXa. In normal plasma vWF is bound to VIII. When thrombin is produced it separates the two and activates VIII to VIIIa. The VIIIa binds to GPIb/IXa complex and in the presence of calcium activates additional factor X\textsuperscript{21}.

![Figure 2.2 Clotting Cascade](image)
2.2.3 Propagation

The VIIIa/IXa complex is called the tenase complex. This tenase complex, together with calcium ions, produces large amounts of Xa. Xa together with Va and calcium form the prothrombinase complex that produces the thrombin needed to convert fibrinogen to fibrin. Thrombin also catalyzes its own production by activating factors V, VIII and XI\textsuperscript{21}.

2.3 Pathophysiology of coagulopathy in chronic renal failure

The pathophysiology of uraemic bleeding is multifactorial. Chronic renal failure patients are often older and have many co-morbidities such as hypertension and atherosclerotic vascular disease\textsuperscript{24}. As such they are often on anti-platelet drugs and anticoagulants.

Sohal et al\textsuperscript{11} grouped the mechanisms of uraemic bleeding into five main categories.

i.) Defective interaction of platelets with vessel walls.

ii.) Defective platelet secretion.

iii.) Defective platelet aggregation.

iv.) Anaemia.

v.) Other factors.

Zwangiga et al\textsuperscript{25} demonstrated adhesion defects in platelets at high shear rates in chronic renal failure patients. Since von Willebrand Factor (vWF) levels are normal or raised in chronic renal failure patients the there appears to be a qualitative rather than a
quantitative dysfunction between vWF and platelet glycoproteins\textsuperscript{26}. Chronic renal failure patients also have higher prostacyclin levels, which inhibit platelet aggregation\textsuperscript{27}, and higher nitric oxide (NO) levels\textsuperscript{28} which cause vasodilatation and also inhibit platelet function.

Deficient stores of Adenosine Diphosphate (ADP) and serotonin, as well as defective production of thromboxane A2 (TXA2) have all been described in chronic renal failure patients\textsuperscript{29-31}.

Moal et al\textsuperscript{32} found that resting GPIIb\ll{III}a expression was normal in chronic renal failure patients, hence the abnormal aggregation due to a qualitative rather than quantitative defect of this receptor. As haemodialysis improves fibrinogen binding to GPIIb\ll{III}a, it appears as if a dialyzable toxin accounts for this inhibition. Kaplan et al\textsuperscript{33} made a detailed quantitative study of these uraemic toxins which he calls “middle molecules”.

Fibrinogen Fragments (FF) are among these molecules and implicated by Kaplan as the substance responsible for inhibiting platelet aggregation. Thekkedath et al\textsuperscript{6} demonstrated that these FF do in fact inhibit platelet aggregation by competing with fibrinogen at the GPIIb\ll{III}a receptor, and that this inhibition is reversible by removing the FF by haemodialysis.

Anaemia is common in chronic renal failure patients\textsuperscript{34}. In normal rheological flow within blood vessels the bulk of the red cell mass travels in the centre of the lumen in a laminar fashion. This displaces plasma and platelets, which travel in close proximity to the endothelium, promoting interactions between the platelets and vessel walls. Red cells also produce ADP and TXA2 which enhance platelet function\textsuperscript{35-36}.
Other factors which play a role in uraemic bleeding include drugs and haemodialysis. Due to co-morbidities chronic renal failure patients are often on anti-platelet drugs or anticoagulants. Chronic renal failure patients are at an increased risk of bleeding compared with normal patients taking these drugs\textsuperscript{37-38}.

Finally the process of haemodialysis activates platelets, coagulation and fibrinolysis, and often anticoagulants are added to the circuit\textsuperscript{3-5}. This may also contribute to the coagulopathy.

2.4 Tests for platelet function

2.4.1 Traditional Methods

The platelet count remains the first line test of platelet function. Platelets were traditionally counted manually but today automated cell counters are used. Automated cell counters use optical or flow cytometric methods to count platelets. Optical counters identify platelets by their light scattering properties or fluorescence after the addition of dye\textsuperscript{39-40}. Flow cytometric methods identify platelets by fluorescent monoclonal antibodies to antigens on the platelet membranes\textsuperscript{41}.

The in vivo bleeding time was first described by Duke in 1912 and was the first in vivo test of platelet function. It is poorly reproducible, invasive, insensitive and time consuming\textsuperscript{42}. However the bleeding time is still used as a first line screening test for severe haemostatic defects like von Willebrand's disease\textsuperscript{43}. The clear advantage of the
bleeding time is that it studies natural haemostasis and does not require expensive equipment.

2.4.2 Platelet aggregometry

Turbidmometric platelet aggregometry was developed in the 1960’s and became the gold standard to test platelet function. Platelet rich plasma is stirred in a cuvette between a light source and a photocell. An agonist such as ADP is added and the platelets aggregate. The resultant increased transmission in light is used as a function of platelet function. Today aggregometry is measured by electrical impedance of whole blood or by light scattering methods.

2.4.3 In vitro platelet function simulation

Platelet aggregometry does not mimic physiological processes in vivo. Newer tests attempt to simulate the process of platelet activation and aggregation that occur in vivo after vessel wall damage.
2.4.3.1 Clot Signature Analyser

This technique involves punching holes into a tube that contains non anti-coagulated blood and results in the formation of a primary haemostatic plug. Alternatively collagen is added to the tube which results in thrombus formation\(^{48}\).

2.4.3.2 Platelet Function Analyser (PFA)

Platelets in citrated whole blood are exposed to high shear conditions within capillary tubes. The flow rate is monitored as platelets form a plug within the centre of a membrane coated with collagen and ADP or adrenaline. The test parameter is called the closure time (CT)\(^{49}\).

2.4.3.3 Cone Platelet Analyser

This test is based upon the adhesion of platelets to an extra cellular matrix under flow conditions. It consists of a cone and plate device in which a blood sample is exposed to a plastic plate under arterial flow conditions. Platelet adhesion and aggregation on the surface of the plate are recorded by an image analyser\(^{50}\).
2.4.3.4 Measuring physical properties of the clot

Physical properties of a clot include formation, retraction and lysis. Retraction and lysis can be measured by calculating the differences in volumes pre and post clotting.

2.4.3.5 Thromboelastography

Thromboelastography was developed in 1948 as a research tool, but rediscovered in the 1980’s. The TEG® device monitors the interaction of platelets within the fibrin mesh of the clot during formation and lysis. The device consists of a cylindrical cup that holds a whole blood sample at 37°C and is oscillated in a rotation cycle of 10 seconds. As the clot forms the torque of the rotating cup is transmitted to an immersed pin. The pin rotation is converted to an electrical signal via a transducer. The strength of the developing clot increases the magnitude of the output, and conversely decreases during clot lysis\textsuperscript{51-52}.

The TEG® gives a graphic representation (fig 2.3) of the changes in viscoelasticity at all stages of the developing and resolving clot. The parameters include the reaction time (R Value, an indication of factor activation and initial fibrin formation), the alpha angle and k value (an indication of the speed of clot formation), the maximal amplitude (MA, an indication of platelet aggregation and clot integrity) and the clot lysis (CL, an indication of clot breakdown)\textsuperscript{53}. 
Figure 2.3: A typical Thromboelastogram

Figure 2.4: The “cup and pin” of the TEG®
Thromboelastography can be performed on different blood samples. Native blood (non-activated blood) can be placed directly into the cup. This however requires that sampled blood be placed directly into the cup with as little delay as possible. Activated blood (using Celite or Kaolin particles) clots faster as these particles activate factor XII, thus giving a thromboelastograph result in less time than native blood. To facilitate transport citrated blood can be used. The sample needs to be recalcified before performing the test. This is done by adding 20 µl of Calcium Chloride to 340 µl citrated blood in the 360 µl cup. Heparinase is an enzyme which cleaves heparin into inactive fragments without affecting the other components of coagulation. TEG® cups impregnated with heparinase are available to determine if the coagulation status is as a result of administered heparin\textsuperscript{54}. 

Figure 2.5: Interpretation of TEG® Graphs
2.4.3.5.1 Clinical application of Thromboelastography

Thromboelastography is currently used in Liver transplantation, Cardiopulmonary Bypass, for the assessment of blood product administration, specifically in Obstetric and Trauma surgery, and to assess coagulation before regional anaesthesia. It can also be applied to monitor the efficacy of anticoagulant and antiplatelet drugs\textsuperscript{54}.
CHAPTER 3

RESEARCH METHODOLOGY

3.1 Introduction

Chronic renal failure patients are at greater risk for bleeding. The cause of the bleeding is multi factorial and includes platelet dysfunction\(^1\), alterations in the fibrinolytic system, and vascular abnormalities\(^2\).

In anaesthesia certain procedures are contra-indicated if the patient has a coagulopathy, including chronic renal failure platelet dysfunction. These include neuraxial anaesthesia such as spinals and epidurals, certain nerve plexus blocks and the placing of invasive lines such as central venous catheters. Chronic renal failure patients are also at higher risk for post operative bleeding complications\(^{11}\).

3.2 Study Design

This is a contextual, prospective, descriptive pilot study. Prospective, as informed consent was obtained prior to data collection, and descriptive as the clotting profile of chronic renal failure patients was examined and described. Since no other research has been conducted on this topic it is a small pilot study.
3.3 Study population

Patients were selected from elective vascular access lists at Chris Hani Baragwanath Hospital and Charlotte Maxeke Johannesburg Academic Hospital. All patients were on the chronic dialysis program at the respective hospitals.

3.4 Study Sample

This pilot study set out to determine the relationship between the maximum amplitude from the TEG® and parameters from laboratory investigations i.e. platelet count, creatinine clearance and a bedside bleeding time.

For a regression study at least 10 subjects are included for each regressor or variable of interest. Since it was very likely that not all predictor variables under study would contribute significantly to the regression line of interest a sample size of at least 30 was required.

The sampling was done according to a consecutive sampling method\textsuperscript{15}.

3.5 Study Period

The study was conducted during the period from October 2008 to March 2010.
3.6 Inclusion criteria

- Adult patients, 18 years and older, in a capacity to give informed consent.
- End stage renal failure patients classified as grade five chronic kidney disease by international convention.
- Patients had to be receiving chronic haemodialysis at the Charlotte Maxeke Johannesburg Academic Hospital or Chris Hani Baragwanath Hospital.
- Patients had to be coming to theatre for vascular access (creation of an arterio-venous fistula or insertion of a permanent indwelling catheter).
- Patients had to have been dialysed in the 48 hour period prior to surgery.
- Patients had to have a full blood count, plasma urea and creatinine performed prior to surgery.

3.7 Exclusion criteria

- Any patient with a diagnosed and confirmed bleeding disorder not related to renal failure.
- Any patient on anticoagulation therapy other than heparin used during dialysis.
- Any patient less than 18 years of age, or greater than 18 years of age but unable to give informed consent.

3.8 Data collection

Patients were recruited from the Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Hospital.
Patients booked for elective vascular access surgery (Permanent Catheter insertion or Arterio-venous fistulae creation) were approached by the principal investigator and interviewed. They were informed about the study and invited to participate provided they met all inclusion criteria.

After agreeing to participate, and a full explanation of the requirements, an informed consent form was signed by the patient and the principal investigator. They were allowed to withdraw from the study at any time.

Pre-operative blood investigations as per inclusion criteria were taken on the day before surgery by the Dialysis Unit staff when the patients presented for dialysis.

Once in theatre and anaesthetized, before the commencement of surgery, the principal investigator sampled venous blood from the patient and performed a TEG® of the blood sample. The principal investigator also performed a bleeding time. The principal investigator chose to perform a bleeding time together with the TEG® to obtain a full evaluation of the patients platelet function and to correlate the findings of the two tests.

The patient’s name, blood investigation results, the TEG®, and the bleeding time were recorded on a data sheet.
3.9 Data Analysis

Data were summarized using descriptive statistics e.g. mean standard deviation and 95% confidence interval. Correlation matrices and regression modeling were explored along ordinary least squares multiple linear regression with the assistance of a biostatistician. Data were analysed using Statistica version 9.1.

3.10 Validity and Reliability

It was not necessary to standardize the general anaesthetics used in this study as none of the anaesthetic techniques affected coagulation. The principal investigator received training on calibration and TEG® test running by a certified Laboratory Technician from the manufacturer. The TEG® at both hospitals was calibrated daily by the principal investigator with control tests provided by the manufacturer. All TEG® tests were performed as per manufacturer instructions. All reagents were new and not expired and stored as per manufacturer requirements. The principal investigator performed all bleeding times as per standard protocol.

3.11 Funding

Both hospital sites had fully functional TEG® machines. The consumables and disposables (cups, pins, reagents and disposable pipette tips) were all generously paid for by the Wits Donald Gordon Medical Centre.
CHAPTER 4

RESULTS AND STATISTICAL ANALYSIS

4.1 Introduction

In this chapter the results of the patient’s laboratory investigations i.e. Full blood count (haemoglobin and platelets), urea and creatinine (as well as calculated GFR Rate using the Cockgraft-Gault formula) and the results of the bedside tests i.e. the bleeding time and the Thromboelastogram are described using descriptive statistics. The results are analyzed to determine if the GFR can predict platelet function (MA on Thromboelastogram).

4.2 Descriptive Statistics of Laboratory and Bedside test results

Descriptive statistics are used to describe the data collected in table 4.1. Thirty-nine patients were enrolled in the study. Fifteen of the 39 patients were male. Only two patients had abnormal platelet counts. The GFR was calculated using the Cockgraft-Gault formula. This formula incorporates serum creatinine, age, weight and sex (see research assumptions chapter one for formula).

Thirteen patients had MA values greater than 69mm, which implies a hypercoagulable state. Only two of the 39 patients had MA values less than 51mm. These two patients also had prolonged Reaction times (R value) which indicate a hypocoagulable state.
<table>
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<td>Age (years)</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>38% Male / 62% Female</td>
</tr>
<tr>
<td>Haemoglobin (Hb) (g/dl)</td>
<td>10.2</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(14.3 – 18.3)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>212</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(137 – 373)</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>14.2</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(2.6 – 7.0)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>504</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(60 – 120)</td>
</tr>
<tr>
<td>Glomerular Filtration Rate (ml/min)</td>
<td>14.3</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(90 – 140)</td>
</tr>
<tr>
<td>Bleeding Time (BT) (min)</td>
<td>10</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(0 – 9)</td>
</tr>
<tr>
<td>R Value (min)</td>
<td>7.4</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(2 – 8)</td>
</tr>
<tr>
<td>K Value (min)</td>
<td>1.3</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(1 – 3)</td>
</tr>
<tr>
<td>Alpha Angle (degrees)</td>
<td>72</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(55 – 78)</td>
</tr>
<tr>
<td>Maximum Amplitude (MA) (mm)</td>
<td>64</td>
</tr>
<tr>
<td>Median and Range</td>
<td>(51 – 69)</td>
</tr>
</tbody>
</table>
4.3 Statistical Analysis

A correlation study of the variables was performed and presented in table 4.2. It is clear from the p values (those less than 0.05 being statistically significant) that only two variables correlate with the MA, namely the haemoglobin and the platelet count. The GFR showed no correlation to the MA. Patient 38 was excluded because of missing data as the patient’s bleeding time was undetermined (the patient failed to clot in the time allotted).

Table 4.2 Correlation Matrix of the Data

<table>
<thead>
<tr>
<th></th>
<th>Hb</th>
<th>Platelet</th>
<th>Urea</th>
<th>Creat</th>
<th>BT</th>
<th>R</th>
<th>K</th>
<th>α</th>
<th>MA</th>
<th>GFR</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>1.0000</td>
<td>-0.3687</td>
<td>-0.1579</td>
<td>-0.0957</td>
<td>-0.0692</td>
<td>0.3514</td>
<td>0.4549</td>
<td>-0.1301</td>
<td>-0.4433</td>
<td>0.1084</td>
<td>-0.2854</td>
</tr>
<tr>
<td>p</td>
<td>---</td>
<td>p=0.023</td>
<td>p=0.344</td>
<td>p=0.568</td>
<td>p=0.680</td>
<td>p=0.030</td>
<td>p=0.004</td>
<td>p=0.436</td>
<td>p=0.005</td>
<td>p=0.517</td>
<td>p=0.082</td>
</tr>
<tr>
<td>Platelets</td>
<td>-0.3687</td>
<td>1.0000</td>
<td>0.2031</td>
<td>0.0771</td>
<td>0.0896</td>
<td>0.0111</td>
<td>-0.5636</td>
<td>0.3974</td>
<td>0.5904</td>
<td>0.0988</td>
<td>-0.774</td>
</tr>
<tr>
<td>p</td>
<td>p=0.023</td>
<td>p=---</td>
<td>p=0.221</td>
<td>p=0.645</td>
<td>p=0.593</td>
<td>p=0.947</td>
<td>p=0.000</td>
<td>p=0.013</td>
<td>p=0.000</td>
<td>p=0.555</td>
<td>p=0.644</td>
</tr>
<tr>
<td>Urea</td>
<td>-0.1579</td>
<td>0.2031</td>
<td>1.0000</td>
<td>0.7734</td>
<td>0.4271</td>
<td>0.2409</td>
<td>-0.0153</td>
<td>0.1363</td>
<td>0.1297</td>
<td>-0.5100</td>
<td>0.0544</td>
</tr>
<tr>
<td>p</td>
<td>p=0.344</td>
<td>p=0.221</td>
<td>p=---</td>
<td>p=0.000</td>
<td>p=0.007</td>
<td>p=0.145</td>
<td>p=0.927</td>
<td>p=0.414</td>
<td>p=0.438</td>
<td>p=0.001</td>
<td>p=0.746</td>
</tr>
<tr>
<td>Creat</td>
<td>-0.0957</td>
<td>0.0771</td>
<td>0.7734</td>
<td>1.0000</td>
<td>0.3146</td>
<td>0.2624</td>
<td>0.0796</td>
<td>-0.0022</td>
<td>0.0245</td>
<td>-0.6304</td>
<td>0.1319</td>
</tr>
<tr>
<td>p</td>
<td>p=0.568</td>
<td>p=0.645</td>
<td>p=0.000</td>
<td>p=---</td>
<td>p=0.054</td>
<td>p=0.875</td>
<td>p=0.635</td>
<td>p=0.990</td>
<td>p=0.884</td>
<td>p=0.000</td>
<td>p=0.430</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>-0.0692</td>
<td>0.0896</td>
<td>0.4271</td>
<td>0.3146</td>
<td>1.0000</td>
<td>0.1365</td>
<td>-0.0222</td>
<td>0.1411</td>
<td>0.1644</td>
<td>-0.1577</td>
<td>0.0044</td>
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<tr>
<td>p</td>
<td>p=0.680</td>
<td>p=0.593</td>
<td>p=0.007</td>
<td>p=0.054</td>
<td>p=---</td>
<td>p=0.414</td>
<td>p=0.895</td>
<td>p=0.398</td>
<td>p=0.324</td>
<td>p=0.344</td>
<td>p=0.979</td>
</tr>
<tr>
<td>R value</td>
<td>0.3514</td>
<td>0.1111</td>
<td>0.2409</td>
<td>0.0264</td>
<td>0.1365</td>
<td>1.0000</td>
<td>0.4659</td>
<td>-0.1164</td>
<td>-0.3685</td>
<td>-0.0946</td>
<td>-0.2780</td>
</tr>
<tr>
<td>p</td>
<td>p=0.030</td>
<td>p=0.947</td>
<td>p=0.145</td>
<td>p=0.875</td>
<td>p=0.414</td>
<td>p=---</td>
<td>p=0.003</td>
<td>p=0.486</td>
<td>p=0.023</td>
<td>p=0.572</td>
<td>p=0.091</td>
</tr>
<tr>
<td>K value</td>
<td>0.4549</td>
<td>-0.5636</td>
<td>-0.0153</td>
<td>0.0796</td>
<td>-0.0222</td>
<td>0.4659</td>
<td>1.0000</td>
<td>-0.7088</td>
<td>-0.6900</td>
<td>-0.0855</td>
<td>0.0846</td>
</tr>
<tr>
<td>p</td>
<td>p=0.004</td>
<td>p=0.000</td>
<td>p=0.927</td>
<td>p=0.635</td>
<td>p=0.895</td>
<td>p=0.003</td>
<td>p=---</td>
<td>p=0.000</td>
<td>p=0.000</td>
<td>p=0.610</td>
<td>p=0.613</td>
</tr>
<tr>
<td>a angle</td>
<td>-0.1301</td>
<td>0.3974</td>
<td>0.1363</td>
<td>-0.0222</td>
<td>0.1411</td>
<td>-0.1164</td>
<td>-0.7088</td>
<td>1.0000</td>
<td>0.4282</td>
<td>0.0923</td>
<td>-2.092</td>
</tr>
<tr>
<td>p</td>
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<td>p=0.013</td>
<td>p=0.414</td>
<td>p=0.398</td>
<td>p=0.486</td>
<td>p=0.000</td>
<td>p=---</td>
<td>p=0.007</td>
<td>p=0.582</td>
<td>p=0.207</td>
<td>p=---</td>
</tr>
<tr>
<td>MA</td>
<td>-0.4433</td>
<td>0.5904</td>
<td>0.1297</td>
<td>0.0245</td>
<td>0.1644</td>
<td>-0.3685</td>
<td>-0.6900</td>
<td>0.4282</td>
<td>1.0000</td>
<td>0.1207</td>
<td>-1.743</td>
</tr>
<tr>
<td>p</td>
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<td>p=0.000</td>
<td>p=0.438</td>
<td>p=0.884</td>
<td>p=0.324</td>
<td>p=0.023</td>
<td>p=0.000</td>
<td>p=0.007</td>
<td>p=---</td>
<td>p=0.470</td>
<td>p=0.295</td>
</tr>
<tr>
<td>GFR</td>
<td>0.1084</td>
<td>0.0988</td>
<td>-0.5100</td>
<td>-0.6304</td>
<td>-0.1577</td>
<td>-0.9946</td>
<td>-0.0855</td>
<td>0.0923</td>
<td>0.1207</td>
<td>1.0000</td>
<td>-1.1885</td>
</tr>
<tr>
<td>p</td>
<td>p=0.517</td>
<td>p=0.555</td>
<td>p=0.001</td>
<td>p=0.000</td>
<td>p=0.344</td>
<td>p=0.572</td>
<td>p=0.610</td>
<td>p=0.582</td>
<td>p=0.470</td>
<td>p=---</td>
<td>p=0.257</td>
</tr>
<tr>
<td>Age</td>
<td>-0.2854</td>
<td>-0.0774</td>
<td>0.0544</td>
<td>0.1319</td>
<td>0.0044</td>
<td>-0.2780</td>
<td>0.0846</td>
<td>-0.2092</td>
<td>-0.1743</td>
<td>-0.1885</td>
<td>1.0000</td>
</tr>
<tr>
<td>p</td>
<td>p=0.082</td>
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<td>p=0.746</td>
<td>p=0.430</td>
<td>p=0.979</td>
<td>p=0.091</td>
<td>p=0.613</td>
<td>p=0.207</td>
<td>p=0.295</td>
<td>p=0.257</td>
<td>p=---</td>
</tr>
</tbody>
</table>
When analyzing the data using a regression model, with MA as dependant variable, only the platelet count could reliably predict MA (p = 0.0027). This is shown in table 4.3. No linear regression occurred for the other variables. The haemoglobin, which showed a statistically significant correlation, did not demonstrate any linear regression. GFR was used in the regression model as it is a far more accurate measure of renal function than urea or creatinine alone.
Table 4.3 Multiple Regression of Data

Regression Summary for Dependent Variable: MA (data) R = .65765252 R² = .43250684 Adjusted R² = .36371979 F(4,33)=6.2876 p

<table>
<thead>
<tr>
<th>Variable</th>
<th>b*</th>
<th>Std.Err. - of b*</th>
<th>b</th>
<th>Std.Err. - of b</th>
<th>t(33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>56.20664</td>
<td>6.926188</td>
<td>8.11509</td>
<td>0.000000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>-0.276734</td>
<td>0.142850</td>
<td>-0.66439</td>
<td>0.342958</td>
<td>-1.93724</td>
<td>0.061315</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.465107</td>
<td>0.143330</td>
<td>0.05355</td>
<td>0.016503</td>
<td>3.24501</td>
<td>0.002692</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>0.123107</td>
<td>0.133577</td>
<td>0.23029</td>
<td>0.249874</td>
<td>0.92161</td>
<td>0.363420</td>
</tr>
<tr>
<td>GFR</td>
<td>0.124129</td>
<td>0.135261</td>
<td>0.09153</td>
<td>0.099740</td>
<td>0.91770</td>
<td>0.365435</td>
</tr>
</tbody>
</table>

4.5 Conclusion

Generally the clotting profile of chronic renal failure patients on dialysis was normal when measured with the TEG®. Only two of the 39 patients showed hypocoagulability (prolonged R time and decreased MA).

The degree of renal dysfunction as measured by GFR did not predict platelet function. Plasma urea (often used by anaesthetists to predict platelet function) showed no correlation to the MA and could not predict it.
5.1 Discussion of statistical results

Chronic renal failure patients are at risk for coagulopathies. Thirty-seven of the 39 patients investigated in this study showed a normal clotting profile, with values tending towards hypercoagulability. It is known that dialysis reverses platelet dysfunction in chronic renal failure. Since all patients included in this study had been dialysed in the previous 48 hours this could explain the mostly normal clotting profiles. Two of the patients however did show hypocoagulability despite their dialysis. It is also interesting to note that one of the study subjects presented to theatre some months later for a craniotomy for a subdural haematoma after falling. She had, however, defaulted her dialysis for weeks prior to the fall. At the time of the study she had a normal clotting profile. This further supports the fact that dialysis reverses the hypocoagulability in chronic renal failure patients.

In general anaesthetic practice we are often presented with chronic renal failure patients in theatre. In deciding whether these patients are at risk for bleeding some anaesthetists assign random cut-offs for serum urea and creatinine. The general thinking is that less severe renal failure implies a lesser risk of bleeding. In this study only end stage renal failure patients were investigated and these patients were all receiving haemodialysis. The severity of the renal dysfunction, measured by GFR did not predict platelet function.
The platelet count predicted platelet function and there was a statistically significant correlation between the haemoglobin and MA. This is explained by the fact (mentioned in chapter two) that one of the causes of the coagulopathy in renal failure is anemia.

The bleeding time was abnormal in twenty of the study patients and also could not predict platelet function. In fact eighteen of these twenty patients had normal clotting profiles. This confirms that bleeding times are poor clinical tests, of little importance in modern medical practice.

5.2 Sample size

Sample sizes in pilot studies are always small. Since this study used a linear regression model at least ten subjects were needed per regressor. There were three regressors, namely MA, bleeding time and platelet count. A sample size of at least 30 patients was required. Thirty nine in total were recruited. A larger sample size would undoubtedly provide more statistically significant data.

5.3 The Thromboelastogram as a tool to measure coagulation

The thromboelastogram is an in vitro test. Hence it measures in vitro coagulation. Since platelets not only interact with each other but also with endothelium in damaged vessels this interaction cannot be measured using the thromboelastogram. Therefore diseases which affect platelet interaction with endothelium such as Von Willebrand’s disease cannot be detected using the thromboelastogram. An advantage of the
thromboelastogram lies in the fact that it measures all constituents of the clotting process and gives a global indication of clotting ability. It is also a fast bedside test which is easy to interpret.

In renal failure the platelet dysfunction occurs due to competitive antagonism of fibrinogen at the GPIIbIIIa receptor by small molecules (particularly fibrinogen fragments) normally filtered by the kidney. Therefore the platelet dysfunction is caused by a dysfunction of platelet to platelet interaction and can be measured using the TEG®. This is the reason why the platelet dysfunction is reversed by dialysis, as the small molecules are filtered.

5.4 Implications for daily practice

All chronic renal failure patients are at risk of bleeding, due to a hypocoagulable state, mostly attributed to platelet dysfunction. Coagulation cannot be assumed to be normal if laboratory parameters such as serum urea and creatinine fall below certain cut-off values. If invasive procedures are planned for these patients, where complications could arise from bleeding, a thromboelastogram is a good investigation to measure clotting status. It is not only of value to the anaesthetist but also to the surgeon to have an indication of clotting status prior to surgery or procedures.
5.5 Implications for further research

The study only investigated end stage chronic renal failure (stage five renal failure) patients presenting to theatre. Other stages of renal failure might show more predictable clotting patterns.

The sample size in the study was small, as it was a pilot study. Perhaps a larger sample size in a further study could show a predictable coagulation pattern.

5.6 Conclusion

All end stage renal failure patients have a potential coagulopathy due to platelet dysfunction. This coagulopathy is reversed by dialysis but is still very unpredictable.

Platelet function cannot be predicted by the severity of renal dysfunction. If a procedure in which bleeding can cause significant complications is planned, thromboelastography can be used to determine clotting status, prior to the procedure. A high index of suspicion for bleeding must be maintained for end stage chronic renal failure patients who have defaulted or have not received regular dialysis for whatever reason.


14. World Medical Association Declaration of Helsinki - Ethical principles for medical research involving human subjects. April 2009


47. Novel techniques involving platelet activity in flow; 1997; Florence, Italy.


APPENDIX A: COPY OF ETHICS CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Wels

CLEARANCE CERTIFICATE

PROJECT

The Thromboelastogram in the End Stage Renal Failure Patient Resenting for Surgery-A Pilot Study

PROTOCOL NUMBER M080910

INVESTIGATORS

Dr D Wels

DEPARTMENT

Department of Anaesthesia

DATE CONSIDERED

08.09.26

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE

08.09.29

CHAIRPERSON

(Professor P E Cleaton Jones)

*Guidelines for written ‘informed consent’ attached where applicable

cc: Supervisor: Prof C Lundgren
APPENDIX B: COPY OF CHANGE OF TITLE CERTIFICATE

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2075/6

Reference: Ms Tania van Leeve
E-mail: tania.vanleeve@wits.ac.za
12 October 2010
Person No. 295942
TAA

Dr Wells
P O Box 731195
Fairland
2030
Johannesburg,
South Africa

Dear Dr Wells

Master of Medicine (in the specialty Anaesthesia): Change of title of research

I am pleased to inform you that the following change of title of your research report for the degree of Master of Medicine (in the specialty Anaesthesia) has been approved:

FROM: The thromboelastogram in the end stage renal failure patient presenting for surgery: A pilot study.

TO: Platelet function as measured by the Thromboelastogram in end stage renal failure patients presenting for surgery: A pilot study.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences
APPENDIC C: INFORMED CONSENT FORM

Informed consent form

I, ______________________________, agree to participate in the study that Dr Wels has explained to me.

I understand that I will be participating in a study to learn more about clotting in patients with kidney failure.

I understand that some information about me will be collected from my file (my age, blood results for kidney function and blood clotting, weight and height) and that it will be treated confidentially.

I understand that some blood will be taken before surgery, and some during surgery. I also understand that a tiny cut will be made on my forearm while I am sleeping to assess my blood clotting.

I understand that my participation is entirely voluntary and that I can pull out at any time. I have Dr Wels’ telephone number and can contact him should I have any questions at a later stage.

Signed at ______________________________ on

______________________________
APPENDIX D: COPY OF POST GRADUATE CERTIFICATE

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011)717-2075/6

Reference: Ms Tania van Leeve
E-mail: tania.vanleeve@wits.ac.za
21 February 2008
Person No: 295942
PAG

Dr M Wels
P O Box 731105
Fairlchilds
2030
Johannesburg
South Africa

Dear Dr Wels

Master of Medicine (in the specialty Anaesthesia): Approval of Title

We have pleasure in advising that your proposal entitled "Platelet function as measured by the Thromboelastogram in end stage renal failure patients presenting for surgery: A pilot study" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

[Signature]

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences
APPENDIX E: DATA SHEET

Name:_____________________________
Hospital number:__________________
Weight:__________________________
Age:____________________________

FBC:____________________________

U&E:____________________________

INR:____________________________

PTT:____________________________

BT:______________________________

TEG: