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Coagulopathy in Severe, Isolated Traumatic Brain Injury: A Prevalence Study

Master of Medicine in Anaesthesia

Ruchi Lawrie

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DECLARATION

I declare that the research reported in this dissertation is from my independent work, and has been composed solely by myself. Neither the whole work nor any part thereof has been, is being, or will be submitted for another degree at any other university. This work has not been reported or published prior to registration for the degree of Master of Medicine in Anaesthesia.

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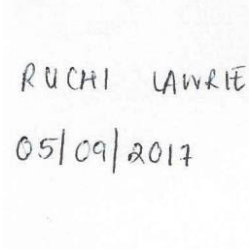

ABSTRACT

Introduction

Traumatic brain injury (TBI) is an important cause of morbidity and mortality in the developing world, and remains the leading cause of death and long-term disability in young adults. Hypocoagulopathy is a well described sequela of severe TBI and is associated with prolonged intensive care unit stays and poor outcomes. This study was conducted to determine the prevalence of coagulopathies in patients with severe, isolated TBI. The secondary outcome was to note any difference in the prevalence of detected coagulopathy between blunt and penetrating TBI.

Methods

This is a prospective observational study of fifty patients with severe, isolated TBI (AIS head >3, AIS body <3), presenting to, or were referred to Groote Schuur Hospital. We drew blood for International Normalised Ratio (INR), activated partial thromboplastin time (aPTT), platelets count, sodium, potassium, urea and thromboelastography (TEG) on all patients at 12 hours (±3 hours), 36 hours (±3 hours) and eligible patients at 60 hours (±3 hours) post injury. Coagulopathy was defined as any one of the following: platelet count<120 x 10^9/L, INR>1.2, PTT>37 seconds, R time<4 minutes or >8 minutes, K time>4 minutes, α angle<47˚ or >74˚, maximum amplitude<54 mm or >72mm, EPL>15%, LY30>8 %, coagulation index<-3 or >3.

Results

The patients were mostly male (*n*=47), with a mean age of 31 years. Median AIS head and body were 5 and 1, respectively. Thirty-six patients sustained blunt, and the remaining 14 penetrating trauma. Sixteen of the fifty patients demised during the course of the study. The cumulative prevalence of coagulopathy, as diagnosed by TEG, was 84% as diagnosed by TEG. Of the total 109 TEGs, 59 samples were hypercoagulable, 10 were hypocoagulable and the remaining 40 normal. There was poor correlation between laboratory-based coagulation assessments and TEG.

Conclusions

Contrary to what is reported in the literature, we found little evidence of a hypocoagulable state as defined by TEG (10 of the 109 samples). Many patients were significantly hypercoagulable (59 of the 109 samples) according to criteria specified by the TEG manufacturer. When considering the CBT results, we had a much higher number of hypocoagulable samples (72 of the 109 samples), with none showing a hypercoagulable state. Moreover, there was poor correlation between coagulation status as measured by TEG described and that found on conventional blood testing. No significant differences in the prevalences of coagulopathy amongst blunt and penetrating mechanisms of injury were noted. Some differences in fluid balance and presenting vitals in the hypocoagulable group when compared to the normal and hypercoagulable groups were noticed, but this does not attain any statistical significance due to the small numbers of hypocoagulable patients in our study.

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

Traumatic brain injury (TBI) is defined as a non-degenerative, non-congenital insult to the brain from an external mechanical force causing temporary or permanent neurological dysfunction, which may result in impairment of cognitive, physical or psychosocial functions, with an associated diminished or altered state of consciousness (Dawodu, 2015). Changes initiated by TBI can persist for months or years after injury and significantly affect the quality of life of not only the head-injured patients, but also their immediate families (Bramlett and Dietrich, 2015). Much of the economic burden of TBI is related to the resultant long term loss of productivity (Humphreys et al., 2013). Furthermore, TBI can lead to progressive brain atrophy and an increased vulnerability to neurodegenerative disorders (Bramlett and Dietrich, 2015).

TBI is an important cause of morbidity and mortality in the developing world (Hyder, 2007), and remains the leading cause of death and long-term disability in young adults. The overall prevalence of TBI in developed countries is 200 per 100 000 population per year. The South African prevalence was reported as 316 per 100 000 population per year (Nell, 1991). These numbers are likely to be a gross underestimate as very mild TBI (not requiring hospitalisation) and severe TBI (death on scene or before hospital admission) may not be accounted for in epidemiological reports (Corrigan et al., 2010). Despite a comprehensive attempt to count all contacts with the medical system, many injuries receive no treatment or treatment may not be recorded in medical record documentation. One study found that 42% of a convenience sample of persons reporting TBI had not received any treatment for it (Setnik and Bazarian, 2007). Furthermore, untreated TBI is common in military personnel engaged in combat and those unlikely to seek medical care; such as persons involved in sports, those who experience domestic violence and substance abusers. Most studies of incidence and prevalence are

based on civilian healthcare statistics. Therefore, all methods of estimating the incidence and prevalence underestimate the number of affected individuals due to uncounted cases (Corrigan et al., 2010).

A 2007 study found injury-related mortality rates in South Africa to be six times higher, and the incidence of road traffic injuries to be double that of the global rate (Norman, 2007). Homicide and interpersonal violence was the leading cause of injury death in this study, followed by road traffic injuries and suicide or self-inflicted violence. Income inequality and poverty, high unemployment, rapid social change, corruption and poor rule of law, gender inequalities and family breakdown as well as drugs and alcohol were cited as major contributors.

A 2015 study conducted in KwaZulu Natal, South Africa (Lewis and Wood, 2015) found that of the 10390 patients included in their study, interpersonal violence (IPV) was responsible for 25% of injuries and 54.7 % of deaths. Most isolated head injuries were caused by IPV in this study. Furthermore, of those who died, 21.4% suffered an isolated head injury. This demonstrates the high rate and burden of head injuries in South Africa.

COAGULOPATHY AND PREVALENCE

Hypocoagulopathy is a well-recognised sequela of severe traumatic brain injury (Zehtabchi et al., 2008) and is frequently associated with prolonged intensive care unit (ICU) stays and unfavourable outcomes (OR 3.75 [CI 95% 1.07-12.51; p=0.04]) (Greuters et al., 2011). The mere presence of a hypocoagulable state was found to increase the likelihood of a poor outcome by a factor of 36 and the odds of mortality by five- (de Oliveira Manoel et al., 2015) to ninefold (Kumar, 2013). The presence of a hypocoagulable state can predispose patients to progressive haemorrhagic injury (PHI), which in turn leads to a fivefold higher mortality (Maegele, 2013) and fewer hospital free days (Folkerson et al., 2015).

Two separate meta-analyses (Epstein et al., 2014, Harhangi et al., 2008) quote the incidence of hypocoagulopathy (as defined by investigators in each individual study; generally international normalised ratio [INR]>1.2, platelet count [PLT]<100 x 10^9/L, or disseminated intravascular coagulation [DIC] score>2) in TBI to be one in three patients and 35% of patients on presentation to hospital. However, varying reports document an incidence between 10%;

as diagnosed by prolonged activated partial thromboplastin time (aPTT), elevated fibrin degradation product (FDP) concentration, or PLT<100 x 10^9/L (Chiaretti et al., 2002) and 72%; as diagnosed by a modified coagulopathy score (Kuo et al., 2004). Some of this variation is partly due to the differing criteria used for the diagnosis of coagulopathy, and some due to the improvement in sensitivity of laboratory testing (Harhangi et al., 2008).

As our understanding of the complex process of coagulation has evolved and improved, different criteria have been implemented to make the diagnosis of a hypocoagulable state. Chiaretti et al. diagnosed the presence of DIC both by the clinical presence of organ dysfunction and abnormal laboratory criteria (prolonged prothrombin time [PT] and aPTT, elevated FDP concentration and PLT<100000 mm^3 or a rapid decline in PLT) (Chiaretti et al., 2002). While this is a practical approach to patient management and mirrors the common practice of treating the patient and not the number, the 100% mortality of the patients that were diagnosed with DIC displays the high specificity but exposes the lack of sensitivity. Kuo et al used a modified DIC score (Kearney et al., 1992), which relies on a combination of laboratory variables (PT, PTT, PLT, fibrinogen and D-dimer) to make the diagnosis. While mortality amongst those who had a modified DIC score of ≥ 4 was 90%, 8 of the 10 patients that met the criteria for this group had fixed and dilated pupils, and 7 had more than 15 mm midline shift on the CT scan (Kuo et al., 2004). While not totally devoid of benefit, it is difficult to motivate for the need for conventional laboratory tests, many of which were designed with a different purpose in mind, in the era of viscoelastic testing (VET).

Hypercoagulopathy is not well studied in TBI patients, partly due to the fact that conventional blood testing is unable to detect this clinical state. While trauma patients have been noted to be hypercoagulable for the first 24 hours post injury (Schreiber et al., 2005), as diagnosed by measuring thrombin activation (decrease in thrombin-antithrombin complex levels from 34 ± 15 μL on day 1 to 18 ± 8μL on day 4 [p<0.01]) that correlated with thromboelastography (TEG) diagnosed hypercoagulable state, there are no studies using conventional blood tests to investigate this in TBI patients. Hypercoagulability as defined by TEG has been described up to 7 days following moderate to severe TBI (Glasgow Coma Scale [GCS]<12), however no conventional blood tests were done in this study, so the relationship between the two remains unexplored (Massaro et al., 2014).

PATHOPHYSIOLOGY

Current evidence (Kumar, 2013, Maegele, 2013, Wijayatilake et al., 2015), based on both human and animal work, suggests that activation of the coagulation cascade due to massive tissue factor release from the injured brain initially creates a hypercoagulable state. This is followed by a microvascular thrombosis-related consumptive coagulopathy similar to that seen in DIC. The result is a hypocoagulable state, which is further compounded by hyperfibrinolysis. Comprehensive analysis of various biomarkers in both head injured and non-head injured patients did not show any significant differences in plasma levels of the biomarkers, although patients with isolated TBI had significantly higher 30-day mortality (22 % vs. 5%) (Genet et al., 2013).

Various alternate and conflicting theories have been proposed, including a hypo perfusion mediated protein C dysregulation theory (Sillesen et al., 2014), a platelet dysfunction theory (Nekludov et al., 2007), a platelet hyperactivity theory (Kumar, 2013) and a micro particle upregulation theory (Morel et al., 2008).

Protein C theory

The protein C theory postulates that in the presence of tissue hypoperfusion in the acute phase of TBI, the vascular endothelium expresses thrombomodulin, resulting in activation of the protein C pathway. The activated protein C decreases plasminogen activator inhibitor (PAI)-1 levels and increases tissue plasminogen activator (tPA), resulting in hyperfibrinolysis (Cohen et al., 2007, Sillesen, 2014). The posttraumatic inflammatory response could result in chronic depletion of protein C, leading to a reduction in the inhibition of coagulation and lysis and therefore promoting a hypercoagulable phase (Maegele, 2013). Thus, a combined hypo- and hypercoagulable state exists.

Platelet dysfunction theory

The platelet dysfunction theory originates from a clinical study investigating TEG platelet mapping, that revealed that platelet function in TBI differs from that in trauma cases without TBI or even chronic alcoholic patients (Nekludov et al., 2007). The main difference found in this study was clearly reduced arachidonic acid (AA) activity in TBI cases, indicating impaired

function of the platelet cyclooxygenase and/or thromboxane receptors. This may partly explain the altered bleeding time in these patients. In a rat model, a relationship between the severity of injury and the degree of adenosine diphosphate (ADP) receptor inhibition was shown, with significant ADP receptor inhibition as early as 15 minutes post injury (Castellino et al., 2014). In a separate rat model study (Donahue et al., 2014), marked ADP receptor inhibition (24.8% ±6.2 vs. control 65.1% ±3.4) was depicted from 15 minutes post injury and throughout the hour that coagulation was monitored. In contrast, AA receptor inhibition was worst at 30 minutes post injury. In a swine model, platelets activated with ADP showed a lower aggregation at 15 minutes post injury (65.1 U vs. 80.4 U, p=0.02) and maintained this difference at the follow-up 2-hour observational time-point (62.7 U vs. 73.5 U, p<0.01). This ADP receptor dysfunction was noted to be associated with increased levels of platelet activation marker transforming growth factor (TGF)-β (Sillesen, 2014). A prospective observational human study confirmed ADP receptor dysfunction (61.2% [IQR 43.1-95.4%)] vs. 15.5% [IQR 12.2-31.6%]) which was found to correlate with the severity of TBI (Davis et al., 2013). The same study also reported poor correlation between platelet numbers and function, implying that platelet count is a poor marker for the presence of coagulopathy. Interestingly, this platelet dysfunction does not improve with transfusion of platelets (Briggs et al., 2015). Importantly, patients found to have ADP receptor dysfunction had a higher in-hospital mortality (32% vs. 8%; p<0.01) (Daley et al., 2016).

Platelet hyperactivity theory

Platelet hyperactivity in TBI is believed to be multifactorial in origin (Kumar, 2013). There may be upregulation of a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (ADAMTS-13), which is essentially responsible for cleaving the prothrombotic ultralarge von Willebrand factor forms into smaller haemostatically active but no longer prothrombotic multimers. Von Willebrand factor is a strong stimulus for platelet activation and adhesion. Together with excessive platelet receptor activation and release of platelet-activating factor (PAF) microthrombus formation occurs. Furthermore, PAF enhances blood-brain barrier (BBB) permeability, promotes oedema formation and release of prothrombotic mediators in the systemic circulation.

Microparticle upregulation theory

The microparticle upregulation theory suggests that cells may release microparticles (MPs) upon activation and cell death. It is thought that these MPs can then play a role in triggering coagulation and inflammation. A small (*n*=16) observational study in human TBI (Morel et al., 2008) showed a significant increase in mean procoagulant MPs of platelet and endothelial origin in the cerebrospinal fluid when compared to controls (4.5±1.8 vs. 0.83±0.28 nM Phtd-Ser Eq; *p*=0.0014). The levels decreased progressively over the first ten days following injury. The authors suggest two possible theories for the appearance of MPs in the cerebrospinal fluid: increased permeability of the BBB in response to proinflammatory mediators such as histamine, bradykinin, AA, and nitric oxide, and direct migration via injured vessels or from blood in the spinal fluid. A small but fascinating human study (Nekludov et al., 2014) shows not only that severe TBI results in increased levels of circulating MPs, but also confirms a transcranial gradient. These results suggest that MPs released from endothelial cells may carry tissue factor out into the circulation, which may have procoagulant and proinflammatory effects. A murine model of moderate head injury showed that platelet contribution to clot formation is decreased around 1 day after TBI, and is likely associated with altered MP populations, with a significant increase in procoagulant MP activity (Midura et al., 2015).

A murine model of TBI designed to investigate the aetiology of microthrombus formation found that 60% of all cerebral vessels (ipsilaterally, but outside the contusion area) were occluded by microthrombi as detected 24 hours after injury by two-photon microscopy (Schwarzmaier et al., 2016). Importantly, the investigators did not detect any improvement following factor XI (FXI) inhibition, implying that microthrombus formation is driven by the extrinsic coagulation pathway. They postulate that prophylactic anticoagulation via inhibition of FXI activation by FXIIa (activated factor XII) may be of therapeutic value pending further studies.

Role of neuroinflammation

Neuroinflammation is a secondary wave of biochemical cascades, resulting in metabolic and cellular changes that occur within seconds to minutes after the primary injury, and can persist

for months or years. While excitotoxicity, oxidative stress, mitochondrial dysfunction and inflammation can individually result in cell death, interaction amongst the processes worsen the outcome following TBI. Of note, excessive microglial activation results in excessive release and upregulation of proinflammatory cytokines such as tumour necrosis factor (TNF) α, interleukin (IL)-1β, IL-6, IL-12 and interferon (IF) γ. Higher expression of cell adhesion molecules in the endothelial cells and increased production of chemokines increases the permeability of the BBB and results in an increased inflammatory response. Interestingly, activated microglia can polarise into distinct phenotypes depending on the microenvironment in which they are activated (Lozano et al., 2015). When exposed to cytokines IL-4 and IL-13, microglia reduce proinflammatory cytokines and increase the production of antiinflammatory cytokines such as IL-10 and TGF-1β. Modulating inflammatory cells and promoting an anti-inflammatory phenotype may prove to be future drug targets in TBI.

Role of alcohol and the adrenergic response

Acute alcohol related blunting of the adrenergic response may play a role in mitigating the early coagulopathy seen in TBI. A recent study (Lustenberger et al., 2011) found that patients who were intoxicated on presentation to hospital had a significantly lower incidence of early coagulopathy (5.4% vs. 15.3%; adjusted p<0.001) and in-hospital mortality (9.8% vs. 16.6%, adjusted p=0.011; adjusted OR 0.39 [CI 95% 0.19-0.81]). A major limitation in this study was the administration of pharmacological withdrawal prophylaxis by means of barbiturate, benzodiazepine, dexmedetomidine or propofol administration, all of which are known to decrease adrenergic activity and cerebral metabolism following TBI, and may have affected survival amongst these patients. A recent study (Cook et al., 2015) in acutely intoxicated trauma patients showed a relatively hypocoagulable state on TEG (longer R time, smaller α angle, lower maximum amplitude [MA]; but not necessarily abnormal values as defined by the manufacturer) that was associated with reduced incidence of DVT (1.4% vs. 16.2%, p<0.01; OR 0.2 [CI 95% 0.05-0.79]). There was no associated change in conventional blood test (CBT) results (aPTT, fibrinogen, INR, platelet count or hemoglobin) amongst the two groups.

Thus, the aetiology of coagulopathy in TBI is most likely multifactorial.

SEVERITY OF INJURY AND PREVALENCE OF COAGULOPATHY

Most of the studies that investigated the relationship between severity of head injury and risk of coagulopathy use CBTs. In a study looking at immunofluorescent staining in brain injured rats and pigs (*n*=18), as well as specimens of contused human brain (*n*=11) removed during surgical decompression, a strong and direct relationship was seen between the severity of coagulopathy and the density of intravascular coagulation (Stein et al., 2002). Severe, isolated TBI has been shown to be independently associated with increased coagulopathy (Lustenberger et al., 2010, Cap and Spinella, 2011) as measured by INR (coagulopathy was defined as INR >1.4 and ≥1.5, respectively). In contrast, a recent prospective study (Juratli et al., 2014) found that unfavourable short and long term neurological outcome after isolated TBI was determined by early haemorrhagic progression of injury and coagulopathy (as documented on CBT) and was irrespective of the severity of the trauma. It is important to note that in this study, 31% of patients underwent early neurosurgery, with an unknown number receiving blood products to correct the coagulation abnormalities, which could have impacted the reported results.

TIME COURSE OF COAGULOPATHY

Description of the time course of coagulopathy in TBI literature is inconsistent and somewhat limited. Most studies report abnormal coagulation within minutes and lasting for 24 hours post injury (Stein and Smith, 2004), whereas others report abnormal results up to 7 days post injury (Massaro et al., 2014). A study (Lustenberger et al., 2010) that aimed to investigate the time course of coagulopathy found that the onset was within 12 hours in 45% of patients and within 24 hours in 65% of patients, with the duration of coagulopathy varying from 24 to 72 hours. These investigators suggest monitoring patients for up to 5 days post injury. Of course, the sensitivity of the tests used to detect coagulopathy will influence the reported duration.

It has been suggested that the time of onset of coagulopathy may have predictive value for patient outcomes. In one study (Franschman et al., 2012), investigators found that delayed/sustained coagulopathy was more frequently associated with computed tomography (CT) abnormalities (intracranial haemorrhage and signs of raised intracranial pressure), higher

in-hospital mortality (51% vs. 33%; $p<0.05$) and unfavourable outcomes at 6 months post TBI when compared to early, short-lasting coagulopathy. In contrast, another study reported that early coagulation abnormalities were associated with a higher incidence of overall complications (Lustenberger et al., 2010).

CONVENTIONAL BLOOD TESTING

CBT for prolongation of the PT, INR, aPTT, and PLT may elucidate an underlying hypocoagulopathy. Currently, there are few conventional laboratory tests that aid in the detection of hypercoagulable states.

INR and aPTT

INR was originally developed to assess the adequacy of dosing of vitamin K antagonists. Only a small fraction of the coagulation pathway is examined by this plasma based test that was designed neither to evaluate coagulopathy in acutely bleeding patients (McCully et al., 2013) nor to predict whether patients are at an increased risk for bleeding after procedures (Segal et al., 2005). Raised INR may point towards a hypocoagulable state, but the absence of a raised INR does not necessarily exclude this. In TBI patients, the most significant peak in INR was at 6 hours with another smaller peak at 36 hours (Lustenberger et al., 2010). However, at the time of the first peak in this study, the subjects were likely to have normal platelet counts. This somewhat decreases the practical and clinical importance of this finding, and shows how the presence of a raised INR can confuse the decision making that influences patient care. Furthermore, in a recent retrospective observational study (Rowell et al., 2014), patients who had a raised INR (>1.4) took longer to receive their neurosurgical intervention (median time 358 minutes [285-478 minutes] vs. 184 minutes [87-343 minutes]), were more likely to receive plasma transfusion (70% vs. 24%, $p=0.004$), and received more units of plasma (2 U [0-6U] vs. 0 U [0-1U], $p=0.006$).

The potential relationship between aPTT and progressive head injury was examined in a systematic review (Zhang et al., 2015). No significant association was shown due to the heterogeneity of results of the four assessed studies (pooled OR 2.39 [CI 95% 0.72-7.95; $p=0.15$]).

Platelet count

Thrombocytopenia complicates TBI in 10% of cases, resulting in a 35% increased risk of mortality at 6 months (Kumar, 2013, Van Beek et al., 2007). A platelet count of less than 100 x 10^9/L was an independent predictor of progression as diagnosed on repeat head CT scan (OR=4 [CI 95%=1.7-10]), need for neurosurgical intervention (OR 3.6 [CI 95%=1.2-6.1]) and mortality (OR 2.6 [CI 95%=1.1-4.8]) (Joseph et al., 2014).

D-dimer

D-dimer, an end-product of both coagulation and fibrinolysis may be one marker of a hyperfibrinolytic state, and may suggest the presence of a hypercoagulable state. In humans, D-dimers have been found to correlate with the severity of brain injury as well as with the chances of progressive haemorrhagic injury (PHI) (Tian et al., 2010). In this study, a d-dimer above 5 mg/L was found to have a strong link with progression of haemorrhagic injury (OR 11.85 [CI 95% 5.67 – 24.75, p=0.000]). A systematic review (Zhang et al., 2015) of the literature determined that raised d-dimer was associated with PHI with a pooled OR of 16.5 (CI 95% 4.94-55.04; p<0.001). D-dimer seems to be an acute phase reactant for haemostatic function, with the value increasing within an hour from the injury (Nakae et al., 2016). Further increases were noted up to 3 hours post injury, followed by a significant decrease. Unfortunately, d-dimer is not a very specific marker for coagulopathy and may be elevated in other inflammatory states such as infection, malignancy and pregnancy, to name a few.

ABNORMAL CONVENTIONAL BLOOD RESULTS AND OUTCOME

A post hoc analysis on data from IMPACT (International Mission on Prognosis and Analysis of Clinical Trials in TBI) (Van Beek et al., 2007), which evaluated the prognostic value of admission laboratory tests, found a clear and individual relationship between PT, INR, aPTT and PLT and poor outcome. PT prolongation (>20 seconds) was associated with a 64% increase in risk of mortality and 42% increased risk of unfavourable outcome (Kumar, 2013, Van Beek et al., 2007). Elevated INR was shown to be independent of age in a logistic regression analysis for both radiologic (OR 2.4 [CI 95% 1.1-11.1, p=0.04]) and clinical

deterioration (OR 9.0 [CI 95% 1.4-58; *p*=0.02]) in a small subset of patients with traumatic subarachnoid hemorrhage (von der Brelie et al., 2015). It is noteworthy that of the 34 patients that showed features of hypocoagulopathy on CBT, 16 were known to be on aspirin, and 2 were on simultaneous aspirin and warfarin treatment. Similarly, patients with traumatic subdural hematoma and coagulopathy had a significantly worse outcome, with twice the in-hospital mortality (55% vs. 23%, *p*<0.001) of noncoagulopathic patients with similar severity of injury (Lemcke et al., 2014).

Apart from having an increased length of ICU stay, fewer ventilator-free days, and increased mortality, coagulopathic patients are more susceptible to other complications such as sepsis (29.9% vs. 1.3%, adjusted *p*=0.003) and diabetes insipidus (28.3% vs. 2.6%, adjusted *p*=0.003) (Lustenberger et al., 2010).

A recent meta-analysis (Yuan et al., 2016) sought to evaluate whether isolated TBI induces pronounced coagulopathy and to examine any relationship with PHI. After evaluating a total of 19 studies, the investigators found that the PHI group had a lower platelet count (pooled mean of sample of difference scores [MD] -19.21 [CI 95% -26.99 to -11.44, *p*<0.001]) and a slightly higher INR value (pooled MD 0.07 [CI 95% 0.02-0.13, *p*=0.006]) when compared to the non-PHI group. There was no difference in mean aPTT and PT amongst the groups. PHI was found to be associated with a higher percentage of INR>1.2 (pooled OR 3.49 [CI 95% 1.97-6.20, *p*<0.001]), PLT<100x10^9/L (pooled OR 4.74 [95% CI 2.44-9.20, *p*<0.001]) and coagulopathy (pooled OR 2.52 [CI 95% 1.88-3.38; *p*<0.001]). This is in keeping with the findings that PT, D-dimer level and INR value are positively associated with a risk of PHI, whereas higher platelet count and fibrinogen suggest a lower risk of PHI (Zhang et al., 2015). Interestingly, no difference in coagulation status between the isolated TBI group and those injured elsewhere on the body was noted. This challenges the theory that severe TBI may result in exaggerated coagulation changes when compared to other areas of the body (Yuan et al., 2016).

From the foregoing literature review, it is clear that the most dreaded and devastating consequence of the hypocoagulable state that has been linked to severe TBI is PHI. Transfusion of platelets or fresh frozen plasma (FFP) to correct thrombocytopaenia and coagulopathy respectively, has naturally been explored as a means to minimise the risk of secondary complications. However, blood and blood product transfusion present their own

subset of risks to the patient such as transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), various immune reactions and infection. A recent retrospective review (Anglin et al., 2013) shows that overall, in TBI patients with moderate coagulopathy (INR 1.4-2.0), FFP transfusion alone or in combination with packed red blood cells (PRBCs) were associated with poorer long-term functional outcomes as measured by the Glasgow Outcome Scale – Extended (GOSE). In the moderate coagulopathy group, patients who received FFPs were more likely to have a lower GOSE score (OR 5.2 [CI 95% 1.72-15.73]), and patients who received both FFPs and PRBCs were even more likely to have a lower GOSE score (OR 7.17 [CI 95% 2.12-24.12]). Platelet transfusion was not significantly associated with outcome in this study. This highlights the need for better transfusion triggers in severe TBI.

THROMBOELASTOGRAPHY

TEG may be used as a tool for the global assessment of coagulation due to its unique ability to identify and assess all phases of haemostasis, and thus allow for the diagnosis of both hypo- and hypercoagulable states. TEG has been extensively validated in trauma-induced coagulopathy as a point-of-care test, and has been used effectively to identify transfusion triggers in such patients (Johansson et al., 2009, Johansson, 2010, Schochl et al., 2012, Da Luz, 2014).

Determining the prevalence of hypercoagulability as detected by TEG and comparing it with that detected with conventional laboratory values, may be beneficial in determining the need for anticoagulation in patients with TBI, as the risk for venous thromboembolism in these patients has been found to be three- to fourfold higher than trauma patients without TBI (Reiff et al., 2009). An older but interesting study (Schreiber et al., 2005) noted that hypercoagulability as diagnosed by a shortened R-time on TEG was the main coagulation abnormality in trauma patients (Injury Severity Score ranging from 11 to 35) during the first four days after injury. They found that 62% of patients were hypercoagulable by TEG on day 1, and 26% up to day 4 post injury. Women were found to be more hypercoagulable when compared to men (R time 2.9±0.7 mm vs. 3.9±1.5 mm). Importantly, this hypercoagulable state was not detected by means of any of the CBTs, which were all normal throughout the duration of the study. There are some limitations to this study: it is unclear whether some, if any, of their study cohort had significant TBI or not, and the use of pharmaceutical deep

venous thrombosis (DVT) prophylaxis in 19 patients. Lastly, a small study has noted the presence of late hypercoagulability as diagnosed on TEG up to 120 hours following TBI (Massaro et al., 2014).

TEG associated hypocoagulopathy as detected in less than 10 percent of patients, has been shown to be a predictor of poor outcome (increased mortality, fewer ICU-free and hospital-free days) in patients with TBI (Windelov et al., 2011). In this retrospective observational study, hypocoagulopathy as diagnosed by TEG at neurosurgical ICU admission was associated with clinical deterioration (57% vs. 16%, p=0.02) and worse outcome (30-day mortality 63% vs. 16%, p=0.008). In the same study, they found no such association with hypocoagulopathy detected by CBT, implying that TEG may be better at detecting a clinically relevant hypocoagulopathy. Moreover, such hypocoagulopathy has been linked with an increased need for neurosurgical intervention. The presence of coagulation abnormalities in patients undergoing emergent neurosurgery may critically affect the patients' course, both in theatre and perioperatively.

COAGULOPATHY AND MECHANISM OF INJURY

Very few studies have been pursued to detect differences in coagulation between blunt and penetrating mechanisms of injury, perhaps because of difficulty in recruiting an adequate number of patients with penetrating head injuries. One study from 1986 found that hypoxia, anaemia, hypotension and DIC were associated with worse outcome on the Glasgow Outcome Scale (GOS)(Kaufman et al., 1986). A large observational study (Black et al., 2002) with the aim of determining a difference in the incidence and type of medical complications and comorbidities between blunt and penetrating head injuries was conducted. More than 50% of patients in this study suffered one or more associated injuries or developed at least one medical complication. Penetrating injuries were associated with higher rates of medical complications, especially those involving the pulmonary and central nervous systems. They found no statistically significant difference in the incidence of coagulopathy between the two groups (7% in the penetrating group vs. 3% in the blunt group), but had a low number (n=12, sample size 317) of patients in whom coagulopathy was detected. Furthermore, they fail to outline the criteria for diagnosing coagulopathy.

In TBI, the time course and required neurosurgical interventions vary by mechanism of injury. Not only were patients with penetrating brain injury more likely to require a neurosurgical intervention (penetrating 51.8% vs. blunt 21.2%), but they were also more likely to have any of the specific interventions, e.g. intracranial pressure (ICP) monitoring (32.2% vs. 16%) and craniectomy (24% vs. 5.2%)(Orman et al., 2012).

SUMMARY

In summary, the literature reports wide variations in the prevalence of coagulopathy, with hypocoagulopathy being the predominant pathology. In our experience, the prevalence of hypocoagulopathy seems to be much lower than the reported value of 35 percent. Furthermore, the time course of onset and duration of coagulopathy has been inadequately defined in the literature. To provide a good standard of care for our patients by preventing secondary insults and minimizing unnecessary transfusion of blood and blood products, it is vital to know and understand the underlying characteristics of coagulopathies. To the best of our knowledge, no study has assessed the prevalence of coagulation abnormalities in isolated and severely head-injured patients by means of both conventional blood testing and TEG over multiple time points. Furthermore, we suspected that conventional blood tests may overestimate the presence of coagulopathy which may not bear clinical significance.

The purpose of this study was to determine the prevalence of coagulation abnormalities in the severely head-injured South African population presenting to Groote Schuur Hospital, both by means of conventional blood testing and viscoelastic testing (TEG). The secondary outcomes were to note any differences in prevalence detected by the two methods of testing or by mechanism of injury (blunt vs. penetrating) as well as to detect any relationships with other clinical variables which may form the basis for further studies.

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

PREWORD

This section of the dissertation is targeted to the Journal of Neurotrauma. Since the target journal is of American origin, United States English has been used in this section. I have followed their specific referencing style (the requirements for authors section from the journal website is attached after the end of chapter two). The journal also has very specific requirements for charts and tables, which are to be electronically uploaded in a separate file and in a different format. In the interest of accessibility for the purposes of the dissertation, I have not changed the format of the graphs. Furthermore, I have not separated the graphs and charts for the journal submission from the other appendices, which may provide useful information for the examiner. Those that would be included in the submission are clearly labelled with the author surname and chart or table number as per their requirements.

METHODS

Study design

We conducted a prospective pilot observational study at Groote Schuur Hospital (GSH) in Cape Town, South Africa. Both the Human Research Ethics Committee (HREC) of the University of Cape Town and the Chief Operations Officer of Groote Schuur Hospital approved the study. Due to the nature of their injuries, patients were unable to give consent. The need for delayed consent or proxy consent was waived by the HREC in view of the minimal risk posed to the patients. Fifty patients admitted to GSH between October 2015 and June 2016 who fulfilled the inclusion criteria were recruited to the study. The laboratory and TEG testing conducted as a part of the study were not available to the clinical team and in no way affected

patient management. All clinical decisions that affected the patients' management were made by the neurosurgical team based on the clinical condition and were independent of patients' inclusion in the study.

Sample size calculation

Based on the meta-analysis by Harangi et al., we expected the prevalence of coagulopathy as defined by conventional blood testing to be around 33 percent.[1] However, informal expert observation noted a somewhat lower number in our population. Therefore, working on an estimate of 15% prevalence of coagulopathy, we determined that a sample size of 39 patients would be required to achieve a 95% confidence interval of detecting an existing coagulopathy. With a sample size of 50 patients, we would achieve a 98% chance of detecting a coagulopathy if it were present with a prevalence between 15 and 33 percent. We therefore decided upon a sample size of 50 patients.

Selection of patients

The inclusion criteria were as follows:

1. Adult patients (aged 18 years and over)
2. Isolated traumatic brain injury (TBI) with
    a. Head Abbreviated Injury Score (AIS) of 3 or more (Appendix A)
    b. Chest, abdomen and extremity AIS of less than three (Appendix A)
3. Glasgow Coma Scale (GCS) of 8 or less (Appendix B)

Exclusion criteria were as follows:

1. Pediatric patients (less than 18 years in age)
2. GCS of more than 8
3. Significant other injuries, resulting in a body AIS score of 3 or more
4. Head AIS of less than 3
5. Patients who received blood products prior to admission to the study
6. Patients who have received tranexamic acid prior to admission to the study
7. Known coagulation abnormalities
8. Patients known to take therapeutic warfarin, enoxaparin, clopidogrel or aspirin

Time zero (T0) was documented as the time of first medical contact (time of ambulance pick up or presentation to the emergency department). In the case of referral from another hospital, time of initial presentation was used when it was documented in the referral letter. If it was unavailable, the time of ambulance pick up for transfer was used.

After patient selection, the following parameters were documented

1. Age
2. Gender
3. GCS on presentation
4. Mechanism of injury (blunt vs. penetrating)
5. Time since injury/first medical contact
6. Head AIS
7. Body AIS
8. Vital signs on presentation
9. Computed tomography (CT) evaluation of intracranial injuries
10. Neurosurgical procedures
11. Type and volume of resuscitation fluid prior to the first sample time
12. Administration of supplemental oxygen or fraction of inspired oxygen
13. Blood testing included the following:
    a. Laboratory testing (Normal values can be found in Appendix C)
        i. Platelet count
        ii. International Normalized Ratio (INR)
        iii. Activated Partial Thromboplastin Time (aPTT)
        iv. Serum sodium
        v. Serum potassium
        vi. Urea
    b. Thromboelastography (TEG) (Appendix D)
        i. R time
        ii. K time
        iii. α angle
        iv. Maximum amplitude (MA)

v. LY30 (Clot lysis at 30 minutes after MA)
vi. Coagulation index (CI)
vii. G value

For the purpose of this study, penetrating head injury was defined as that in which the dura mater had been breached by either a sharp object such as a knife, or high velocity projectiles such as in a gunshot wound, with evidence of cerebral tissue damage on CT scan.

Blood sampling and testing

The first blood sampling (time 1 or T1) for INR, aPTT, platelet count, sodium, potassium, urea and TEG was done at 12 hours (±3 hours) post injury (T0+12 hours), the second (time 2 or T2) at 36 hours (±3 hours), and if eligible, the third (time 3 or T3) at 60 hours (±3 hours). The criteria for repeat blood sampling at 60 hours are listed in Appendix E. While there was a time margin of 3 hours on either side of each sampling time, most samples were taken close to the 12 hour, 36 hour and 60 hour goals. Some patients were admitted to the neurosurgical intensive care unit, and already had an arterial line in situ. Strict aseptic technique was followed to draw blood from the existing arterial line. The dead space in our arterial line sets (Arrow® arterial catheterization set, TruWave™ pressure monitoring set from Edwards Lifesciences™) is 3 ml. As arterial lines are not heparinized at the study hospital, the first 7 ml of blood was aspirated and discarded prior to drawing the specimens. Most of the patients were still in the trauma unit at the time of collecting the first sample, therefore did not have an arterial line in situ, requiring a venous sample to be drawn. During phlebotomy, a venous tourniquet was used and strict aseptic technique was followed. All samples were drawn by a single investigator in the same order (clotted blood, ethylenediaminetetraacetic acid [EDTA], followed by citrated tubes) with a view to eliminate the possibility of tissue factor contamination in the citrated tubes. Patients were assigned a study number to preserve confidentiality.

TEG SAMPLES

All TEG samples were run by a single investigator on a Thromboelastograph® Hemostasis Analyzer 5000 (Haemoscope Corp, IL). Blood was collected in a citrated tube (BD Vacutainer®; 0.109 M buffered Na_3 citrate). All samples were run per the manufacturer's specifications

(time from blood sampling to testing was between 15-30 minutes). One milliliter of the citrated blood was pipetted into a kaolin tube and inverted 10 times. TEG® 5000 plain cups were used, into which 20 μL of 0.2 M $CaCl_2$ was pipetted. Thereafter, 340 μl of kaolin activated blood was pipetted into the plain cup. Each sample was allowed to run until LY30 was reached. The manufacturer's quality control guidelines were adhered to. All contaminated specimens and consumables were discarded according to hospital protocols.

LABORATORY SAMPLES

All laboratory samples were drawn by a single investigator, labelled and taken to the on-site National Health Laboratory Services at Groote Schuur Hospital, where all the samples were tested urgently by the laboratory staff.

Definition of coagulopathy

For TEG, manufacturer defined criteria were adopted to detect coagulopathy (R time <4 minutes or >8 minutes, K time >4 minutes, α angle <47° or >74°, MA <54 mm or >72 mm, EPL>15%, LY30>8%, CI<-3 or >3, G<6.0K or >13.2K). For the conventional laboratory tests, the following were used to detect the presence of coagulopathy: platelet count <120 x 10^9/L, INR >1.2, PTT >37 seconds.

STATISTICAL ANALYSIS

Data were collated in an Excel (version 15.30, © 2017 Microsoft, Redmond, WA, USA) spreadsheet for further analysis. Allocation to groups and within group counting was performed using pivot tables in Excel. Where appropriate, correlation was tested using STATISTICA (version 13.2, © 2017 Dell Inc., Tulsa, OK, USA). Distributive data relating to the numbers of patients in the various groups were conducted using Chi-square analysis. TEG variables were compared across the three time intervals using ANOVA (analysis of variance) for repeated measures. The volumes of fluid given to each category of coagulation patient (normal, and hypo- and hypercoagulable groups) were tested for significance using a one-way ANOVA. Lilliefors test was used to assess independent TEG variables. Spearman correlation was used to assess correlation. The strength of the association was assessed by means of the r-value and the level of significance.

RESULTS

Of the 50 patients recruited for the study, 47 (94%) were male. Median values of AIS head and AIS body were 5 and 1 respectively. The median worst GCS was 5, with 38 patients requiring intubation prior to arrival at GSH (19 on scene, 19 at the referring hospital). Thirty-four of the patients suffered from blunt, and the remaining 16 penetrating injuries. Median Rotterdam and Marshall scores were 3 and 4 respectively (Appendix F). Sixteen patients demised during the course of the study, with 9 demising before the second (36 hour) sample could be drawn. There were 109 sample points in the study, of which 59 were hypercoagulable by TEG, only 10 were hypocoagulable and the remaining 40 were normal. Please see Appendix G for descriptive statistics.

Conventional blood tests (CBTs) are poorly geared to detect hypercoagulability, so as expected, none of the samples met the criteria for hypercoagulability. Of the 109 samples, 72 were found to be hypocoagulable. Of these, 69 samples met the preset criteria for hypocoagulability by means of raised INR, and only 3 met the PTT criteria. There was a very poor correlation between hypocoagulability on CBTs and coagulation status as seen on TEG. In fact, many of the hypercoagulable TEGs were associated with a raised INR. (Appendix H)

Thirteen samples met the platelet criteria for a hypocoagulable state. Of these, 11 samples were associated with a hypercoagulable or normal TEG, while only two were associated with a hypocoagulable TEG. Of the total of 10 thrombocytopenic patients, only 3 were thrombocytopenic on presentation, with 6 becoming thrombocytopenic at either the second (*n*=4) or third (*n*=2) sampling point. One patient did not have a valid platelet result at the T1 due to platelet clumping noted in the laboratory, but had two further samples that were thrombocytopenic (with no further platelet clumping noted).

Of the CBTs, only the aPTT displayed some relationship with the coagulation status on the TEG. The mean aPTT ratio amongst the hypercoagulable patients was 0.94 whereas that of the hypocoagulable patients was 1.03. However, marked variation in aPTT ratios, ranging from 0.91 to 0.16, was observed in hypocoagulable patients. Since there were only 10 samples in this group, any interpretation of the results must be done with caution. (Appendix I)

No significant difference is evident in either the numbers or type (hypo- or hypercoagulopathy) of coagulopathy between blunt and penetrating mechanisms of injury at

any given time. (Appendix J) Amongst those who suffered blunt trauma, 46 of the 85 TEGs were hypercoagulable, and 6 were hypocoagulable. In the penetrating injury group, 13 of the 24 samples were hypercoagulable and only 4 samples were hypocoagulable.

Sixteen patients demised during the course of the study. Of those that died, three were hypocoagulable (one patient only had one sample, the other two were hypocoagulable by TEG at T1 and then normal at T2), 10 were hypercoagulable (all 10 at T1, 4 survived to have a sample at T2; of which all were normal) and the remaining three (two had only one sample) showing normal coagulation status. (Appendix K)

None of the study patients had received any blood or blood products prior to recruitment. The decision to administer blood and blood products after recruitment was made by the neurosurgical team and was based on the patients' clinical state. This resulted in a total of 8 patients receiving packed red blood cells. No platelets or coagulant containing blood products were administered to any of the study patients. Of those that received packed red blood cells (PRBC), two patients were hypocoagulable at some point in the study. Of these, one was hypocoagulable by TEG at the first sampling point (prior to the administration of any PRBC, normal INR and platelet count), and remained hypocoagulable at the second sampling point (720 ml PRBC administered, normal INR, platelet count=101 x 10^9/L). The other patient was hypercoagulable by TEG at the first sampling point (prior to the administration of any PRBC, normal INR and platelet count) and became hypocoagulable by TEG (prolonged R time) at the second sampling point (720 ml PRBC administered, normal INR and platelet count). The other 6 either displayed features of a sustained hypercoagulable or normal coagulation state on TEG. Three patients developed a low platelet count following transfusion of significant volumes of packed red blood cells (960 mL [plt = 87, normal TEG], 1080 mL [plt=80, normal TEG] and 720 mL [plt 101, hypocoagulable TEG with low MA and G value]).

Four patients received synthetic colloids (hydroxyethyl starch with a substitution ratio of 130/0.4 [®Fresenius Kabi Norge A.S., Halden, Norway]) prior to recruitment to the study. An additional 7 patients received synthetic colloids after recruitment. Of these 7, 3 also received PRBC as a part of their resuscitation. Interestingly, none of the patients that received colloids displayed any features of a hypocoagulable state on TEG.

Twenty-two patients had 24 neurosurgical interventional procedures. Of these, 9 patients had insertion of neuromonitors only, 5 had a craniotomy for washout of a collection, 8 had both

craniotomy and insertion of monitors in a single procedure, and 2 had other procedures (1 patient had an extraventricular drain inserted, and the other had digital subtraction angiography and removal of a penetrating object in theatre).

We have attempted to describe the coagulation trends found in this study. (Appendices L and M) All TEG variables were normally distributed. The individual TEG criteria were assessed to determine whether any of them showed a strong link with overall coagulation status and fluid balance. Of these, K time and MA showed weak correlation coefficients (0.21 and -0.26 respectively) with fluid balance.

Hypocoagulable patients detected by TEG criteria at the T1 had received more fluid than the other subgroups (mean fluid balance 3930 mL in the hypocoagulable group vs. 2383.13 mL and 1748.57 mL in the normal and hypercoagulable groups, respectively), despite having similar severity of injury (median AIS head 5 in the normal and hypercoagulable groups and 5.5 in the hypocoagulable group; median AIS body was 1 across all groups). Similarly, hypocoagulable patients detected by TEG criteria at T2 had a mean interval fluid balance of 1116.67 mL vs. 296.32 mL and 521.15 mL in the normal and hypercoagulable groups, respectively. However, both subsets of hypocoagulable patients were small (6 and 3 at T1 and T2, respectively), so these differences did not achieve any statistical significance.(Appendix G and N) Interestingly, the hypocoagulable group at T1 had a lower systolic blood pressure (93.83 vs. 123.19 and 121.11mmHg in the normal and hypercoagulable groups, respectively) and higher pulse rate (107.5 vs. 89.81 and 94.32 bpm [beats per minute] in the normal and hypercoagulable groups, respectively) despite similar severity of injuries (median AIS head 5.5 in the hypocoagulable group vs. 5 in the normal and hypercoagulable groups; and AIS body 1 across all groups).(Appendix G and O) Interestingly, the hypercoagulable group had a slightly higher base deficit at T1 (-5.096 vs. -4.769 and -4.383 in the normal and hypocoagulable groups, respectively) when compared to the other two groups. There was no significant difference in pH amongst the groups at T1.

DISCUSSION

To the best of our knowledge, this is the first study to examine the coagulation status of fifty isolated and severely head-injured patients over multiple time points. Furthermore, this is the first study to compare coagulopathy by means of both conventional blood testing and

viscoelastic testing in these patients. The main finding of this study is that a hypocoagulable state as determined by TEG is much less prevalent than would be expected by reports in the literature.[1-3] A hypocoagulable state as determined by CBT was detected in 66 percent of samples. There was poor congruence between the two testing modalities, with patients displaying features of a hypocoagulable state by means of CBT having features of a hypercoagulable (37 samples) or normal (25 samples) state on TEG. We intentionally employed traditionally used cutoff values for CBT in this study with the aim of making our results comparable to the literature. While this may be partially responsible for the large number of samples displaying a hypocoagulable state as detected by CBT, it serves to question the clinical relevance of these cutoff values. Furthermore, we have detected that over 50 percent of samples were hypercoagulable by TEG. By closely examining the trends in coagulation over time, we have shown that there is little evidence of an initial hypercoagulable state being followed by a hypocoagulable state, as would be expected in a consumptive coagulopathy. This calls into question one of the main proposed theories of coagulopathy in TBI.

Windelov *et al* also reported a low prevalence of hypocoagulability as diagnosed on TEG (10%), although they also reported a low prevalence as diagnosed by CBT (21%).[4] This may be due to a number of reasons. Conventional blood tests that were being used previously, such as INR, aPTT and platelet count are static tests and demonstrate poor sensitivity for monitoring the dynamic process of coagulation.[2] aPTT evaluates factors I, II, V, VII, IX, X XI and XII, which form the intrinsic and common final pathways, and is primarily used to monitor heparin anticoagulation.[5] Prothrombin time (PT) and its derived measure, INR, are used to evaluate the extrinsic and common final pathways of coagulation. This includes factors I, II, V, VII and X. PT was initially developed to aid in therapeutic anticoagulation monitoring with vitamin K antagonists. In the early 1980s, the INR was developed to standardize the expression of the prothrombin time ratio and hence minimize the intercenter variation due to the use of different reagents. Both INR and aPTT are *in vitro* tests performed on citrated, platelet poor plasma, and are not temperature sensitive. The *in vitro* nature of these tests has an important interpretive implication, as any condition in which coagulation may occur due to accelerated cellular function (e.g. platelets) may be missed.

Raised PT and INR have been implicated to be associated with an increased risk of progressive hemorrhagic injury (PHI), resultant irrevocable loss of brain tissue and unfavorable outcome in a multitude of studies.[6-14] A recent meta-analysis investigating the correlation between coagulopathy in TBI and PHI reported a pooled difference in means of 0.07 (CI 95% 0.02-0.13; *p*=0.0006).[15] This does not seem to be a significant difference, especially when it is noted that 3 of the 6 studies reported little to no difference. A recent prospective observational study in trauma patients who received fresh frozen plasma (FFP) transfusion found that while administration of FFP resulted in a reduction in INR, median TEG values remained within normal limits and clotting factor levels retained adequate function to produce normal clotting both before and after FFP transfusion.[16] Interestingly, patients who had a raised INR (>1.4), the median time to neurosurgical intervention (NI) was longer (358 minutes [285-478 minutes] vs. 231 minutes [96-363 minutes]), and were more likely to receive a monitoring device as their sole NI.[17] The investigators found no association between high INR and any individual abnormal TEG parameter.[16] Furthermore, when considering patients with similar presenting GCS and AIS head, FFP transfusions alone (OR 5.20 [CI 95% 1.72-15.730]) or in combination with PRBCs (OR 7.17 [CI 95% 2.12-24.12]) were associated with poorer long-term functional outcomes as measured by Glasgow outcome scale – extended (GOSE).[18] Low dose recombinant factor VIIa (rFVIIa) has been shown to be effective in correcting coagulopathy (INR>1.2 or platelet count<100 x 10^9/L) and hence preventing PHI without an increased risk for thromboembolic events.[7]

Thrombocytopenia has previously been linked to increased mortality at 6 months, but has only been reported in 7-10% of TBI patients.[19] In contrast, in our study, 10 patients (20%) were thrombocytopenic (platelet count<120 x 10^9/L). This may be attributed to the overall severity of head injuries in our sample. It is noteworthy that of the 13 thrombocytopenic samples, 11 had normal or hypercoagulable TEGs. This implies that a low absolute platelet count does not necessarily mean hypocoagulability. G value, a calculated parameter reflecting clot strength, has been reported to be a more sensitive measure of platelet function.[20, 21] No clear relationship between G value and platelet count was noted in our study.(Appendix P) The lack of association between platelet count and hypocoagulability by CBT is not in agreement with the results of a meta-analysis from 2016, which indicated that PHI was significantly associated with a platelet count <100 x 10^9/L.[15] It seems that the converse has

also been noted in the literature, viz. the presence of a normal platelet count does not preclude clinically significant bleeding tendencies.[22] However, in that study, six of the 20 TBI patients received extensive haemostatic treatment in the form of plasma, desmopressin, tranexamic acid and platelet concentrates, making the results difficult to interpret. While thrombocytopenia has been associated with an increased risk of progressive hemorrhagic injury,[6] so have certain CT findings, such as the presence of intraparenchymal contusions of a certain size.[9, 23] Evidence seems to be growing that platelet function rather than absolute platelet count is likely to be more informative when assessing coagulation status in brain-injured patients.[22]

In contrast to previous reports, we found a much higher proportion of hypercoagulable patients in our study sample.[1, 3] Of the 109 samples, 59 were found to be hypercoagulable by TEG. Thirty-four patients in our study were hypercoagulable by TEG at some time point and only 2 of those patients became hypocoagulable at any time point. This seems to imply that a DIC type picture is far less common than previously thought. Five patients that were categorized as hypercoagulable on TEG that demised prior to the second sample. It is possible that they may have become hypocoagulable at some time point had they survived longer, which could make it erroneously appear that the number of patients displaying features of DIC is smaller. Hypothetically, if all five of those patients would become hypocoagulable still leads to a much smaller proportion (14%) of patients displaying features of DIC than reported in the literature (33-35%).[1]

Hypercoagulability as diagnosed by TEG is documented in trauma.[24] A small study (*n*=25) found that all of their patients were hypercoagulable by manufacturer defined criteria for both MA and G value between day 4 and day 5 following TBI.[20] Unfortunately, our study was only able to follow up patients up to 60 hours post injury. Despite this, we also showed a sustained hypercoagulable state. Furthermore, thromboelastometric (ROTEM) analysis showing shorter clotting times and higher clot firmness has been linked with survival in a recent study.[25] While native TEG and ROTEM parameters are significantly different in trauma patients, celite activated samples can be considered comparable.[26]

Assuming clotting cascade activation is a consequence of massive tissue factor release from the injured brain, we postulated that penetrating injuries that result in severe traumatic brain injury may be a particularly 'at risk' group for coagulopathy. We did not find any significant

differences in the number or type of coagulopathy as diagnosed by TEG between the blunt and penetrating trauma groups at any time, which is consistent with findings in a previous report.[27] Interestingly, in that study, there was a slightly higher proportion of moderate (GCS 9-12) and severely (GCS≤8) injured patients in the penetrating group (80%) when compared to the blunt group (68.5%).

The severity of head injuries in those that demised was such that many of these patients were deemed unsalvageable and their deaths were expected. These patients were provided all supportive treatment, but were not managed actively (i.e. not taken to theatre for ICP monitor placement or admitted to ICU for further management). Many of them remained in the trauma unit. Literature often excludes patients who are deemed unsalvageable, often leading to an underestimate in mortality in head injury outcome studies.[28, 29] In the present study, there were no differences in numbers or type of coagulation abnormalities in the subgroup that demised during the course of the study, the median AIS head was higher (6 vs. 5), and the median AIS body was similar (both 1) to the study population overall.

Improvements in our understanding of the cell-based nature of coagulation and the role of tissue factor and platelets, have necessitated the development and use of tests that can provide more reliable information regarding in vivo hemostasis.[30-32] TEG and ROTEM are two such tests which can provide information about all the stages of hemostasis – from clot development to fibrinolysis. The fact that point-of-care (POC) test results are rapidly available to provide a clinically useful approach to targeted blood product administration in hemostatic resuscitation leads to reduced blood product transfusion (73.1% vs. 53.9% [*p*=0.03]), reductions in FFP administration when compared to INR triggers (26.9% vs. 65.5% [*p*=0.003]) and improved clinical outcomes.[33] In addition to the obvious reduction in potential harm to the patient by administration of fewer blood products, preservation of life-saving resources in a resource poor environment is crucial.

POC coagulation testing has some limitations. Firstly, the availability of the equipment and knowledge to run the test accurately to achieve consistent results is a hurdle in both developed and developing countries.[34] Secondly, while it is possible to adjust the temperature of the test, it is not routinely done. Failure to do so in hypothermic patients can mask the severity of coagulopathy. Lastly, these tests are not geared to assess endothelial contribution to hemostasis and hence this cannot be assessed.

The literature surrounding TBI defines severe GCS as being less than eight, but does not subdivide it into any further levels, likely because GCS is not a linear scale.[22, 35-37] While GCS may be a useful surrogate measure of injury severity, and hence aid to triage and prognosticate injury trajectory, it does not equate to outcome.[38] Accordingly, we have selected the most severely injured patients by only recruiting those with a GCS of less than eight, but have not further subdivided the patients into categories based on their GCS. GCS can be greatly influenced by external factors such as sedation, whether iatrogenic or self-inflicted. Furthermore, GCS is time sensitive; a rapid deterioration in GCS may imply more urgency when compared to a gradual decline.

The aim of CT classification of head injuries in this study was to ensure that patients who presented with a low GCS had significant cerebral injuries to account for the low GCS, and hence to decrease the risk of recruiting inappropriate patients. In this study, we have presented data for both Rotterdam and Marshall scores for each individual patient (Appendix F). While both are validated scoring systems in TBI, the sensitivity and specificity may differ due to the dichotomous nature of scoring systems. One study suggested that while the Marshall score has good predictability when assessing mortality, the Rotterdam score may be better for prognostication.[39] We had a significant difference in calculated scores. While 24 patients had a Marshall score of 4, only 8 patients had a Rotterdam score of 4. There was no clear association between the score and the presence of coagulopathy on TEG. This is a descriptive study, with the potential to assist in planning future studies targeted at evaluating these two scoring systems. Hence, we have reported both scores for each patient.

A recent study showed a significant gender difference in TEG variables, with healthy female patients to be slightly hypercoagulable when compared to their male counterparts.[40] Female patients had a shorter R time (6.3 [5.2-8.2] vs. 8 [6.8-8.9]; p=0.012) and K time (2.1 [1.8-2.4] vs. 2.9 [2.6-3.2]; p<0.001), larger α angle (59.1$\pm$11.0 vs. 51.1$\pm$8.1; p<0.001) and larger MA (59.4$\pm$5.8 vs. 54.3$\pm$5.6; p=0.001). Most (94%) of the patients in the present study were male, reflecting our typical TBI patients, which makes the presence of a hypercoagulable state as diagnosed by TEG significant.

Two studies have shown a difference between simultaneously drawn arterial and venous samples and TEG variables.[41, 42] In both studies, there was a significant difference between the arterial and venous catheter sizes (20 G arterial catheter, vs 9F central venous sheath vs 7F pulmonary artery catheter in one study; and although size is not explicitly stated in the other, the comparison done was between an arterial catheter and a central sheath, therefore a significant difference in lumen diameter is likely). It seems that significant shear force from the smaller lumen diameter may result in platelet aggregation, which may account for the differences seen (CVC [central venous catheter] R time 8.4±2.7 vs. arterial R time 9.8±3.1 vs. central sheath R time 12.7±4.8; *p*=0.004 and CVC MA 60.4±11.7 vs. arterial MA 56.2±11.4 vs. central sheath 50.5±13.3; *p*=0.008), rather than whether the sample was drawn from an arterial or venous site. In the present study, when patients had a functioning arterial catheter in situ, it was deemed unethical to obtain a venous sample and therefore blood was drawn via the arterial catheter. While it is possible that this may affect the results, similar gauges were used for both samples (20 G, 5 cm arterial catheters are used most commonly at our institution, and 20 G needles were used for phlebotomy). Furthermore, since all samples were drawn by a single investigator, the negative pressure applied during blood drawing is likely to be similar and unlikely to be the source of the differences seen.

While we endeavored to document parameters such as temperature and clinical evidence of alcohol at presentation, much of the data was not available, and hence detailed analysis of these parameters could not be pursued. Interestingly, while patients with more severe brain trauma are more likely to have an early and consistent pyrexia and prolonged stay in ICU, predicted probability of death increased as brain temperature dropped below 36°C.[43] We found no appreciable difference in temperature trends when divided by coagulation status, although patients who demised during the course of the study seemed to have a trend towards a higher temperature.(Appendix Q) Acute alcohol intoxication can reportedly make TEG measurements (prolonged R and K times and decreased α angle) appear relatively hypocoagulable when compared to non-intoxicated trauma patients.[44] Surprisingly, acute alcohol intoxication is associated with a significantly lower incidence of in-hospital mortality and lower frequency of coagulopathy by conventional blood testing on admission, despite similar severity of injury by AIS head scoring.[45] One possible confounder in that study was the use of pharmacological alcohol withdrawal prophylaxis in the form of barbiturates,

benzodiazepines, dexmedetomidine or propofol, all of which decrease cerebral metabolism and hence may have had some protective effect.

Management of fluid balance and fluid choice is a crucial part of the treating any critically ill patient. Overall, at our institution, patients with TBI tend to receive slightly hypernatremic fluids, such as normal saline, with an aim to avoid cerebral edema. In a porcine model of TBI and hemorrhagic shock, normal saline was associated with early activation of coagulation, anticoagulation and endothelial systems when compared to FFP and colloid resuscitation. Furthermore, the use of normal saline may play a role in electrolyte abnormalities such as hypernatremia and hypokalemia which complicate patient management.[46] While we noticed a trend of a more positive fluid balance in the hypocoagulable group at T1, the numbers were too small to pursue any meaningful statistical analyses.(Appendix N) A small retrospective human study found no association between cumulative fluid balance and the development of refractory intracranial hypertension, but did note a strong association with the development of pulmonary edema (HR 1.69 [CI 95% 1.40-2.04, p<0.001]).[36] High or low cumulative fluid balances (>3673 mL [6078$\pm$2112 mL] and <637 mL [-389$\pm$941 mL] respectively) are associated with poor short-term outcomes. [47] While four patients received synthetic colloids (HES 130/0.4) prior to recruitment to the study, and an additional 7 received synthetic colloids after recruitment (of which 3 also received PRBC in addition to colloids), none of these patients displayed any features of a hypocoagulable state on TEG. None of the study patients had received any blood or blood products prior to recruitment to the study. Of the 8 patients that subsequently received PRBC after recruitment, only 2 were hypocoagulable by TEG. It seems that dilutional coagulopathy is unlikely to be the sole contributor to presence of a hypocoagulable state.

While some differences were noted in presenting vitals (lower mean systolic blood pressure and higher mean pulse rate, Appendix O) amongst the hypocoagulable group when compared to the hypercoagulable and normal groups, none of these were statistically significant due to the small numbers of hypocoagulable patients in the study. This finding is contrary to a previous report which found that patients with a prolonged R time at admission TEG had a higher admission mean arterial blood pressure (129 vs. 101 mmHg) and pulse rate (99 vs. 89 beats per minute).[48] Unfortunately, the investigators did not indicate how many of their 69 study patients were in the hypocoagulable group.

South Africa, a developing country, has the fourth highest adult human immunodeficiency virus (HIV) prevalence (19.1%) worldwide, as well as a high incidence rate of tuberculosis(TB) (834 per 100000 in HIV positive cases and 509 per 100000 in HIV negative cases).[49, 50] Both of these conditions are known to be associated with a relatively hypercoagulable state.[51, 52] It is highly likely that some patients in this study may have undiagnosed HIV or TB despite the lack of clinical features of either illness, and it is possible that this could have affected the coagulation testing.

This study has a number of strengths and limitations that merit discussion. To the best of our knowledge, this is the first study to look at both conventional blood testing and viscoelastic testing in severely brain injured patients longitudinally, while excluding patients with other significant injuries. We therefore report the findings in 50 isolated and severely head-injured patients.

This was a single center study, and all the limitations of a single center study apply. Of note, our hospital is one of the two tertiary level public hospitals in the province that are equipped to manage traumatic brain injury. However, it is difficult to extrapolate these results to the entire population as the patient demographics may differ. We were not able to do concurrent TEG platelet mapping studies or fibrinogen levels, which may have yielded interesting results. Unfortunately, certain data is unavailable due to differing documentation styles of the admitting staff – for example the presence of clinical evidence of ethanol intoxication, and temperature upon arrival. Many of the patients in the study were unidentified at the time of presentation to the hospital and during the study, thus the availability of collateral and background medical history was limited. Certain recorded parameters such as details of fluid administration, urine output and interim vitals were taken from the patients' records. There is always a possibility that some of this data could be missing, underestimated or erroneously recorded in a typical busy hospital setting. Referral notes for patients referred on via a primary or secondary hospital were scrutinized, however the information provided was of varying quality and the possibility of missing some data exists.

There are a number of strengths to this study. One investigator recruited all the study patients, performed all venipunctures, blood sampling and running of TEG samples, thus eliminating much bias, as well as sampling and test errors. All the data were also captured by the same investigator in a systematic manner. The possibility of misreporting of data is thus

minimized. All CT scans were evaluated and scored by a single investigator to maintain consistency of scoring.

CONCLUSION

Contrary to what is reported in the literature, we found little evidence of a hypocoagulable state as defined by TEG (10 of the 109 samples) in severely brain-injured patients that presented to Groote Schuur Hospital. On the contrary, many patients were significantly hypercoagulable (59 of the 109 samples) according to criteria specified by the TEG manufacturer. When considering the CBT results, we had a much higher number of hypocoagulable samples (72 of the 109 samples), with none showing a hypercoagulable state. Moreover, there was poor correlation between coagulation status as measured by TEG described and that found on conventional blood testing. No significant differences in the prevalences of coagulopathy amongst blunt and penetrating mechanisms of injury were noted. Some differences in fluid balance and presenting vitals in the hypocoagulable group when compared to the normal and hypercoagulable groups were noticed, but this does not attain any statistical significance due to the small numbers of hypocoagulable patients in our study.

APPENDICES

Appendix A

Abbreviated Injury Score

The Abbreviated Injury Scale (AIS) is an anatomical-based coding system created by the Association for the Advancement of Automotive Medicine to classify and describe the severity of injuries. It represents threat to life associated with the injury rather than a comprehensive assessment of severity of the injury. The score describes 3 aspects of the injury - type, location and severity.

Type indicates which anatomical structures are involved:

1. Whole area
2. Vessels
3. Nerves
4. Organs (including muscles and ligaments)
5. Skeletal (including joints)
6. Loss of consciousness (head)

Location is classified by body region:

1. Head
2. Face
3. Neck
4. Thorax
5. Abdomen
6. Spine
7. Upper extremity
8. Lower extremity
9. Unspecified

Severity of injuries is classified as follows:

1. Minor - 0% probability of death
2. Moderate - 1-2% probability of death
3. Serious - 8-10% probability of death
4. Severe- 5-50% probability of death
5. Critical - 5-50% probability of death
6. Maximum - 100% probability of death

Appendix B

The Glasgow Coma Scale

It is used to assess the level of consciousness following head injury, especially by means of serial evaluations. Three responses are assessed; eyes, verbal and motor, with a minimum score of 3 and a maximum score of 15.

	Eyes	**Verbal**	**Motor**
1	No eye opening	Makes no sounds	Makes no movements
2	Opens eyes to painful stimulus	Incomprehensible sounds	Extension to painful stimulus (decerebrate posturing)
3	Opens eyes to verbal command	Inappropriate words	Abnormal flexion to painful stimulus (decorticate posturing)
4	Spontaneous eye opening	Confused, disoriented	Flexion/withdrawal to painful stimulus
5	N/A	Orientated, converses normally	Localizes painful stimulus
6	N/A	N/A	Obeys commands

Appendix C

Normal TEG values as specified by the manufacturer

1. R time (reaction time, time to first measurable clot formation): 4-8 minutes
2. K time (achievement of a certain clot firmness): 0-4 minutes
3. α angle (kinetics of clot development): 47-74 degrees
4. MA (maximum amplitude, maximum strength of clot): 54-72 mm
5. LY30 (percent lysis 30 minutes after MA): 0-8%
6. EPL (estimated percent lysis): 0-15%
7. Coagulation Index (linear combination of R, K, α angle and MA): -3-3
8. G Value (dynes/cm^2): 6-13.2

Appendix D

Normal laboratory values as specified by the NHLS

1. Platelet count 171-388x10^9/L
2. Sodium: 136-145 mmol/L
3. Potassium: 3.5-5.1 mmol/L
4. Urea: 2.1-7.1 mmol/L
5. INR 0.8-1.0
6. aPTT 20-36 seconds (Control specified on the laboratory report)

Appendix E

Criteria for repeat blood sampling at 60 hours post injury (20% outside of the normal values for coagulation testing and 10% outside the normal values for electrolyte abnormalities)

1. Sodium <123 or >159 mmol/L
2. Potassium <3.15 or >5.61 mmol/L
3. Platelet count <120x10^9/mL or >540x10^9/mL
4. INR <0.6 or >1.4
5. PTT <16 seconds or >43 seconds
6. TEG
    - R time <3 minutes or >10 minutes
    - K time >5 minutes
    - α angle <38 degrees or >88 degrees
    - CI <-4 or >4
    - EPL >20%
    - LY 30 >10%

Appendix F

Details of CT scans

1. CT characteristics of head injuries
2. Numbers of patients by Marshall and Rotterdam scores
3. Details of CT scoring

Table 1

CT characteristic		**Number of patients**
Basal cisterns	Normal	10
	Compressed	22
	Absent	17
	Total	49
Midline shift	≤ 5 mm	25
	>5 mm	24
	Total	49
Epidural mass lesion	Present	4
	Absent	45
	Total	49
Intraventricular blood or SAH	Present	46
	Absent	3
	Total	49
Intracerebral lesions	Absent	12
	High or mixed density, ≤ 25 cm^3	34
	High or mixed density, >25 cm^3	3
	Total	49

Table 2

	1	2	3	4	**Total**
Rotterdam score	9	9	23	8	49
Marshall score	0	9	16	24	49

Table 3

Patient number	**Basal cisterns**	**Midline shift**	**Epidural mass lesion**	**Intra-ventricular blood or SAH**	**Lesions**	**Surgically evacuated lesion?**	**Rotterdam score**	**Marshall score**
1	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
2	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
3	Compressed	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	2	3
4	Compressed	> 5mm	Absent	Present	Absent	No	3	4
5	Compressed	> 5mm	Absent	Present	Absent	No	3	4
6	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
7	Normal	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	1	2
8	Normal	≤ 5 mm	Absent	Absent	High or mixed, ≤ 25 cm3	No	2	2

9	Compressed	> 5mm	Absent	Present	Absent	No	3	4
10	Compressed	> 5mm	Present	Present	High or mixed, ≤ 25 cm3	No	2	4
11	Normal	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	1	2
12	Compressed	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	2	3
13	Absent	> 5mm	Absent	Present	Absent	No	4	4
14	Normal	≤ 5 mm	Absent	Present	Absent	No	1	2
15	Absent	> 5mm	Absent	Present	Absent	No	4	4
16	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
17	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
18	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
19	Compressed	> 5mm	Absent	Present	Absent	No	3	4
20	Absent	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	4	4
21	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
22	Compressed	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	2	3

23	Absent	≤ 5 mm	Present	Absent	High or mixed, ≤ 25 cm3	No	3	3
24	Compressed	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	2	3
25	Normal	≤ 5 mm	Absent	Present	Absent	No	1	2
26	Compressed	≤ 5 mm	Present	Present	High or mixed, ≤ 25 cm3	No	1	3
27	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
28	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
29	Absent	> 5mm	Absent	Present	Absent	No	4	4
30	Normal	≤ 5 mm	Absent	Present	Absent	No	1	2
31	Normal	> 5mm	Present	Absent	Absent	No	2	4
32	Absent	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	4	4
33	Absent	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	4	4
34	Compressed	> 5mm	Absent	Present	High or mixed, >25cm3	No	3	4
35	Normal	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	1	2
36	Compressed	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	2	3

37	Compressed	> 5mm	Absent	Present	High or mixed, >25cm3	No	3	4
38	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
39	Normal	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	1	2
40	Absent	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	4	4
41	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
42	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
43	Compressed	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	2	3
44	Absent	≤ 5 mm	Absent	Present	High or mixed, >25cm3	No	3	3
45	N/A	N/A	N/A	N/A	N/A	N/A		
46	Absent	> 5mm	Absent	Present	Absent	No	4	4
47	Absent	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	3
48	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4
49	Normal	≤ 5 mm	Absent	Present	High or mixed, ≤ 25 cm3	No	1	2

50	Compressed	> 5mm	Absent	Present	High or mixed, ≤ 25 cm3	No	3	4

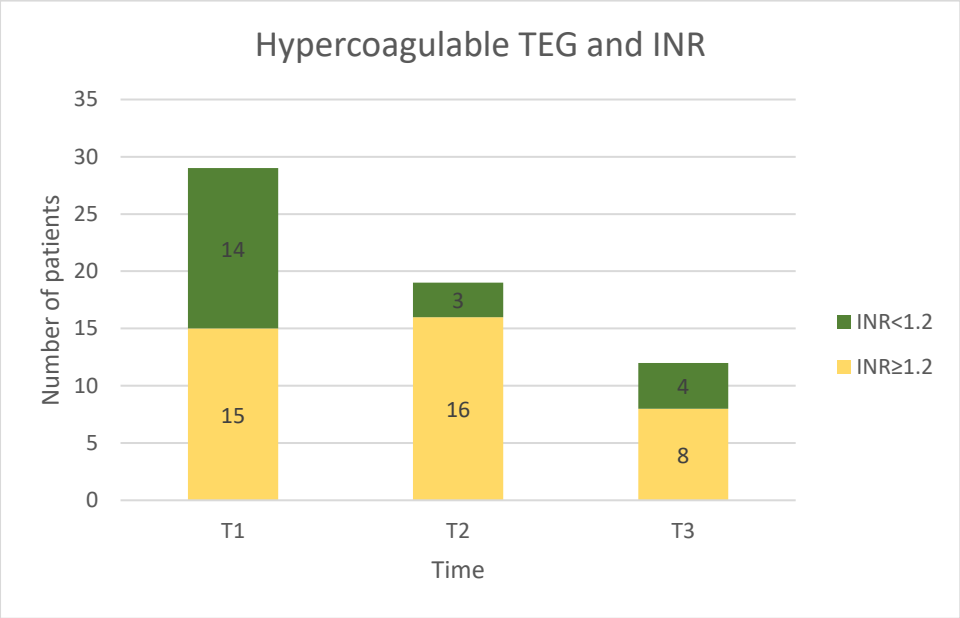
Appendix G

Descriptive statistics by 12 hour TEG coagulation status

		Normal	Hypocoagulable	Hypercoagulable
Patients	Number	16	6	28
Age	Mean years	33.75	24.05	31.06
Mechanism of injury	Number of blunt	13	3	20
	Number of penetrating	3	1	8
AIS head	Median	5	5.5	5
AIS body	Median	1	1	1
Worst GCS	Median	5.5	4	5
Location of intubation	On scene	5	1	13
	Referring hospital	5	4	10
	Groote Schuur Hospital	6	1	5
Vitals	Mean systolic blood pressure	123.19	93.83	121.11
	Mean pulse rate	89.81	107.5	94.32
	Mean pH	7.323	7.33	7.326
	Mean base deficit	-4.769	-4.383	-5.096
	Mean lactate	3.356	4.5	4.125
Average fluid balance	Mean	2383.13	3930	1748.57
CT Marshall score	Median	3	4	4
CT Rotterdam score	Median	2	3	3
Died	Number	3	3	10

Appendix H

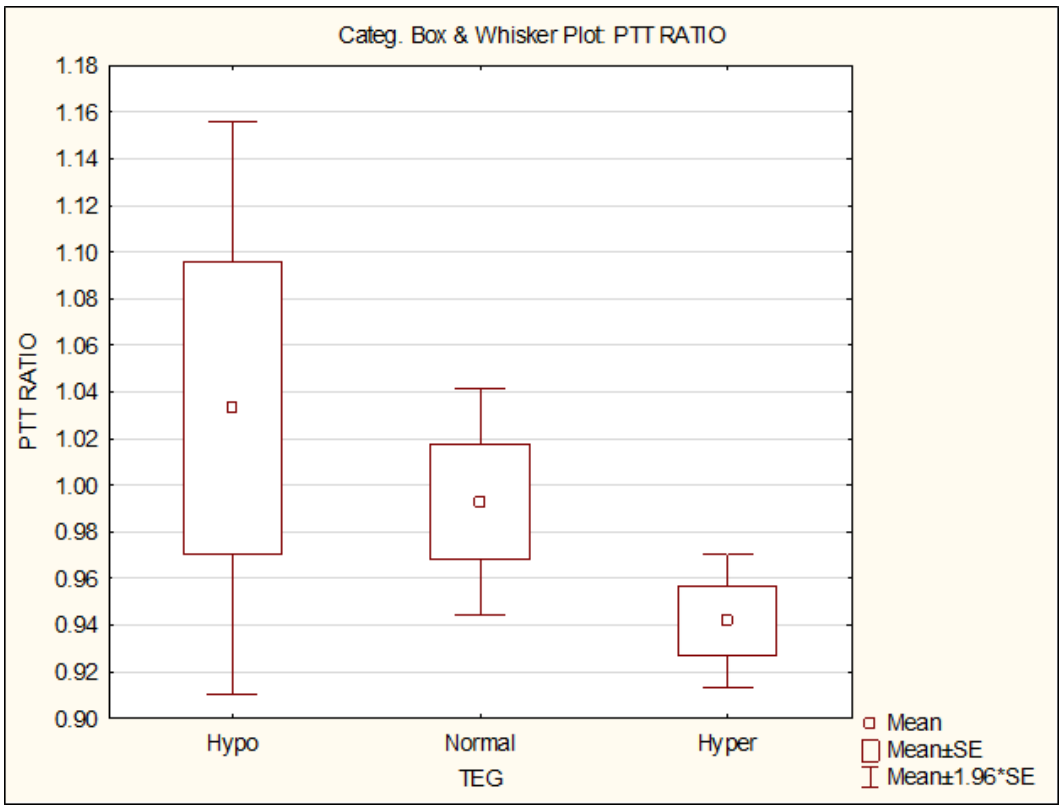
Number of hypercoagulable TEGs and each time point when classified by INR.

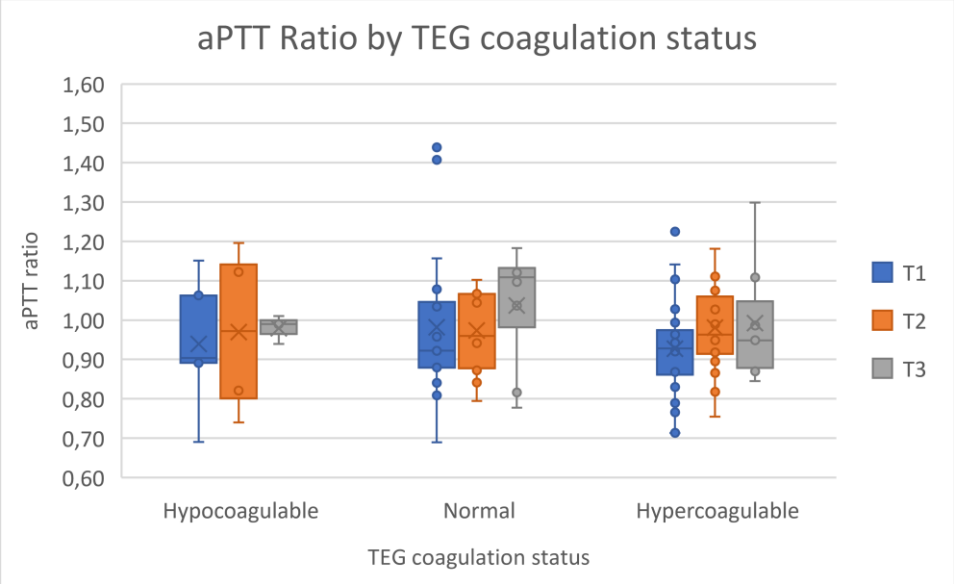


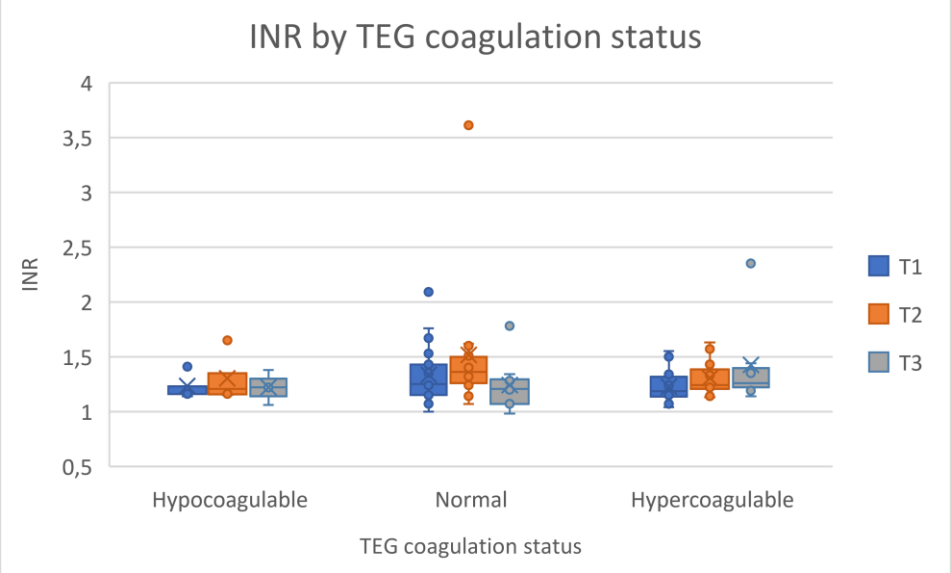
Appendix I

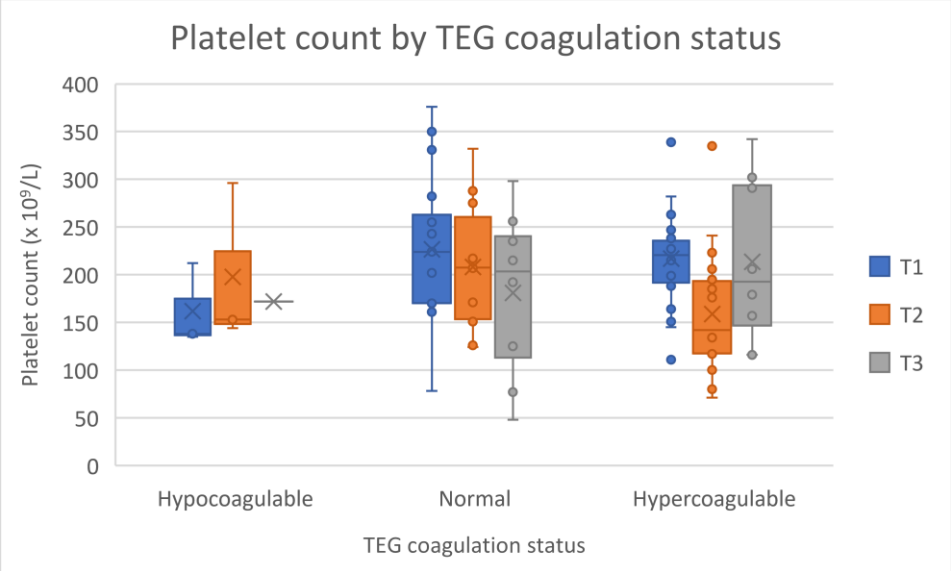
Conventional blood testing and coagulation status by TEG:

1. aPTT ratio by TEG coagulation status
2. aPTT ratio by time
3. INR
4. Platelet count




aPTT Ratio by TEG coagulation status
aPTT ratio
1,60
1,50
1,40
1,30
1,20
1,10
1,00
0,90
0,80
0,70
0,60
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum


INR by TEG coagulation status
INR
4
3,5
3
2,5
2
1,5
1
0,5
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum


Platelet count by TEG coagulation status
Platelet count (x 10⁹/L)
400
350
300
250
200
150
100
50
0
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum

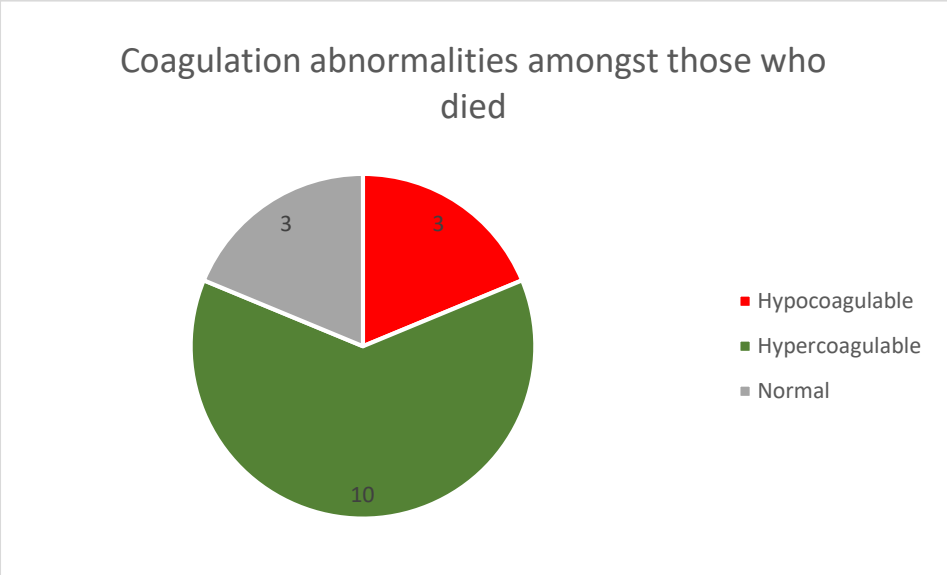
Appendix J

Coagulation status according to TEG by mechanism of injury and time point

		Time			Total
Mechanism of injury	**Coagulation status by TEG**	**T1**	**T2**	**T3**	
Blunt	Hypercoagulable	20	16	10	46
	Hypocoagulable	3	2	1	6
	Normal	13	15	5	33
	No sample	0	3	20	23
Penetrating	Hypercoagulable	8	3	2	13
	Hypocoagulable	3	1	0	4
	Normal	3	4	0	7

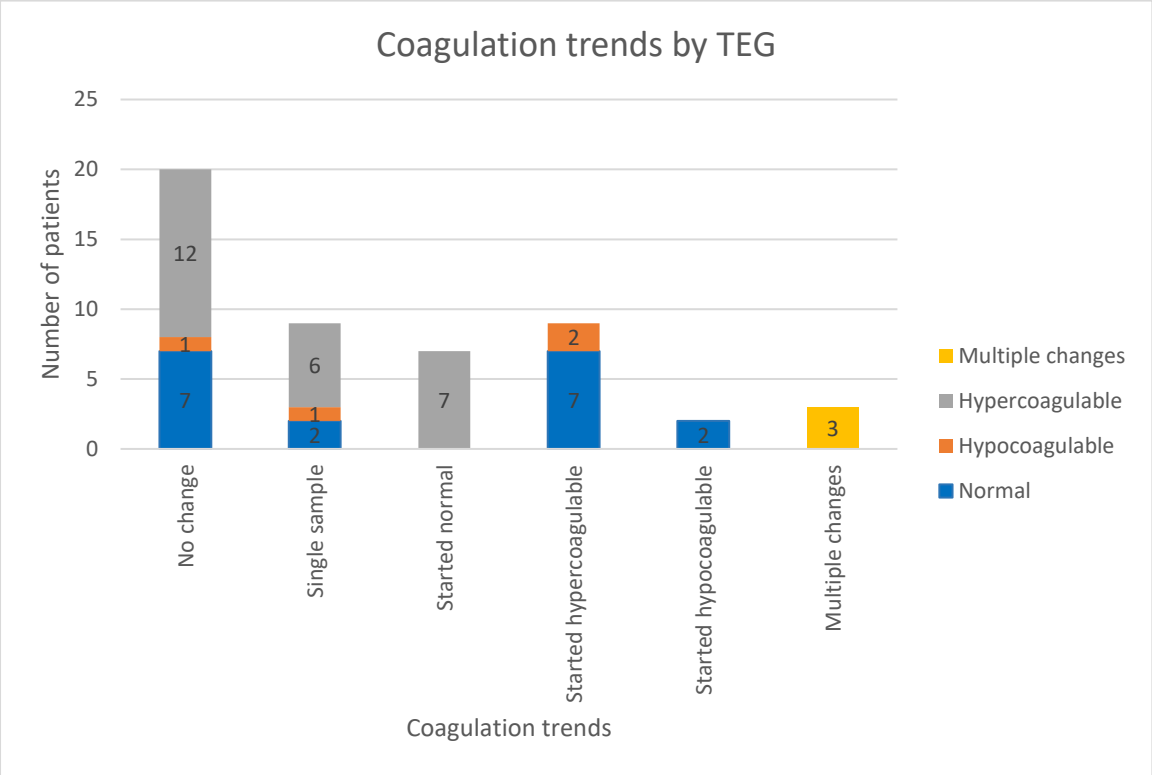
Appendix K

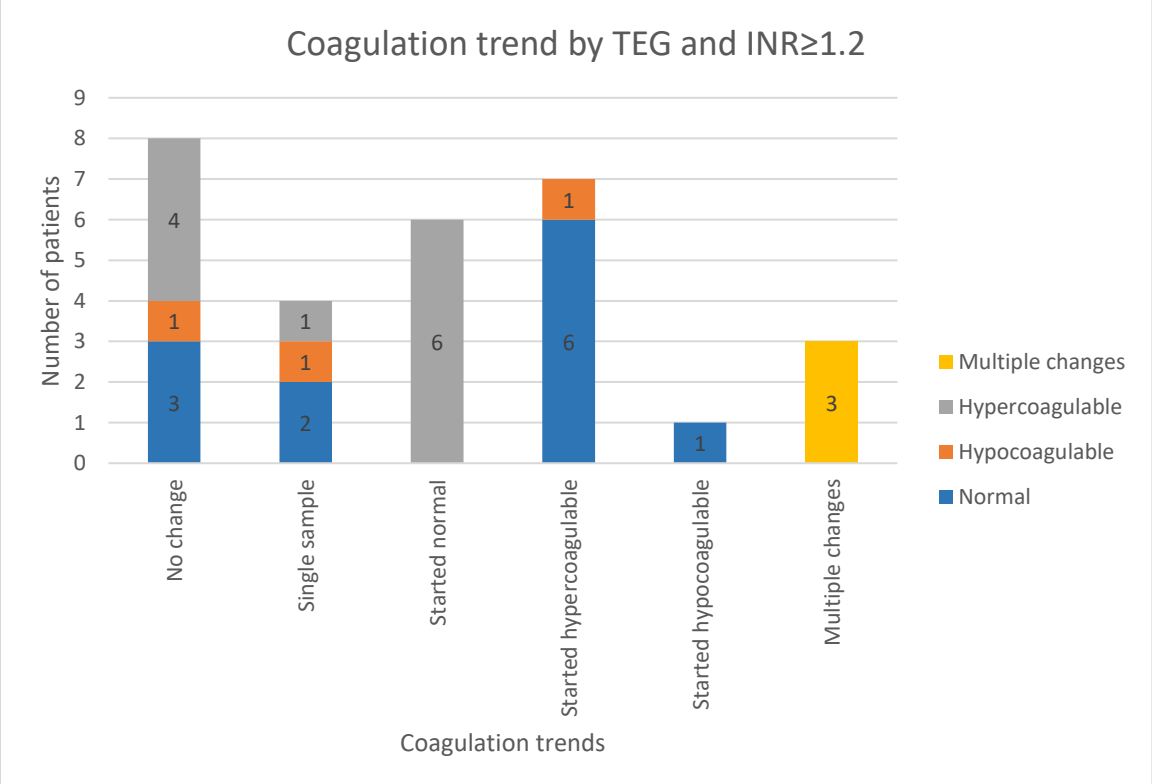
Coagulation abnormalities amongst those who died



Appendix L

Coagulation trends by TEG (1) and Raised INR in comparision to TEG (2)

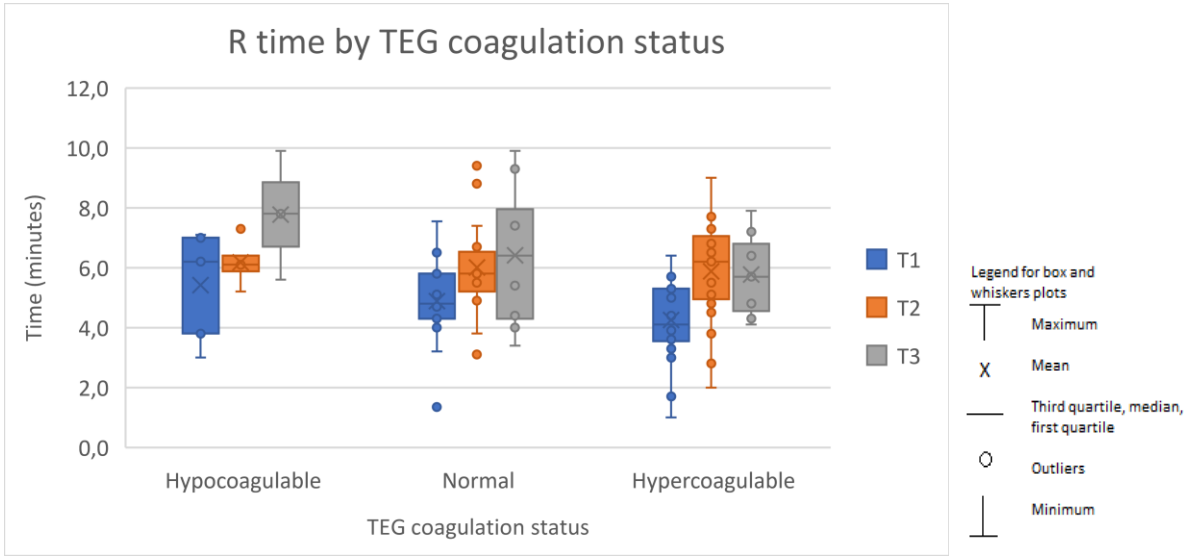


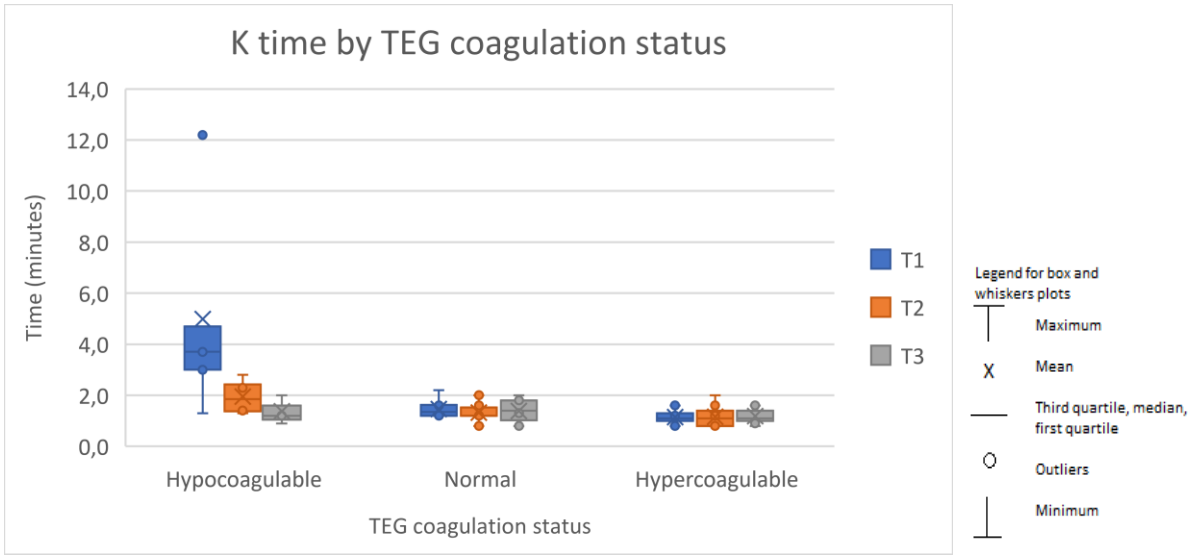


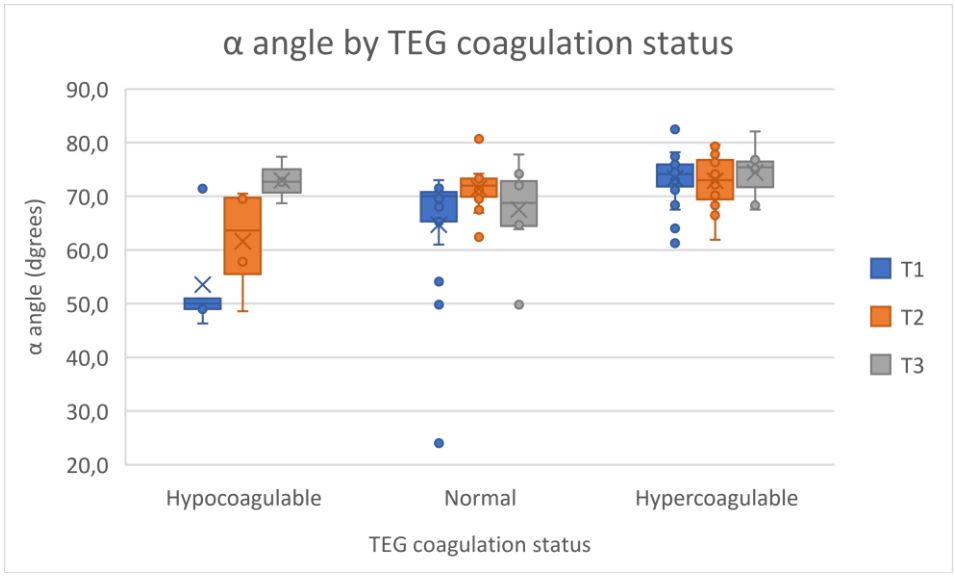
Appendix M

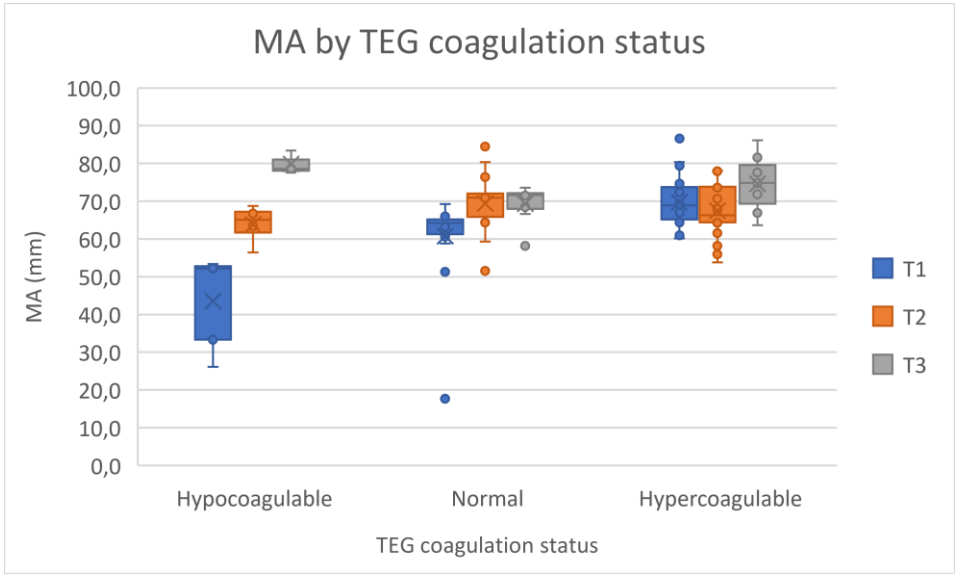
TEG variable trends by time

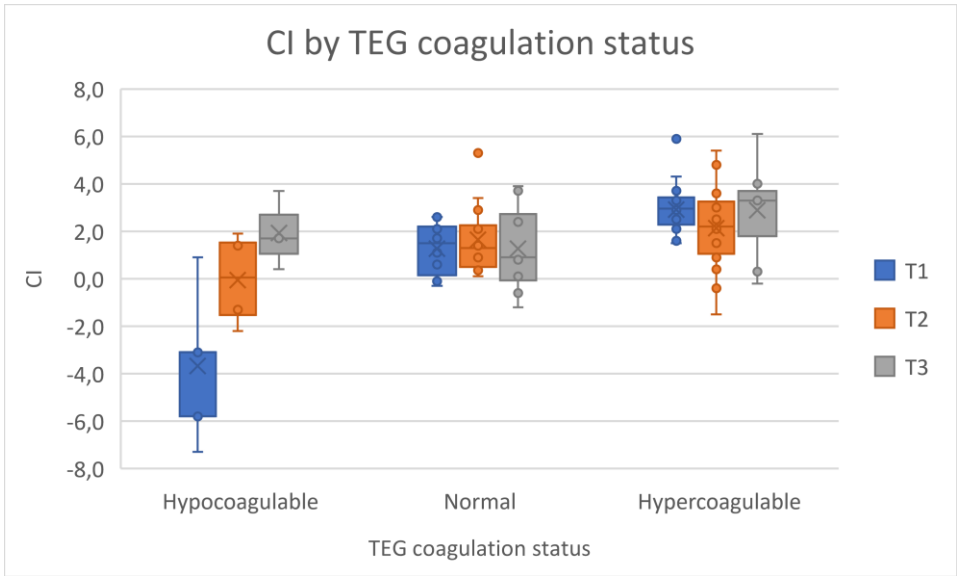
1. R time
2. K time
3. α angle
4. MA
5. CI
6. G value

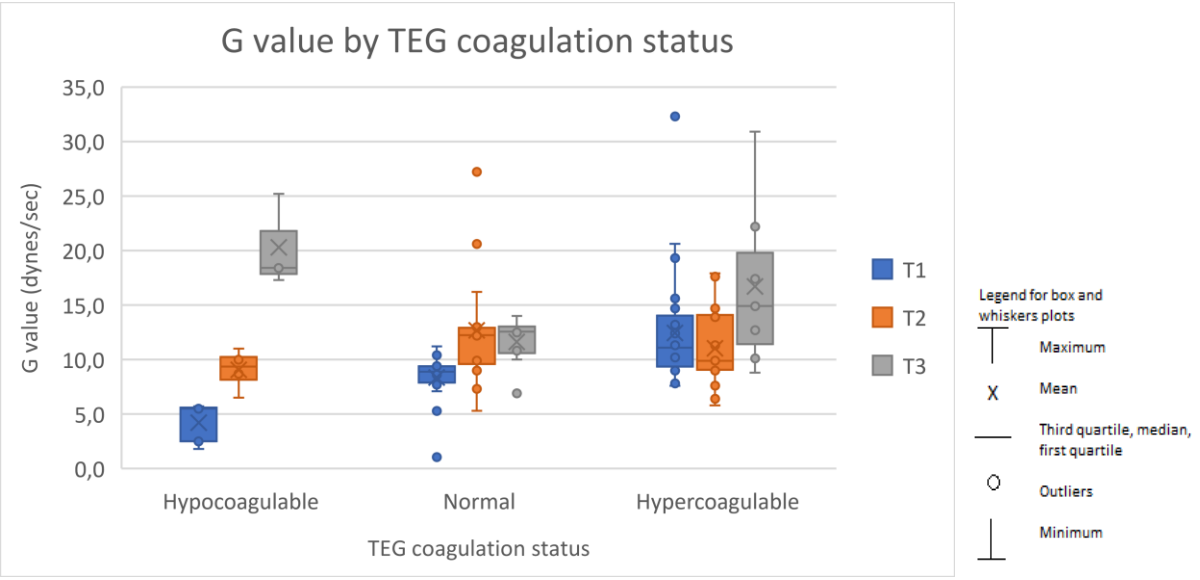





α angle by TEG coagulation status
α angle (dgrees)
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum

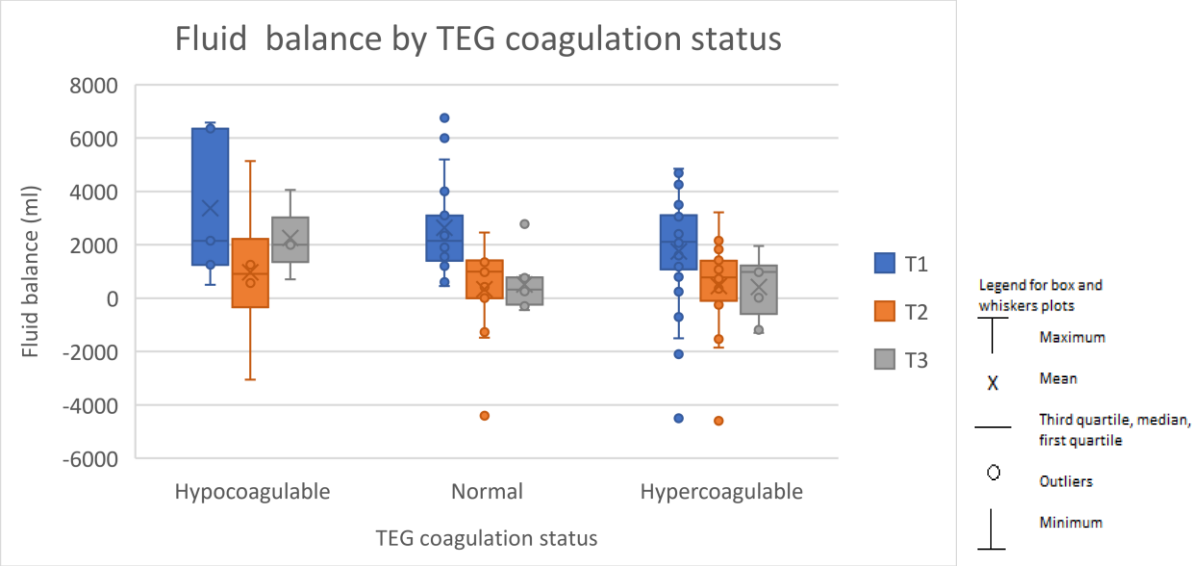

MA by TEG coagulation status
MA (mm)
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum


CI by TEG coagulation status
CI
8,0
6,0
4,0
2,0
0,0
-2,0
-4,0
-6,0
-8,0
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum


G value by TEG coagulation status
35,0
30,0
25,0
20,0
15,0
10,0
5,0
0,0
G value (dynes/sec)
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum

Appendix N

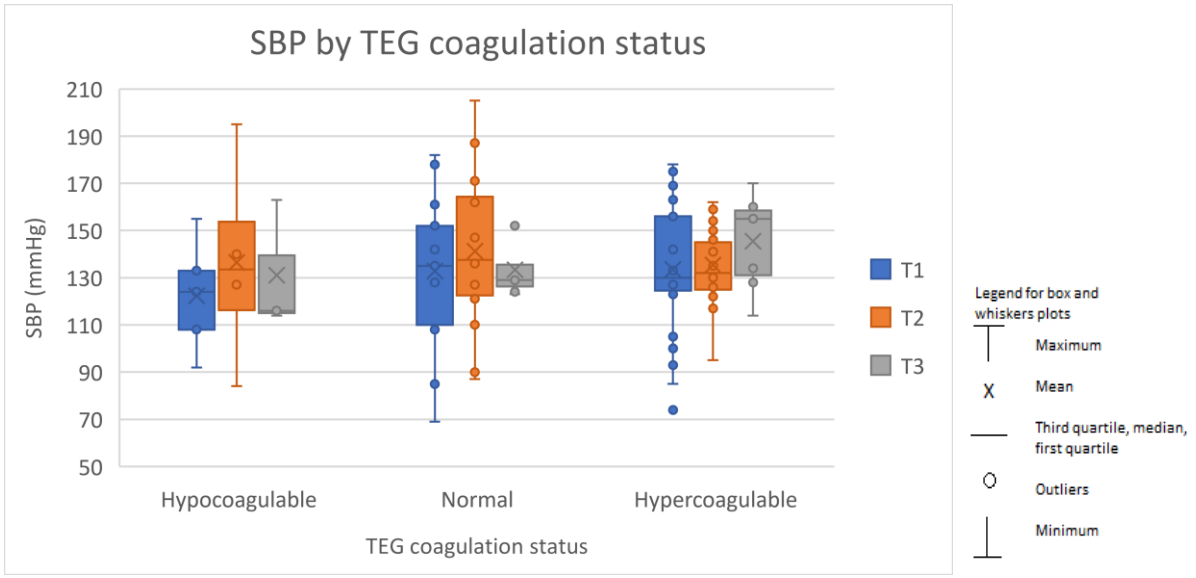
Fluid balance by TEG coagulation status

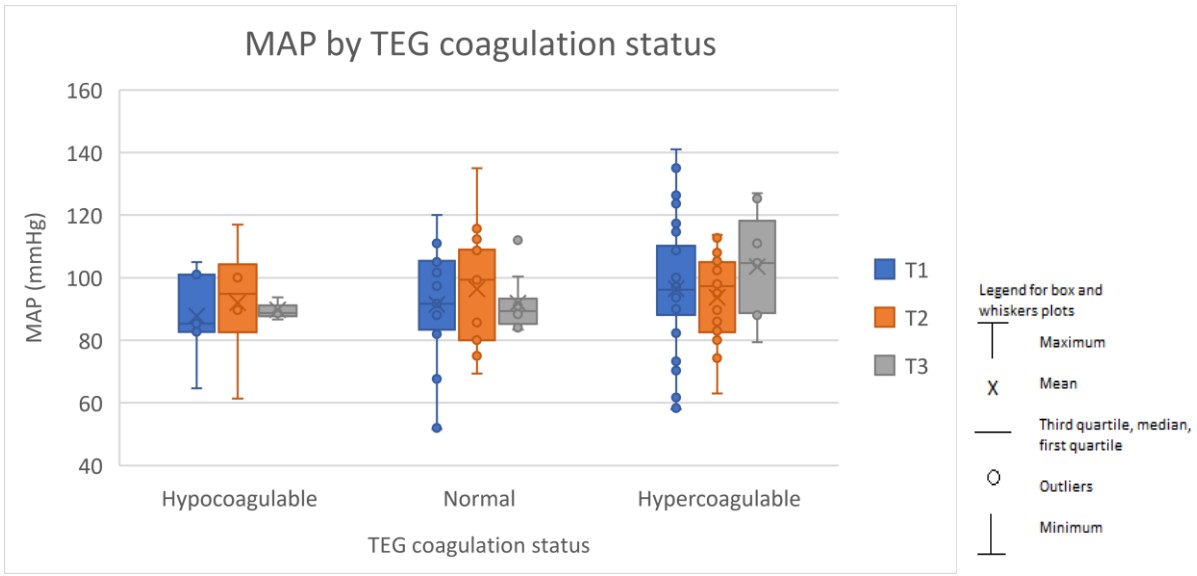


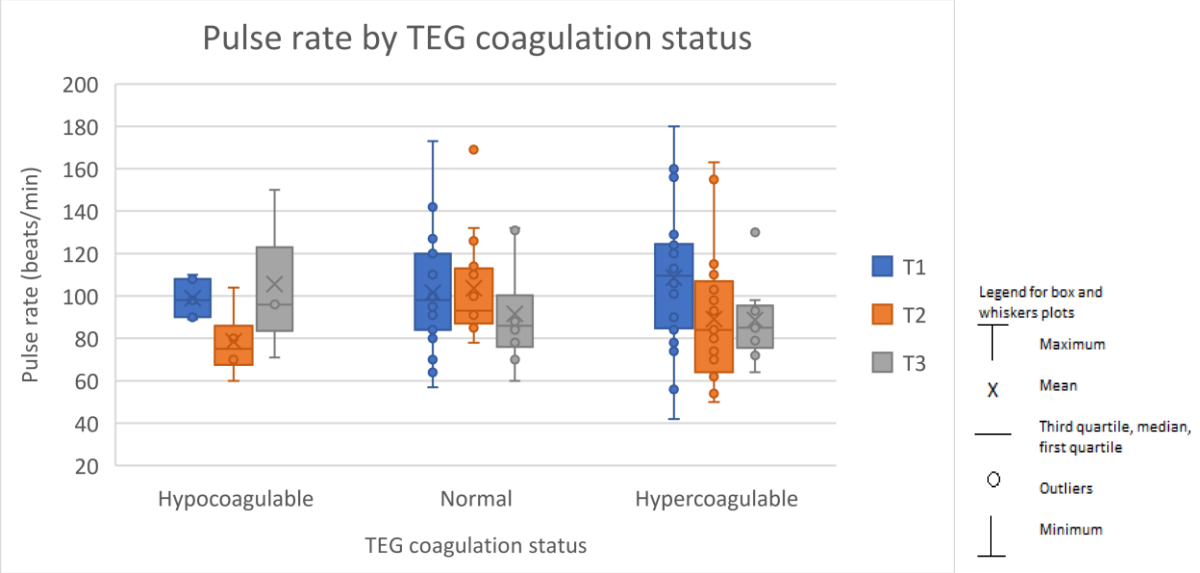
Appendix O

Vital signs by TEG coagulation status:

1. Systolic blood pressure (SBP)
2. Mean arterial blood pressure (MAP)
3. Pulse rate (PR)

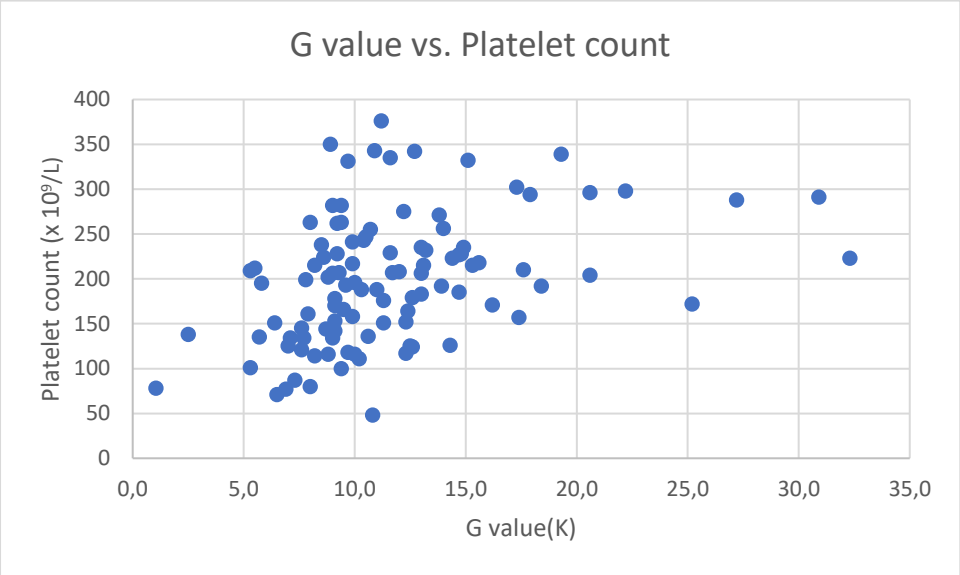





Pulse rate by TEG coagulation status
Pulse rate (beats/min)
200
180
160
140
120
100
80
60
40
20
Hypocoagulable
Normal
Hypercoagulable
TEG coagulation status
T1
T2
T3
Legend for box and whiskers plots
Maximum
Mean
Third quartile, median, first quartile
Outliers
Minimum

Appendix P

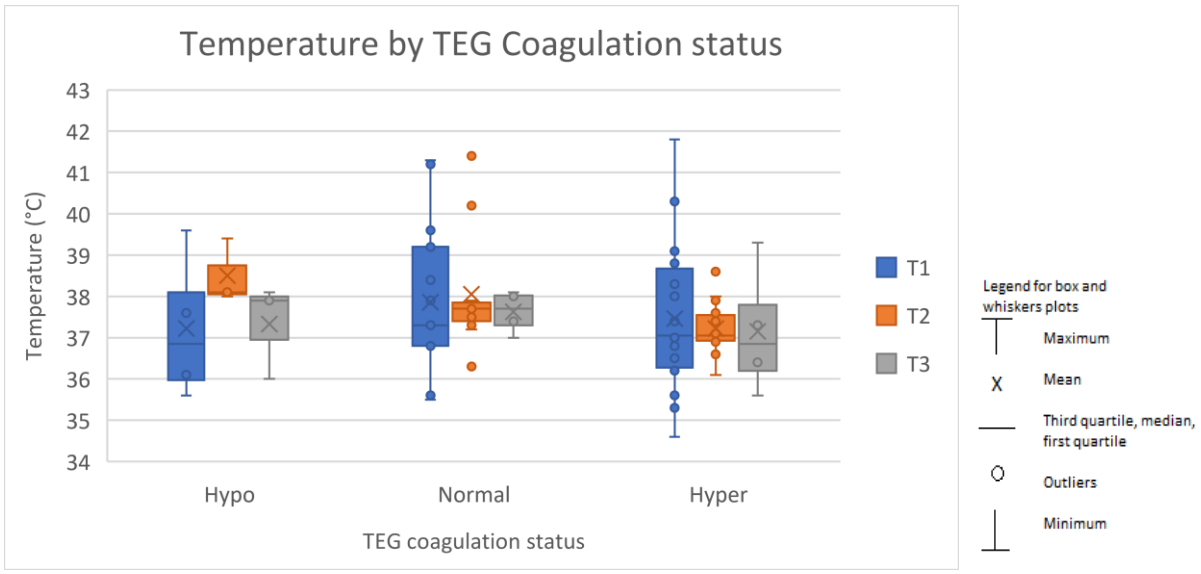
Relationship between G value and platelet count

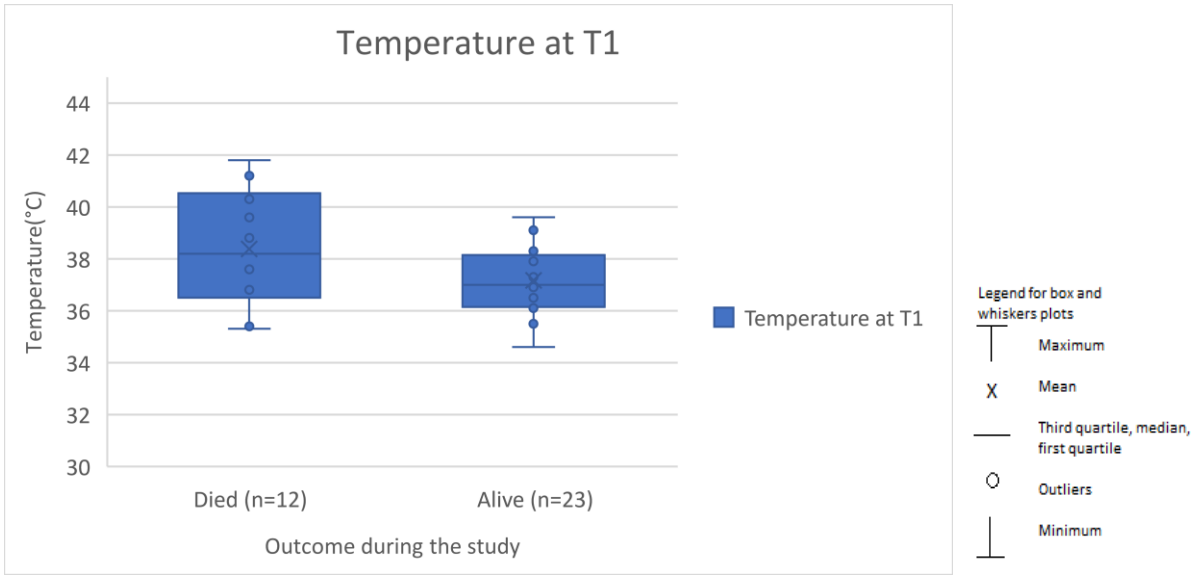


Appendix Q

Temperature trends:

1. By TEG coagulation status
2. At T1 by short term outcome (during the study)





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24 June 2015

HREC REF: 380/2015

Dr AR Reed
D23, Anaesthesia
NGSH

Dear Dr Reed

PROJECT TITLE: COAGULOPATHY IN SEVERE, ISOLATED TRAUMATIC BRAIN INJURY: A PREVALENCE STUDY :(MMed-candidate-R Lawrie)

Thank you for submitting your study the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th June 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Ruchi Lawrie will also be involved in this study.

The HREC note that this is a valuable study, with minimal risk to study participants. Therefore, for this study, the HREC has waived the requirement for delayed consent from participants or proxy consent.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp TJBurgess

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Dr A. R. Reed
Anaesthetics Department
D23 – New Main Building

E-mail: ruchi@lawrie.co.za / anthony.reed@westerncape.gov.za

Dear Dr Reed

RESEARCH PROJECT: Coagulopathy in Severe, Isolated Traumatic Brain Injury: A Prevalence Study (MMed Candidate R. Lawrie)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

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d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please introduce yourself to the person in charge of an area before commencing.
f) Please discuss the study with the HOD before commencing.
g) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
h) Confidentiality must be maintained at all times.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 16 September 2015

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COVER PAGE FOR THE JOURNAL OF NEUROTRAUMA

Coagulopathy in Severe, Isolated Traumatic Brain Injury: A Prevalence Study

Dr Ruchi Lawrie[1], DA(SA), Dr Anthony Reed[1], FCA(SA), Dr Nicholas Meyersfeld, FCA(SA), Dr Crispin Thompson[2], FC Neurosurg (SA), Professor Michael James[1], FCA(SA), Dr Malcolm Miller[1], Cert Crit Care (SA)

[1] Department of Anaesthesia and Critical Care, D23, Groote Schuur Hospital & University of Cape Town, Main Road, Observatory, Cape Town, South Africa

[2] Department of Neurosurgery, F3, Groote Schuur Hospital & University of Cape Town, Main Road, Observatory, Cape Town, South Africa

Contact information:

Dr Ruchi Lawrie
ruchi@lawrie.co.za
+2772 611 5475

Dr Anthony Reed
Anthony.reed@uct.ac.za
+2782 560 1022

Dr Nicholas Meyersfeld
nmeyersfeld@gmail.com
+2782 901 7629

Dr Crispin Thompson
crispinza@gmail.com
+2779 032 2970

Professor Michael James
Mike.james@uct.ac.za
+2783 503 7051

Dr Malcolm Miller
Malcolm.miller@uct.ac.za
+2782 785 4202

LIST OF ABBREVIATIONS

Abbreviation	Description
AA	arachidonic acid
ADAMTS-13	a thrombospondin type 1 motif, member 13
ADP	adenosine diphosphate
AIS	abbreviated injury scale
aPTT	activated partial thromboplastin time
BBB	blood-brain barrier
CBT	conventional blood test
CI	confidence interval
CI	coagulation index
CT	computed tomography
DIC	disseminated intravascular coagulation
DVT	deep venous thrombosis
EDTA	ethylenediaminetetraacetic acid
EPL	estimated percentage of lysis
FDP	fibrin degradation product
FFP	fresh frozen plasma
FXI	factor XI
FXIIa	activated factor XII
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
GOSE	Glasgow outcome scale – extended
GSH	Groote Schuur Hospital
HIV	human immunodeficiency virus
HR	harm ratio

ICP	intracranial pressure
ICU	intensive care unit
IF	interferon
IL	interleukin
IMPACT	International Mission on Prognosis and Analysis of Clinical Trials in TBI
INR	international normalized ratio
LY30	clot lysis at 30 minutes after MA
MA	maximum amplitude
MAP	mean arterial blood pressure
MD	mean difference
MP	microparticle
NI	neurosurgical intervention
OR	odds ratio
PAF	platelet-activating factor
PAI	plasminogen activator inhibitor
PHI	progressive haemorrhagic injury
PLT	platelet count
POC	point-of-care
PR	pulse rate
PRBC	packed red blood cell
PT	prothrombin time
R time	reaction time
rFVIIa	recombinant factor VIIa
ROTEM	thromboelastometry
SBP	systolic blood pressure
T0	time 0, time of injury
T1	time 1, 12 hours (±3 hours) after T0

T2	time 2, 36 hours (±3 hours) after T0
T3	time 3, 60 hours (±3 hours) after T0
TACO	transfusion associated circulatory overload
TB	tuberculosis
TBI	traumatic brain injury
TEG	thromboelastography
TGF	transforming growth factor
TNF	tumour necrosis factor
tPA	tissue plasminogen activator
TRALI	transfusion related acute lung injury
VET	viscoelastic testing