Coagulopathy in Isolated Traumatic Brain Injury:

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This research report is submitted in partial fulfilment of requirements for the degree of Masters of Medicine in Neurological Surgery,

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DECLARATION

I, Prince Darsi Boungou-Poati declare that this research report is my own work. It is being submitted for the degree of Masters of Medicine in Neurological Surgery at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

Dr Prince Darsi Boungou-Poati

.....day of 2020

PUBLICATIONS AND PRESENTATIONS

1. Presented preliminary findings at the 28th Society of Neurosurgeons of South Africa (SNSA) Congress 2019 on 10 August 2019.

ABSTRACT

Background: Although South Africa has one of the highest incidences of Traumatic Brain Injury (TBI) globally, the incidence of Traumatic Brain Injury-associated coagulopathy (TAC) and its associated risk factors in patients with isolated TBI has not been evaluated in the country.

Methods: This study was conducted in the neurosurgical units at the Chris Hani Baragwanath Academic Hospital (CHBAH) and the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), over a period of 12 months. Patients admitted with isolated head injury in the neurosurgical units at the two hospitals were included. This was a cross sectional study done on the day of admission and mortality data collected on day 3. We sought to determine the incidence of coagulopathy, its risk factors and mortality outcome.

Results: A total of 121 patients with isolated TBI were included. TAC occurred in 40.5% of all patients. Independent risk factors for TAC in isolated TBI were found to include a Glasgow Coma Scale(GCS) score of ≤8, presence of surface collections, midline shift, raised intracranial pressure (ICP), absent pupillary reflex, hypotension, penetrating injury and lower age. TAC patients had approximately 26 times increased odds of dying compared to those that did not have TAC (OR=26; 95 % Confidence interval (3.27 –206.5); p-value = 0.025).

Conclusion: The occurrence of coagulopathy in TBI patients was high and it was a significant predictive factor for mortality. Independent risk factors for TAC in isolated TBI included a GCS score of ≤8, raised ICP, absent pupillary reflex and penetrating injury. These results are in keeping with findings in high income countries, highlighting the need for TAC to be given increased attention in the neurosurgical units in South Africa.

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ABBREVIATIONS

Activated partial thromboplastin time	aPTT
Charlotte Maxeke Johannesburg Academic Hospital	CMJAH
Chris Hani Baragwanath Academic Hospital	CHBAH
Glasgow Coma Scale	GCS
International Normalized Ratio	INR
Intracranial pressure	ICP
National health Laboratory Services	NHLS
Prothrombin time	PT
Traumatic Brain Injury	TBI
Traumatic Brain Injury-associated coagulopathy	TAC

CHAPTER 1

1.0 Introduction

According to the World Health Organisation, by the year 2020, traumatic brain injury (TBI) will overtake most diseases as the major cause of mortality and disability [1]. Globally TBI has been quoted in some studies to account for one in seven deaths [2, 3]. Therefore, TBI deserves some attention as an important public health concern, with an estimated 10 million people affected annually by TBI [1]. Although the burden of TBI is a global problem, Low and Middle Income Countries (LMICs) are disproportionally more affected than high income countries [4-6]. This is evidenced by a global incidence of 106 cases per 100 000 which is much lower than the estimated 150 to 170 per 100 000 in Sub-Saharan Africa [4-6].

Although South Africa has one of the highest incidence of TBI globally, with an adult incidence of 316 brain injuries per 100 000 persons compared to a global average of 106 per 100 000 persons, literature on the topic from South Africa and other LMICs remains relatively scant[4, 6-8].The occurrence of coagulopathy in TBI patients is high and it is an independent significant predictive factor [9-11], but it remains under studied and is not given enough attention in the neurosurgical units in our setting.

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1.1 Literature review

Coagulopathy is one of the main complications of TBI, that appears between 6 to 72 hours following the TBI[7]. Coagulopathy upon arrival in emergency centres is now considered a powerful independent predictive factor related to outcome and prognosis in TBI patients [12-14]. Although Glasgow Coma Scale (GCS), midline shift and pupillary reactivity are widely accepted as the best predictors of outcome and mortality in TBI patients, there is emerging evidence that laboratory parameters for coagulopathy may be a better predictor [15, 16]. Prothrombin time has been proposed by the International Mission for the Progression and Clinical Trial (IMPACT) as a powerful independent prognostic factor after TBI[16]. Studies have demonstrated up to 10-fold increase in mortality in patients with TBI- associated coagulopathy compared to those without the complication [17]. Coagulopathy in TBI patients has been shown to be associated with higher rates of craniotomies, transfusion requirements, a greater incidence of multiple organ dysfunction syndrome (MODS), longer intensive care unit (ICU) and hospital stay [12, 17-19].

The relationship between TBI and coagulopathy is well documented, and a meta-analysis of 34 studies focusing on the occurrence of coagulopathy in TBI showed that the average frequency of coagulopathy in patients admitted with TBI was 1 in three[16]. However, some studies have reported a prevalence of coagulopathy as low as 7% while others presented levels as high as 100% [20-23]. This difference in the prevalence of coagulopathy in TBI is mainly accounted for by the differences in severity of injury of patients between the studies and the definition of coagulopathy within the studies. The criteria for coagulopathy varies considerably and parameters used in different studies include international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer,

fibrinogen, Factor XIII, disseminated intravascular coagulation(DIC) score, modified DIC score or modified coagulopathy and alpha-2 plasmin inhibitor amongst others[3, 9, 10, 12, 13, 15, 17, 18, 20, 23-29]. In most TBI studies, coagulopathy of TBI has been diagnosed by abnormalities of the INR or PT, aPTT and platelet count[12, 17-19, 30].

Previously, the dilution of clotting factors following high volume therapy was thought to be the primary cause of coagulopathy[17, 31]. However, a growing body of literature on the topic has shown that coagulopathy after traumatic injury is multifactorial and involves all components of the haemostatic system[17, 31]. A relative inhibition of stable clot formation by anticoagulation and fibrinolysis together with activation or dysfunction of fibrin generation all play a role in coagulopathy[17, 26, 31]. Tissue trauma, shock, haemodilution, hypothermia, acidaemia and inflammation are the six initiators that have been suggested in current literature to be contributing factors to traumatic coagulopathy [17, 31]. Demographic factors such as age have also been shown to be important independent risk factors for coagulopathy in TBI[17].

From the growing evidence, it is important for studies that seek to study coagulopathy in TBI to consider the associated risk factors. However, despite the growing body of literature on this topic, few studies have focused on the unfavourable effects of coagulopathy in TBI and associated risk factors. Importantly, no such studies have been published from Sub-Saharan Africa, and South Africa in particular.

1.2 Definitions

The following definitions were used in this study:

TBI: CT scan confirmed brain tissue injury without other major injuries, although TBI is not synonymous with CT scan changes, this definition was used to simplify diagnosis.

Coagulopathy: For the purposes of this study, coagulopathy was defined in a similar way to how Greuters et al. [12] defined it as "an aPTT greater than 40 seconds, and/or an INR greater than 1.2 and/or a platelet count less than $120*10^9$ per litre."[12] Furthermore, this coagulopathy should not be related to any haematological pathological process, long term administration of drugs or pre-existing condition, but should be solely related to the TBI[12].

Increased ICP: CT scan confirmed increase in ICP as indicated in the radiologist report.

1.3. Aim and objectives

The aim of the study is to establish the frequency of and risk factors for TBI-associated coagulopathy (TAC), in patients with isolated traumatic brain injury.

The objectives of this study in our setting are as follows:

1. To describe the mechanism of injury, type of injury and the demographic details of patients with TAC with isolated TBI.
2. To describe the neurological findings, CT scan findings and the haematological features, such as INR and platelets.
3. To investigate risk factors associated with TBI-associated coagulopathy

4. To compare the outcome of patients with TAC to those without in patients with isolated TBI by means of day 3 survival rates.

CHAPTER 2

2.0 Materials and methods

2.1 Study population

This study was an analytical descriptive cross-sectional study of patients admitted for isolated head injury in the neurosurgical units at the Chris Hani Baragwanath and Charlotte Maxeke Academic Hospitals from 1 January 2019 to 31 November 2019.

2.1.1 Sample size

The minimum sample size required for this study was 117 patients. This was computed in statistical software, Stata/IC version 15.1, based on the sample size for proportion formula for a single population:

$n = \frac{(1.96)^2\, pq}{(ME)^2}$, where **ME** is the margin of error, **p** is sample proportion from previous studies and **q** is **1-p**; assuming a prevalence of coagulopathy in TBI patients of 30% at a 5 % level of significance and 80 % power.

2.1.2 Sampling method

Convenience sampling was used in this study and each consecutive patient admitted was included until the number calculated for the sample size was reached. The researcher could not ensure that there was no under or over representation of different races, genders or age

groups because of sampling method used. However, the study population was representative of the population served by the hospitals which made convenience sampling a reasonable compromise[32].

2.1.3 Inclusion and exclusion criteria

The following inclusion criteria was used: Pure head injury adult patients admitted to neurosurgery.

The following exclusion criteria was used: Patients with significant comorbidities that can affect coagulopathy.

2.2 Study setting

This study was conducted in the neurosurgical units at the Chris Hani Baragwanath Academic Hospital (CHBAH) and the Charlotte Maxeke Johannesburg Academic Hospital(CMJAH). Both are central hospitals providing quaternary hospital services and act as national referral centres. They are the two main academic teaching hospitals of the University of Witwatersrand Medical School. Chris Hani Baragwanath Academic Hospital is the largest hospital in South Africa and reputably third largest in the world, it has approximately 2800 beds and 70% of all its admissions are emergencies, while Charlote Maxeke Academic Hospital has a total of 1088 beds [33].

2.3 Data collection

The data collection tool (Appendix 1) was used to collect data in this study. Blood samples were collected as part of the current routine protocol in the management of TBI patients at CHBAH and CMJAH. Laboratory results were collected from the National Health

Laboratory (NHLS) Centres at the CHBAH and CMJAH. The data were entered in data collection form using Epi Info™.

2.4 Data analysis

For my research report, I have conducted data analysis, with the help of a statistician, of both adult males and females admitted at CHBAH and CMJAH. Data were rechecked for incompleteness, inconsistences and range of values for each of the variables using the statistical software Stata/IC, version 16.0.

All data analysis was done in Stata. Demographic characteristics and neurological outcomes will be presented using descriptive statistics, such as, frequencies, proportions, medians and interquartile ranges. These were presented as tables and graphs. Continuous data such as INR, PTT, aPTT and platelet count was checked for normality using the Skewness/Kurtosis test, and as such, medians and inter-quartile ranges were reported for non-normal distributed data. Bivariate analyses for categorical variables was analysed using the Chi-squared or Fishers exact and Wilcoxon signed rank tests. Statistical significance was determined at p-value < 0.05. To assess the factors associated with TBI-associated coagulopathy, stepwise multivariate logistic regression was utilized in Stata. We used a p-value of 0.20 for removal so as to ensure that all possible confounding effects are incorporated.

2.5 Ethical considerations

Approval to conduct the study was sought from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Permission to conduct the study at Chris

Hani Baragwanath Academic Hospital and CMJAH was requested from the hospital's Chief Executive Officer after receiving approval by the Ethics Committee (Appendix 4 and 5). Consent was sought from all the patients.

There was no harm to the participants and no direct benefit to them, but the participants were informed that by accepting to be a participant in the study, they study findings could help improve the management of other patients with head injury in the future. All the identifying information was removed from the data and a study number was allocated to each enrolled patient. The collected data were protected by a password and only the researcher and supervisor had access to them to ensure confidentiality. This study was conducted in accordance with the Declaration of Helsinki [34] and the South African Good Clinical Practice Guidelines [35].

2.6 Funding

All funds required during the study period were covered by the researcher. No external funding was obtained. The cost of the study was approximately R10 000.

CHAPTER 3

3.0 Results

Table 3.1 below summarizes the demographic and clinical profile of the patients and categorizes them into two groups, one of those with, and the other of those without TBI-associated coagulopathy.

Table 3.1: Summary statistics for study characteristics

	Coagulopathy			
Characteristic	**No** (N = 72)	**Yes** (N = 49)	**Total** (N = 121)	**P-value**
Age				
Median (Q1, Q3)	30.5 (22.5, 46.0)	42.0 (32.0, 50.0)	41.0 (31.0, 49.0)	0.012
	N (%)	**N (%)**	**N (%)**	
Gender				0.023
Male	51 (70.8)	33 (67.3)	84 (69.4)	
Female	21 (29.2)	16 (32.7)	37 (30.6)	
Ethnicity				0.433
African	32 (44.4)	26 (53.1)	58 (47.9)	
Coloured	15 (20.8)	11 (22.4)	26 (21.5)	
White	14 (19.4)	4 (8.2)	18 (14.9)	
Indian/Asian	11 (15.3)	8 (16.3)	19 (15.7)	
Mechanism of injury	**No** (N=70*)	**Yes** (N=49)	**Total** (N=119)	0.518
MVA	10 (14.3)	10 (20.4)	20 (16.8)	
PVA	10 (14.3)	3 (6.1)	13 (10.9)	
Assault	19 (27.1)	21 (42.9)	40 (33.6)	
Fall	20 (28.6)	6 (12.2)	26 (21.8)	
Other	11 (15.7)	9 (18.4)	20 (16.8)	
Type of injury	**No** (N=66**)	**Yes** (N=43***)	**Total** (N=109)	0.194
Blunt open injury	16 (24.2)	11 (25.6)	27 (24.8)	
Blunt close injury	13 (19.7)	3 (7.0)	16 (14.7)	
Penetrating injury Gunshot	14 (21.2)	11 (25.6)	25 (22.9)	
Penetrating injury Knife	13 (19.7)	12(27.9)	25 (22.9)	
Penetrating injury Other	10 (15.2)	6 (14.0)	16 (14.7)	

*Two patients without coagulopathy had missing data on mechanism of injury
**6 patients without coagulopathy had missing data on type of injury
***6 patients with coagulopathy had missing data on type of injury

Of the 121 patients with isolated TBI, 49 (40.5%) had coagulopathy on admission to the neurosurgery department. In both groups patients were predominantly male (67.3 and 70.8%). When comparing the patients with coagulopathy versus those without, those with coagulopathy were older (42 vs. 30.5 years) and most had a penetrating injury (51.4 vs. 18.8%). Africans had the highest proportion of TBI-associated coagulopathy (53.1 %), followed by Coloureds (22.4 %), followed by Asians/Indians (15.3 %), with the least proportion among the Whites (8.2 %). TBI-associated coagulopathy was much higher in assaulted patients (27.1 vs 42.9%). However only the age and gender had statistically significant differences between the group with coagulopathy and that without.

Table 3.2 below summarizes the clinical profile of the patients and also categorizes them into two groups of those with and without TBI-associated coagulopathy. On admission physiological, neurological and laboratory findings were more abnormal in patients with coagulopathy than those without. Most patients with TAC had a GCS of lower than 8 when compared to those without (41.3 vs. 22.4%). Patients with TAC group had a lower systolic blood pressure than those without (SBP: 119 vs. 135 mmHg), had higher pulse rates (101 vs. 85.5 beats per minute) and were more acidotic (7.1 vs. 7.3 pH).

Table 3.2: Summary statistics of clinical findings			
	Coagulopathy		
Characteristic	**Yes**	**No**	
	(N = 49)	**(N = 72)**	**P-value**
GCS 12 to15 N(%)	16 (32.7)	28 (38.8)	
GCCS 9 to 11N(%)	13 (26.5)	28 (38.8)	0.38
GCS ≤ 8N(%)	20 (40.8)	16 (22.2)	
Systolic BP in mmHg			0.006
Median (Q1, Q3)	119.0 (89.0, 139.0)	135.0 (90.0, 140.0)	
Diastolic BP in mmHg			0.699
Median (Q1, Q3)	89.0 (58.0, 114.0)	80.0 (63.0, 109.0)	
Pulse in beats per minute			0.026
Median (Q1, Q3)	101.5 (73.0, 124.0)	85.5 (64.5, 109.5)	
Saturation measured as a %			0.034
Median (Q1, Q3)	95.0 (92.0, 98.0)	94.0 (91.0, 97.0)	
INR			0.045
Median (Q1, Q3)	2.2 (1.2, 3.1)	1.1 (0.9, 3.2)	
Platelets count in 10*7 per litre			0.034
Median (Q1, Q3)	201.5 (108.5, 316.0)	258.0 (156.0, 419.0)	
HB in g/dl			0.558
Median (Q1, Q3)	12.1 (10.3, 13.5)	12.3 (10.2, 14)	
pH			0.322
Median (Q1, Q3)	7.1 (6.9, 7.3)	7.3 (7.2, 7.4)	

Table 3.3 below shows CT scan findings from our sample. The majority of the patients had skull fractures (71.4%) and evidence of surface collections (55.4%). About a third of the patients had midline shift (29.9%), very few had increase of ICP (26%) and even fewer had intra cerebral bleeds (10%).

Table 3:3 Summary statistics for CT scan findings (N = 121)

Characteristic	Presence	Frequency (Percentage)
Evidence of surface collection		
	No	54 (44.6)
	Yes	67 (55.4)
Intra cerebral bleed		
	No	109 (90.0)
	Yes	12 (10)
Increase of ICP		
	No	89 (73.6)
	Yes	32 (26.4)
Midline shift		
	No	85 (70.2)
	Yes	36 (29.8)
Bone structure involvement (skull fracture)		
	No	35 (28.9)
	Yes	86 (71.1)

Table 3.4 below shows the results of a stepwise multivariate logistic regression analysis which identified some independent risk factors associated with coagulopathy. Odds ratios, 95 % confidence intervals and p-values shown are shown in the table. Our results suggest that having systolic blood pressure less than 90 mm Hg, having GCS less or equal to 8,

having an intra cerebral bleed, being younger than 40 years, having evidence of surface collection, having midline shift, having an ICP increase, not having a reactive pupil and having a penetrating or open injury were independent risk factors associated with coagulopathy in isolated TBI patients.

Table 3.4: Factors associated with (traumatic brain injury associated) coagulopathy

Variable	Level	Odds Ratio (95% CI)	P-value
GCS	>8	Reference	
	<=8	2.64 (1.61; 4.04)	0.006
Intra cerebral bleed			
	No	Reference	
	Yes	1.32 (1.08; 5.77)	0.041
Systolic blood pressure in mmHg	>=90	Reference	
	<90	1.64 (1.08; 1.91)	0.035
Age in years	40	0.65 (0.35; 0.81)	0.042
Evidence of surface collection			
	No	Reference	
	Yes	2.22 (1.42; 3.41)	0.027
Type of injury			
	Blunt closed injury	Reference	
	Blunt open injury	1.34 (1.08; 1.88)	0.031
	Penetrating injury	2.35 (1.06; 4.98)	0.044
Size of pupil			
	Reactive	Reference	
	Non-reactive	1.54 (1.15; 1.94)	0.034
Increase of ICP			
	No	Reference	
	Yes	2.88 (1.31; 4.30)	0.004
Midline shift			
	No	Reference	
	Yes	2.41 (2.15; 3.15)	0.001

Table 3.5 below shows that overall mortality on day 3 was 11,57% with mortality seen in those who had coagulopathy on admission being 26.5% versus 1.5% mortality seen in those patients who did not have coagulopathy. The odds ratio (95% CI) for mortality with coagulopathy was 26 (CI: 3.27 –206.5) with a p value less than 0.0005 when compared to those without coagulopathy.

Table 3.5: Outcome of TAC patients			
	N (%) **Dead at day 3**	N (%) **Alive at day 3**	N (%) **Total**
Coagulopathy	13 (26.5)	36 (73.5)	49
No Coagulopathy	1 (1.4)	71 (98.6)	72
Total	14(11.57)	107(88.4)	121

CHAPTER 4

4.0 Discussion

South Africa is burdened with a high incidence of TBI, with Johannesburg having a reported adult incidence of TBI in Johannesburg of as high as 370 per 100 000 persons [36]. This study is the first study in South Africa to the author's knowledge reporting on the frequency of TBI-associated coagulopathy (TAC) and associated risk factors, in patients with isolated traumatic brain injury. Coagulopathy is one of the major consequences of TBI and is widely accepted to be an important prognostic indicator[12, 17-19]. The relationship between TBI and coagulopathy is well documented, and a meta-analysis of 34 studies focusing on the incidence of coagulopathy in TBI showed that the average frequency of coagulopathy in patients admitted with TBI was 1 in three [23]. However, some studies have reported incidence of coagulopathy as low as 7% while others presented levels as high as 100% [20-23]. This difference in the prevalence of coagulopathy in TBI is mainly accounted for by the differences in severity of injury of patients between the studies and the definition of coagulopathy between the studies.

In this study the occurrence of coagulopathy on admission to the emergency unit was found to be 40.5%. This is higher than the average 33% reported in the meta-analysis by Epstein et al but lower than studies that reported prevalence as high as 100%. The reason for this slightly higher finding could be that we used a definition of coagulopathy with a very low threshold which included cases of mild coagulopathy. However, this was still lower than the occurrence of TBI associated coagulopathy of 54% in the first 24 hours post-trauma in a study that used the same definition used in this study[12]. This could have been due to the fact that a low PT could not be consistently used as diagnostic measure in this current study as this test was not done in many of the patients.

Previously, the dilution of clotting factors following high volume therapy was thought to be the primary cause of coagulopathy [17, 31]. However, a growing body of literature on the topic has shown that coagulopathy after TBI is multifactorial and involves various components[17, 31]. Wafaisade et al.[17] in their retrospective study of 3,114 found independent risk factors for coagulopathy in isolated TBI to be amongst others a GCS ≤8, hypotension at scene and/or at Emergency Room (ER), pre-hospital i.v.-fluids ≤2,000 ml and age ≥75 years[17]. In another study, Talving et al.[3] in their retrospective cohort of 236 patients found independent risk factors for coagulopathy in isolated TBI to be amongst others a GCS score of <8, hypotension upon admission, cerebral oedema, subarachnoid haemorrhage, and midline shift.[3] In this current study, a stepwise multivariate logistic regression analysis identified the following independent risk factors for isolated TBI associated coagulopathy: being of lower age; having a penetrating injury; having a systolic blood pressure <90 mm Hg; having GCS ≤8; not having a reactive pupil; having an intra cerebral bleed; having evidence of surface collection; having midline shift and having an ICP increase.

Being younger was found to be an independent risk factor for TBI, with a decrease of 35% in the odds of having coagulopathy for every one-year increase in age in the group that had coagulopathy compared to that without. This is inconsistent with all the other study findings and could be explained by the fact that the average age of our study participants was much lower at 42 years with the oldest patient in the study being 55 years. Most other studies had samples including patients over the age of 75 and higher average ages. Our finding suggests that in our study population within the age ranges of 22 to 55 years, an increase in age could be protective. However even in this study the average age of participants with coagulopathy was higher (42 vs. 30.5 years) than that of those without coagulopathy which is in keeping with findings from other studies. Consistent with findings from previous studies, males

constituted 69% of the cohort and formed the majority of the participants with TAC. Ethnicity was found to not be associated with TAC. More than half of the patients with TBI were Africans which may be simply explained by the ethnic distribution of the population at the study site.

The predominant mechanism of injury that resulted in TBI was assault followed by falls. However, TAC occurred in most assault victims followed by participants injured in motor vehicle accidents (MVAs). Some studies have demonstrated a trend of TAC occurring with a higher frequency among patients who had sustained penetrating versus blunt injury and this reached statistical significance.[3] However, in this study, this may just reflect the proportionally higher number of penetrating as compared to blunt injuries in our study population. Additionally, in this study having a penetrating injury was found to be a stronger independent risk factor for having coagulopathy than having a blunt injury in the logistic regression.

In a retrospective cohort of 246 patients, coagulopathy during the first 24 hours post-trauma provided an independent prognostic factor for poor outcome. In keeping with findings from other studies hypotension as represented by a systolic BP of less than 90 was found to be an important independent risk factor for coagulopathy[3, 17]. In this has been explained to be possibly be via the activation of the Protein-C-pathway by the hypotension[26, 31]. The use of high volume fluids during resuscitation leading to dilution of coagulating factors amongst others has also been implicated as a possible cause[24, 26] In this study we did not record the use of IV fluids given and therefore could not assess if the amount of fluid given was also a risk factor associated with coagulopathy.

Having a low GCS less or equal to 8 and not having a reactive pupil was found to be one of the strongest independent risk factors as it more than doubled the odds of having coagulopathy. In this study the low GCS score and non-reactive pupils could also be seen as an indicator for severity of injury. Therefore this supports studies that have demonstrated that the extent of brain injury plays an important part for the development of coagulation disorder.[9, 12, 13, 20, 30] Furthermore, adverse CT scan findings such as having an intra cerebral bleed, having evidence of surface collection, having midline shift, having an ICP increase were all found to be strong independent risk factors. Another study has shown evidence of surface collections and intracerebral bleeds as risk factors, but unlike in this study those findings were not statistically significant[17].Tissue trauma, shock, haemodilution, hypothermia, acidaemia and inflammation are the six initiators that have been suggested in current literature to be contributing factors to traumatic coagulopathy[17, 31]. Patients with TAC had lower systolic blood pressures, had higher pulse rates and were more acidotic supporting this suggestion.

The overall mortality at day three among patients who had TAC upon admission stood at 25.6%, with the odds of dying in the group that had coagulopathy being 26 times more than that of those who did not, confirming the usefulness of coagulopathy as a marker of prognosis. The resultant poor outcomes are likely attributable to sustained intracerebral haemorrhage, ischaemic secondary injury and microvascular thrombosis[11, 13, 16, 21]. This is lower than other mortalities reported in others studies of around 50%, however these other studies were retrospective and had the patients' final long-term outcomes[3, 17, 29].

CHAPTER 5

5.0 Limitations

Certain limitations emerged during this study. Although hypothermia is an important risk factor for coagulopathy, it was inconsistently recorded at the trauma emergency unit and therefore was not assessed in this study. PT and aPTT were also not requested for a number of participants therefore this laboratory tests could not be consistently used in the diagnosis of coagulopathy. This study used a convenient rather than a randomised sampling method therefore, the results cannot be indisputably generalised to other settings. This study only collected mortality outcome at day three and therefore might have underestimated the overall mortality rate. Data the use of antiplatelet and anticoagulants given was not collected and therefore the impact on the outcome of having received anticoagulants or antiplatelet was not studied. However, these findings cannot be ignored and should stimulate further investigations into the topic.

CHAPTER 6

6.0 Conclusions

This is the first study investigating the frequency and risk factors associated with the development of TAC and its effect on mortality in patients with isolated TBI in South Africa. The occurrence of coagulopathy in isolated TBI patients was high, particularly among patients with a penetrating head injury. We found that having systolic blood pressure less than 90 mm Hg, having GCS less or equal to 8, having an intracerebral bleed, lower age, having evidence of surface collection, having midline shift, having an ICP increase and not having a reactive pupil are associated with TBI-associated coagulopathy.

6.1 Recommendations

This is a very important study and the findings have the potential to improve the management and outcome of patients with traumatic brain injury. We recommend that a national multicentre study with a randomised sample or more similar studies across the different metropoles in South Africa be conducted. This will allow us to generalise the results and possibly establish a guideline on haemostatic resuscitation with regards to isolated traumatic brain injury.

Appendix A: Data collection Sheet

Data Collection Sheet				
Folder number:		Date of admission:		
Birth date:		Gender: Male☐ Female☐		
Ethnicity: Black☐ Coloured☐White☐ Indian☐ Asian☐				
Name of hospital				
Time of incidence:		Time of arrival to hospital:		
Mechanism of injury: MVA☐ PVA☐ Assault☐ Fall☐ Other_____				
Severity: Mild☐ Moderate☐ Severe☐				
Type of injury: Blunt open injury☐ Blunt closed injury☐ Penetrating Injury: (Gunshot☐ Knife☐ Other sharp object☐)				
Clinical Status				
Parameter	Day 1			
GCS				
Size of pupil				
Systolic BP				
Diastolic BP				
Pulse				
Saturation				
Temperature				
Lab Results				
Parameter	Day 1			
INR				
PT				
aPTT				
Platelets				
HB				
PH				
Investigations				
CT Scan Findings	Evidence of surface collection: Yes☐ No☐ Intra cerebral bleed: Yes☐ No☐ Increased ICP: Yes☐ No☐ Midline shift☐ Effacement of basal cisterns☐ Effacement of sulci and gyri☐ Bone Structure Involvement: Yes☐ No☐ Other significant findings:			
Outcome: Complication of infarct Re-bleed **Glasgow Outcome Score on death or discharge:**				
Blood products given:				
Type				
Number of units				
Day given				

Appendix B: Human Research Ethics Committee Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr PD Boungou-Poati

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180974

NAME: (Principal Investigator)	Dr PD Boungou-Poati
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Neurosurgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Coagulopathy in isolated traumatic head injury
DATE CONSIDERED:	28/09/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr J Ouma
APPROVED BY:	Dr N Naran, Deputy Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/01/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore reports and re-certification will be due early in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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