PREVALENCE AND ASSOCIATED FACTORS OF MASSIVE TRANSFUSION IN ADULT MAJOR TRAUMA PATIENTS AT EMERGENCY DEPARTMENT HOSPITAL KUALA LUMPUR

DR RAHIMAH BINTI ABDUL WAHAB

Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree of Master Of Medicine (Transfusion Medicine)

UNIVERSITI SAINS MALAYSIA
ADVANCED MEDICAL AND DENTAL INSTITUTE (AMDI)

2016

DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Masters of Medicine in Transfusion Medicine. It is also not to be sent to any other universities. With that, this research might be used for consultation and will be photocopied as reference.

_____

Dr. Rahimah Binti Abdul Wahab

P-IPM0002/13

ACKNOWLEDGEMENT

In the name of Allah, the Most Compassionate, the Most Merciful. Salutation is upon His Messenger Muhammad S.A.W., his family and his companions. I would like to express my deepest gratitude and thanks to the following individuals who have helped me during the preparation of this dissertation.

1. Dr Nur Arzuar Abd. Rahim, Supervisor, Paediatrician and Lecturer, Head of Regenerative Medicine Cluster of Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia
2. Dato` Dr Faraizah Abd. Karim, Co-supervisor and Honorary Lecturer of Transfusion Medicine Program AMDI-USM, Deputy Director of National Blood Centre
3. Dr Rohayu Hami, lecturer of AMDI-USM, for help and assistance of statistical method and analysis
4. Dr Noorsuzana Mohd Shariff, lecturer lecturer of AMDI-USM, for help and assistance of statistical method and analysis
5. Encik Nizuwan Azman, staff at Bioinformatic and Biostatistic Section for help and assistance of statistical method and analysis
6. Dr Mohd Faizal Sadikin, Emergency Physician of Hospital Kuala Lumpur
7. All staffs of Unit of Record Hospital Kuala Lumpur from every department involved (Emergency Department, Surgery, Orthopedic, Neurosurgery) that assist me in completing data collection
8. My husband and kids (Wan Hafizul Amin, Wan Sarah Ibtisam and Wan Hajar Ifrah), for love and massive support, my parents and parents in laws, thank you, an endless gratitude for help and understanding.

TABLE OF CONTENTS

CHAPTER 4 : RESULT

LIST OF TABLES

LIST OF SYMBOLS

%	Percent
=	Equal to
≥	More than and equal to
≤	Less than and equal to
>	More than
<	Less than

LIST OF ABBREVIATIONS

ABG	arterial blood gas
AIS	abbreviated injury of score
ARDS	acute respiratory distress syndrome
ATC	acute trauma coagulopathy
BE	base excess
bpm	beat per minutes
CT	computed tomography
EDHKL	Emergency Department of Hospital Kuala Lumpur
FAST	focused assessment sonography in trauma
FFP	fresh frozen plasma
GCS	Glasgow coma scale
g/dl	gram per desilitre
Hb	hemoglobin
HKL	Hospital Kuala Lumpur
HR	heart rate
ISS	injury severity score
mmHg	milimetre mecury
mmol/l	milimol per litre
MT	massive transfusion
MTP	massive transfusion protocol

NBC	National Blood Centre
NMT	Non massive transfusion
NT	No transfusion
NTRD	National Trauma Registry Data
PC	packed cell
PLT	Platelet
PT/APTT	activated prothrombin time/activated partial thromboplastin time
ROTEM	rotational thromboelastomery
SBP	systolic blood pressure
SD	specific deviation
TEG	thromboelastography
TIC	trauma induced coagulopathy
TRALI	transfusion related acute lung injury
WHO	World Health Organization

ABSTRAK

Latarbelakang. Garis panduan trauma massif untuk kes trauma major adalah berdasarkan kombinasi keputusan makmal dan penilaian klinikal. Beberapa keputusan makmal yang diperlukan tidak diperoleh dengan segera. Keputusan tepat dan cepat oleh doktor pada keadaan pesakit semasaa adalah penting. Transfusi massif melibatkan jumlah beg darah yang banyak maka memerlukan komunikasi yang berkesana diantara doktor yang merawat dengan tabung darah. Identifikasi awal kemungkinan transfuse massif pada kes trauma akut membantu resusitasi kecemasan yang berkesan terhadap pesakit.

Objektif. Menentukan prevalens trauma major di kalangan pesakit dewasa yang terlibat dengan trauma major serta menentukan faktor yang berhubungan dengan transfusi yang banyak bagi kes major trauma .

Kaedah. Kajian retrospektif di kalangan pesakit dewasa yang terlibat trauma major tanpa sebarang penyakit sedia ada yang dimasukkan ke Jabatan Kecemasan dan Kemalangan Hospital Kuala Lumpur anatra Jun 2015 sehingga Mei 2016. Tujuh faktor berhubungan transfusi darah masif telah ditetapkan iaitu detak jantung ≥120kali/minit, tekanan darah sistolik ≤90 mmHg, skala koma *Glasgow* ≤8, patah tulang pinggul yang tidak stabil, positif cairan pada pemeriksaan sonografi segera berfokuskan trauma, pengurangan pengalkalian darah >6 mmol/L, hemoglobin ≤11 g/dL dan luka tembus.

Results. 134 pesakit telah disertakan dalam kajian, 3 kes telah ditransfusi masif (2.27%). Factor yang menunjukkan hubungan bermakna dengan transfusi masif pada kes trauma major adalah nilai hemoglobin ≤11g/dl (*p*-value 0.029, 95% CI 1.423, 739.568). Lain-lain faktor berhubungan tidak mempunyai kebermaknaan secara statistik kerana terhadnya jumlah sampel.

Kesimpulan. Prevalens transfuse masif pada kes trauma major dalam kajian ini adalah rendah (2.2%). Walaupun begitu, hanya nilai hemoglobin ≤11 g/dL yang bermakna sebagai indikator perlunya tranfusi massif dalam kajian ini.

ABSTRACT

Background. Our current guideline in managing major trauma in need of massive transfusion was based on both laboratory and clinical judgement. Some laboratory investigation is not immediate available that is not in keeping with rapid dynamic of trauma coagulopathy. Clinician prompt action on patient`s clinical presentation is essential. Massive transfusion need a lot of blood products thus it required effective communication between clinician and blood bank. Early recognition of massive transfusion likelihood in major trauma aid in prompt damage control resuscitation in major trauma patient.

Objective. To determine the prevalence of major trauma patient among adult and to determine the associated factors with massive transfusion in subjects enrolled.

Methods. Retrospective study on adult major trauma patients without unfavorable premorbid condition presented to Emergency Department of Hospital Kuala Lumpur between June 2015 until May 2016. Associated factors are predefined with seven variables that are heart rate ≥120/min, systolic blood pressure ≤90 mmHg, Glasgow coma scale ≤8, displaced pelvic fracture, FAST scan positive for fluid, base deficit ≥6 mmol/L, hemoglobin ≤11 g/dL and penetrating injury.

Results. There were 134 patients been recruited, with 3 subjects in massive transfusion group. (2.27%). Multivariate analysis showed only factor of haemoglobin ≤11 g/dL (OR 32.443, *p*-value 0.029, 95% CI 1.423, 739.568) found to be significantly associated with adult major trauma patients. Other factors do not statistically statistic due to small sample size.

Conclusions. Prevalence of massive transfusion in adult major trauma patients in EDHKL was low (2.2%), however only haemoglobin ≤11 g/dL found to be significantly associated with massive transfusion in this study.

CHAPTER 1

INTRODUCTION

1.1 Title

Prevalence and associated factors of massive transfusion in major trauma among previously healthy adult patients at Emergency Department Hospital Kuala Lumpur

1.2 Overview

Massive transfusion was early recognized and developed in military practice since World War I. The fact that abundant trauma cases with high likelihood of transfusion in military field due to haemorrhage, the understanding of haemorrhagic pathophysiology is evolving as well as the massive transfusion practice both in military and civilian practice. In massive and uncontrolled bleeding as in commonly seen in major trauma cases, transfusion is an empiric mode of treatment to restore the oxygenation, maintaining the circulatory volume and prevention of ongoing bleeding by overcome the coagulopathy (Segatchian & Samama, 2012)

Massive transfusion has been defined based on volume of blood loss or volume of blood transfused (Australia National Blood Authority). Definition of transfusion of $\geq$ 10 units of red blood cells (RBCs) is mostly used in many research (Rainer et al., 2011., Elmer

et al., 2013; Callcutt et al., 2013). This is correspond with other definition, in which transfusion is considered massive when there is transfusion of a volume equal to the patients` total blood volume in less than 24 hours (National Blood Centre Ministry of Health Malaysia, 2008a; Makroo et al., 2011). Other definitions includes loss of half of blood volume within 3 hours or use of 50 units of blood components in 24 hours and use of 6 units RBCs in 12 hours (Smith et al., 2014). In real-time clinical situation, massive transfusion is highly anticipated in bleeding cases that required more than 4 unit of packed red cells within 1 hour with clinically still in need of transfusion, or blood loss more than 150ml/minute with unstable haemodynamic status (Smith et al., 2014).

Trauma is a major cause of mortality worldwide which reported as 4 million deaths a year (Curry et al., 2012). It is the leading cause of death worldwide in below 45 years age group (Curry et al., 2012; Rainer et al., 2011). Forty percent deaths were mainly caused by massive haemorrhage due to exsanguinations and occurred in the initial few hours of the event (Sauia et al., 1995). Associated risks of mortality in trauma are early coagulopathy, acidosis and hypothermia (Rainer et al., 2011). These lethal events are also known as the lethal triad. Traditionally, clinicians thought that coagulopathy in trauma patients was due to the dilution effect of massive transfusions of crystalloid and packed red cells (Livingston et al., 2014). There is now a growing appreciation that the causes of coagulopathy is multifactorial and may be induced by the inflammatory response to traumatic injuries, independent of fluid resuscitation and transfusion (Livingston et al., 2014). Thus, the development of massive transfusion protocol is expected to guide resuscitation, facilitate communication and logistical support, and prevent coagulopathy before it occurs (Livingston et al., 2014).

Malaysia`s National Trauma Registry in 2009 reported that major trauma accounted to 1.2% from total of 166,768 admissions in emergency and trauma centre nationwide with 27.9% mortality. The highest risk group of age is 15 – 34 years old which accounted to 56.6% of incidence (National Trauma Database, Ministry of Health Malaysia, 2009).

The polemic is arise between the aim of lifesaving and dose-related adverse effects in massive transfusion (Seghatchian and Samama, 2012). Massive transfusion carries a significantly mortality rate of 40% which increases with the number of volume expanders and blood components used (Seghatchian and Samama, 2012). The large amount of blood products used lead to the dilution effect resulting the vicious cycle of coagulopathy, hypothermia and acidosis that may complicate the haemorrhagic trauma event (Kashuk et al., 1982; Gustavo et al., 2010). Nonetheless, massive transfusion may exposed the recipient to biological response modifiers that may cause unwanted harmful effects (Seghatchian and Samama, 2012).

Most previous studies that are mainly a long-term retrospective studies, showed that there were significant adverse outcome among patients who had been massively transfused. One of these studies, by Livingston (2014) found that adolescent and paediatric patients who received massive transfusion had poor clinical outcomes, including increased length of hospital stay and higher in-hospital mortality (Livingston et al., 2014). Mitra (2012) reported that massively transfused elderly patient had significant mortality (21.1% in elderly, $p < 0.01$) compare to younger patients (Mitra et al., 2012). Rainer et al. also

reported that mortality were significantly higher by 54.3% in trauma patient with massive transfusion and had longer hospital length of stay (Rainer et al., 2011).

Massive transfusion protocol was postulated to significantly improve the outcome in major haemorrhage patients by early communication between both physician and blood bank personnel (Malone et al., 2006; Callcut, et al., 2013). Strategies for controlling haemorrhage in the protocol is aimed for good oxygenation restoration, volume replacement as well as early prevention of coagulopathy (Malone et al., 2006; Segatchian and Samama, 2012; Smith et al., 2014). Besides, time to initiate the balanced resuscitation is postulated to be a major determinant for the improved outcomes (Callcut et al., 2013). Therefore early recognition of cases that need an activation of massive transfusion protocol (MTP) is important. There are various of predictive factors scoring for massive transfusion in emergency and trauma settings. Several factors that are included type of high risk injury, haemodynamic (blood pressure and heart rate), haemoglobin level, and base deficit. Each scoring factor differ in variable factors included and point scoring (Brockamp et al., 2012).

An example of massive transfusion predictive factors scoring in Asia region done by Rainer (2011) at Prince Wales Hospital in Hong Kong, also known as PWH score (Rainer et al., 2011; Brockamp et al, 2012). They found seven variables for predicting massive transfusion needs in major trauma which are heart rate ≥120/minutes (HR), systolic blood pressure (SBP), Glasgow Coma Scale ≤8 (GCS), displaced pelvic fracture, computed topography scan (CT scan) or Focused Assessment Sonography in Trauma (FAST) positive for fluid, base deficit >5 mmol/L, and haemoglobin ≤7 g/dL; and haemoglobin 7.1-10 g/dL (Rainer et al, 2011).

LITERATURE REVIEW

1.3.1 Pathophysiology of Major Trauma

Massive bleeding and tissue injury are the main causes for adverse clinical consequences in major trauma. Sauia (1995) wrote that forty percent death in major trauma were caused by massive bleeding and higher risk to have early mortality in first few hours (Sauia et al., 1995). Nevertheless, this major cause of death in trauma is potentially preventable (Spahn et al., 2013). Haemorrhagic shock due to massive bleeding in trauma is initiated by hypovolemia and tissue hypoperfusion which latter causes inflammatory response and acidosis (Smith et al., 2014). Trauma causes tissue injury that trigger the haemostasis system activation comprising of vascular endothelium, platelet activation, coagulation and fibrinolysis, in which if severe enough may lead to disseminated intravascular coagulopathy and hyperfibrinolysis (Elmer et al., 2012). Presence of both tissue injury and massive haemorrhage in major trauma with systemic hypoperfusion lead to the endogenous coagulopathy is associated with higher risk of multiorgan failure and poor outcomes (Frith et al., 2012; Spahn et al., 2013).

1.3.1 Acute Trauma Coagulopathy

Multifactorial primary condition has been recognised as a trigger for acute traumatic coagulopathy. Those factors are combinations of bleeding-induced shock, tissue injury related thrombin-thrombomodulin-complex generation and the activation of anticoagulant and fibrinolytic pathways (Frith et al., 2012). Hypoperfusion increases the expression of

thrombomodulin on endothelium in which later forms a complex with thrombin, thus reduces the amount of thrombin. As a result, fibrin production is decreased and there will be an increment in circulating activated protein C (Smith et al., 2014). Haemodilution is resulted from initial fluid resuscitation for replacing volume in bleeding trauma patient and this can lead to dilutional coagulopathy (Bolliger et al., 2010). Both acidosis and haemodilution causes altered enzyme activity, reduced thrombin activity thus aggravate the coagulopathy (Schöchl et al., 2012).

Lethal viscious cycle in trauma occured as coagulopathy progresses, which worsened the harmorrhage and the existing systemic shock. This unfavorable state presented as as refractory coagulopathy, progressive hypothermia and persistent metabolic acidosis (Smith, et al., 2014).

It is reported that one out of four trauma patients had coagulopathy on admission with significant higher risk of bleeding and mortality (MacLeod et al., 2014). MacLeod (2014) defined the ATC in their study as prolongation of PT > 13.3 seconds. The prolongation of PTT was low in trauma (2.5%) thus in their study, only PT measurements been considered in the definition of ATC (Mac Leod, 2014). Current trauma management guideline is recommended on immediate treatment of haemostatic resuscitation to ensure prompt recognition of patient with risk of traumatic coagulopathy and minimise the blood loss (Curry et al., 2012; Spahn et al., 2013). Haemostatic resuscitation is early administration of procoagulant products such as fresh frozen plasma, cryoprecipitate, platelet and other coagulation factor concentrates along with transfusion of red cells and

limiting fluid infusion (Frith et al., 2012). Apart from controlling the coagulopathy, the damage control resuscitation in trauma is essential by controlling the bleeding source as soon as possible, correction and prevention of hypothermia, restoring tissue perfusion and subsequently attain stable haemodynamic status (Smith et al., 2014).

1.4 Massive Transfusion in Major Trauma

Massive transfusion (MT) is widely defined in many studies as the use of $\geq$ 10 units of packed red cells within 24 hour (Elmer et al., 2013). It is also be defined as massive transfusion of $\geq$ 50 blood components in 24 hour (Smith et al., 2014). Holcomb (2010) wrote in his article that traditionally, the use blood and blood products with fluid resuscitation is always not in proper algorithm and resulting in large volume of fluid infusion, red cells transfusion then only plasma, cryoprecipiate and platelet be considered in small volume (Holcomb J.B., 2010). This practice is been revised since the knowledge of acute traumatic coagulopathy (ATC) start to be established and dilutional effect of over-resuscitation take into account (Holcomb J.B., 2010).

Current practice of massive transfusion has evolved by US military experience in Iraq, whereby balance resuscitation has been introduced (Fraga et al., 2010). The aim is, to achieve well balance of haemodynamic and haemostatic resuscitation in bleeding major trauma management (Kua et al., 2014). Balanced resuscitation is aggressive resuscitation with minimal fluids, early use of red cells transfusion, fresh frozen plasma, platelet and cryoprecipitate (Holcomb J. B., 2010). This strategy is to encounter ATC by haemostatic resuscitation and avoiding dilutional effects. Balanced resuscitation can avoid dilutional

coagulopathy that may worsened the haemorrhage especially in massive transfusion (Seghatchia and Samama, 2012). The earliest suggestion red cells, fresh frozen plasma and platelet ratio was 1:1:1 that been had adopted from Iraq war experience (Fraga et al., 2010).

1.4.1 Massive transfusion protocol

Since acute trauma coagulopathy occured in early period of injury with significant poor outcomes, prompt action is needed to overcome this. The approach need timely risk assessment and standardised protocols (Maegele et al., 2003). Massive transfusion protocol (MTP) can reduce risk of mortality and morbidity in trauma cases (Morris A. H., 2003). The other aim of MTP is to ensure effective sources utilization that promotes judicious use of blood in safe timely supply of blood products, as well as the need to incorporate proper and valid laboratory testing for monitoring of laboratory value that related to therapy effectiveness (Shaz et al., 2009). Hence, MTP need effective cooperation and communication between laboratory personnel, clinician and blood bank personel, and it is effectively done in agreed local evidence-based algorithm (Elmer et al, 2012; Rossaint et al., 2016).

1.4.2 Blood and blood products usage in balanced massive transfusion

The understanding of trauma coagulopathy changes the paradigm to the using of higher ratio of plasma to red cells in trauma massive transfusion. Borgman (2007) analysed restrospectively the association of ratio of plasma to red cells and survival rate in massively transfused patients in military hospital (Borgman et al., 2007). They found that patients who were receiving low ratio of plasma to red cells (1:8) had highest mortality rate (65%) and highest percentage of hemorraghic death (92.5%), as compared in high ratio group (1:1.4) with mortality rate of 19% and hemorrhagic death 37% (Borgman et al., 2007). This finding brought the suggestion to utilize formula based trauma massive transfusion with ratio plasma to red cells of 1:1 especially in those with high risk of hypocoaguable state (Borgman et al., 2007). In other study Bhangu (2013) in which they did a meta-analysis study on plasma to red cells ratio from published literature of trauma massive transfusion (Bhangu et al., 2013). They found that ratio of plasma to red cells of $\geq$1:2 has significant reduction in mortality, while there was no additional benefit identified in 1:1 over 1:2 transfusion ratios (Bhangu et al., 2013). There was another thought that the association of high plasma to red cells ratio and survival rate is biased (Snyder et al., 2009). In their study by Snyder (2009) they found that higher ratio of plasma to red cells (>1:2 vs <1:2), had 63% lower mortality risk (Snyder et al., 2009). They also analyse the timing of product administration and found that survived patients received plasma later than the red cells (>60 minutes). Thus, they speculating that the survival rate is biased by highlighting the administration of plasma without clear data regarding how early it had been transfused (Snyder et al., 2009). There is recent study by Holcomb (2015) in which they done a prospective pragmatic randomized controlled trial of effectiveness of plasma, platelet and

red cells ratio at 1:1:1 and 1:1:2 (Holcomb et al., 2015). They found that there is no significant differences in 24 hour or 30 days mortality between these two ratio. In this study, patient received blinded package of bloods according to ratio and be availabe within 10 minutes, the transfusion order is platelet than alternate plasma and red cells. This study also showed 1:1:1 ratio group had better haemostasis outcome and less mortality within 24 hour and no additional adverse effects even more products been used. This study findings support the practice of fix ratio 1:1 of plasma to red cells. It is suggested further study of the impact on judicious use of blood and outcome in separate times, early (within 24 hour) and 30 days (Holcomb et al., 2015).

The plasma use for fix ratio transfusion in preferrable thawed AB plasma that shortened plasma supply time (Callum et al., 2009). AB plasma does not contain anti-A and anti-B thus preferrable to be transfuse in emergency situation in which in recipients`s blood group yet to be identified (Shaz et al., 2013). Usually, longer time is needed for plasma to be ready compare to red cells, approximately 35-45 mins due to thawing process and logistic issue (Sorensen and Fries., 2012).

The formula driven approach in transfusion management of major trauma has advantage over laboratory base practice as it it did not require long turn around time (TAT), as conventional laboratory based is guided by PT/APTT which have TAT ranges between 29-235 minutes (Toulon et al., 2009). Arguments on it`s practice are the possibility exposure of harmful biological substance especially in plasma and platelet to patients with unknown risks, increase risk of adverse events of transfusion such as TRALI, risk of FFP wastage and may compromised the availibility for other clinically indicated in need of

plasma ie: exchange transfusion in thrombocytopenic purpura (Callum et al., 2009). The use of fixed protocol is mainly during acute haemorrhage, once haemorrhage is controlled, transfusion should be guided laboratory findings (Holcomb et al., 2015).

1.4.3 Goal directed haemostatic resuscitation in major trauma blood transfusion

Alternative approach to transfusion in trauma cases is based on goal-directed coagulation using thromboelastography (TEG) or rotational thromboelastometry (ROTEM) (Bougle et al., 2013). These techniques give rapid result and represent the coagulation abnormality reflecting either plasmatic coagulation system, platelet function or fibrinolysis (Brazzel, C., 2013). The result can be obtained within as early as 5-10 minutes, but could be longer in detecting hyperfibrinolysis (30-60mins) (Wang W. et al., 2016; Schochl et al., 2012). Thus it can guide the transfusion need either for FFP, platelet or cryoprecipitate (fibrinogen source) which make possible of judicious use of blood products, reduce wastage of products and limiting the adverse effects of transfusion (Malone et al., 2013).

Despite the goal-directed coagulation profile and rapid results of TEG, it`s efficacy and accuracy has not been proven to be more superior than conventional coagulation test (Da Luz et al, 2014). A Cochrane systematic review by Hunt (2015) shows no evidence of TEG accuracy and small evidence for ROTEM accuracy as diagnostic tool of trauma induced coagulopathy, but their findings were limited to small number of studies (Hunt et al., 2015). Da Luz (2014) in their descriptive observational study showed that there was

limited evidence of TEG/ROTEM superiority in improving blood transfusion strategy and the overall outcome in patients`s survival (Da Luz et al., 2014). Study on trauma patient`s outcome in TEG guided and standard massive transfusion protocol by Tapia et al. showed that TEG-guided resuscitation is effectively equivalent to standard massive transfusion protocol (with fix 1:1:1 ratio of red cells, plasma and platelet) in blunt injury but there was no significant different in outcome (Tapia et al., 2013). They also suggested that standard blood products ratio was not suitable for all trauma patients since there was worse outcome found in penetrating trauma with standard MTP group, thus the recommeded the use of TEG to guide on blood products transfusion (Tapia et al., 2013). TEG was suggested most suitable to be used as research purposes until more clinical data been obtained (Hunt et al., 2015).

Latest recommendation by the European Trauma Guideline is to use the goal-directed method in assessing the haemostatic resuscitation on major trauma bleeding. However there is a need that haemostatic resuscitation to be guided with standard laboratory coagulation tests and clinical evidence (Rossaint et al., 2016).

1.4.4 Role of pharmacology in trauma haemostatic resuscitation

An adjunct to haemostatic resuscitation is the use of pharmacology agent that can promote coagulation or inhibit the fibrinolysis. Use of tranexamic acid (TXA) is beneficial in cases with likelihood need of massive transfusion ie: patients with significant blood loss or at risk of massive bleeding (Schocl et al., 2012). Tranexamic acid is trans-4-

aminomethylcyclohexane-1-carboxylix acid, a lysin derivate that act as plasmin inhibitor that inhibit fibrinolysis (antifibrinolytic). A randomized control trial study of CRASH-2 showed that early administration (within 3 hours) of tranexamic acid in bleeding major trauma cases had higher survival rate with no significant clinical adverse effects. However the study data did not supported for fewer transfusion requirement with the use of tranexamic acid (Robert et al., 2013). European trauma guideline highly suggested that tranexamic acid to be given as soon as possible in cases of haemorrhagic trauma and cases with risk of major bleeding (Spahn et al., 2013). Elmer et al., also wrote in their article that tranexamic acid should be available in trauma unitas it has time-sensitive effectivenes (Elmer et al., 2013).

As addressed by the European Trauma Management Guideline, rFVIIa is considered only after all measures of damage control resuscitation has been taken, that includes blood and blood products transfusion, surgery approach, antifibrinolytic and correction of acidosis and hypothermia (Rossaint et al., 2016). This is because rFVIIa can only effectively initiates the thrombin burst in optimized coagulation system by direct binding to the activated platelet surface with optimal enzymatic activity (Hoffmann M., 2003). rFVIIa has poor respond if pH <7.2, platelet count <100 X 10^9/l and systolic blood pressure $\leq$ 90mmHg (Knudson *et al*., 2011). A randomized controlled trial, double-blinded study on usage of rFVIIa in controlling traumatic haemorrhage showed that rFVIIa significantly reduce transfusion in blunt trauma cases that received massive transfusion however there was no significant result in penetrating cases (Boffard *et. al*., 2005). In this study, 200 μg/kg rFVIIa given after transfusion 8 unit of RBC and followed with 100 μg/kg second and third dose of 1 hour and 3 hour after (Boffard *et. al*., 2005). However rFVIIa is not recommended in isolated traumatic brain injury as it was proven causing poor outcome

in traumatic brain injury (TBI) (DeLoughery et al., 2011). rFVIIa adverse effect includes increase risk of thromboembolic events (O'Connell et al, 2006). However, risk of thromboembolic event was not demonstrated in bleeding trauma cases that been given rFVIIa (Dutton *et al.*, 2011). The recommendation of rFVIIa in bleeding major trauma cases is based on risk and benefit clinical judgement (Smith et al., 2014). If need to be use, the patient`s relatives need to be informed of it`s out of standard recommended usage with possible adverse effects (Spahn et al., 2013).

The use of coagulation factor concentrates may avoid the use of huge volume of FFP in treating actively bleed patient in a way to maintain the fibrinogen level (Theusingger et al., 2014). Fibrinogen concentrate and prothrombin complex concentrate recommended to be used in bleeding trauma algorithm with the benefits of point-of-care method ie: TEG and ROTEM, if there is functional fibrinogen deficit or fibrinogen level <1.5-2.0 g/l (Rossaint et al., 2016).

Prothrombin complex concentrate has been suggested in bleeding trauma algorithm if there is prolonged clot formation finding in ROTEM (Theusingger et al., 2014).

The use of coagulation factors concentrate are effective in treating trauma coagulopathy and can reduced the transfusion requirement, which subsquently may improve patient`s outcome (Innerhofer et al., 2013).

1.4.5 Adverse effects of massive transfusion

Massive transfusion of allogeneic blood is known to have adverse effects whereby large volume of blood has been exposed to patients (Segatchian and Samama, 2012). Such adverse effects inlude increase risk of sepsis, cardiac overload and exposure to vary biological response modifier (Segatchian and Samama, 2012).

Large volume of plasma associated wih possible risk of ARDS ie: TRALI as reported by Inaba (2010) especially in non-coagulapathic trauma patients (Inaba *et al*., 2010). The risk is higher if >6 units FFP been transfused. Thus, it is suggested that early FFP transfusion is only been considered in patients that the anticipated need of >10 packed cells in 24 hour as part of hemostatisc resuscitation (Elmer et al., 2012). There is report of increase risk of mortality and multiorgan failure (MOF) after FFP transfusion in trauma (Bochicchio et al., 2008). Contradictry, there was a study that found less MOF and sepsis if blood components (other than red cells) were given earlier and was transfused at higher ratio (Cotton et al., 2009).

Infusion of massive volume of packed cells and FFP may cause citrate accumulation and resulted in hypocalcemia and hyperkalemia (Elmer et al., 2012). Fluctuation in potassium level may occured in massive transfusion cases as stored red packed cells contain accumulated potassium (Lier et al., 2008).

Another adverse effects of massive transfusion is possible transfusion transmitted infection such as ie: human immunodefiency virus, hepatits B, dengue etc (Allain et al.,

2008). Bacterial contamination of stored blood particularly platelet is also a concerning risk, and both risks are increasing with increase unit of transfused blood (Elmer et al., 2012).

1.5 Prediction score of massive transfusion in major trauma

Time to initiate the balanced resuscitation is postulated to be a major determinant in improved outcomes of major trauma patients (Callcut et al., 2013). Accurate predictive models that can be performed on admission able to identify the patients who will benefit from damage control resuscitation, thus optimizing benefit and minimizing risk of intractable trauma coagulopathy (Holcomb J. B., 2010). A number of studies that were mostly retrospective done in attempt to come out with the predictive factors for anticipating the needs of massive transfusion in bleeding major trauma cases. Several published massive transfusion predictive score studies has been summarized by Curry (2012). However, the scoring system were not sensitive enough to determine risk of massive haemorrhage, thus the score is used only as predictive measures particularly for risk of trauma coagulopathy (Curry et al., 2012).

Prediction scores for massive transfusion and coagualopathy in trauma (Curry et al., 2012)

Reference	Type of study	Aim of prediction score	No. patients	Validated Y/N	Predictors	ROC
Cosgriff et al.	Retrospective analysis, prospective collection of data	Prediction of coagulopathy	58	N	pH SBP Temperature ISS	
Ruschholtz et al	Retrospective analysis, prospective collection of data	Prediction of early transfusion	1103	N	free fluid in abdomen unstable pelvic ring # age SBP	admission from scene
Yücel et al. Maegele et al.	Retrospective analysis	Prediction of MT (≥10U RBC) TASH-Score Updated TASH-Score	6044	Y using a 1517 pt set Y using a 5834 pt set	SBP Hb Intra-abdominal fluid Complex long bone or pelvic # PR BE Gender	0.892
Schreiber et al.	Retrospective analysis Early prediction of MT (≥10U RBC)	Early prediction of MT (≥10U RBC)	558	N	Hb INR Penetrating mechanism	0.804
McLaughlin et al.	Retrospective analysi	Early prediction of MT (≥10U RBC s)	302	N	SBP pH Hct PR	0.839
Cancio et al.	Retrospective analysis	Prediction of MT 536 N	536	N	RTS PR SBP DBP	0.708
Nunez et al.	Retrospective review and validation	Validation of previous scoring systems & predict MT with ABC score	596	Y of other scores N of ABC	Penetrating mechanism SBP PR Positive FAST	0.859
Stanworth et al.	Retrospective analysis	Prediction of MT	5693		Penetrating mechanism SBP Time to arrival in ED Age Base Deficit PT	0.81

ROC : receiver operating curve, SBP: systolic blood pressure, RTA:road traffic accident, PT:prothrombin time, APTT :activated thromboplastin time, ULN : upper limit ofnormal, ISS: injury severity score, MT :massive transfusion, RBC : red blood cell, PR : pulse rate, BE : base excess, INR : international normalised ratio, RTS :revised trauma score, DBP : diastolic blood pressure, FAST :Focussed Assessment with Sonography for Trauma, ED : emergency department.

Among widely used massive transfusion predictive score are Trauma Associated Scoring for Hemorrhage (TASH), and Assessment of Blood Consumption (ABC). Both are derived from civillian subjects with difference in number of variables, in which TASH has 6 variables, and ABC only listed 4 variables (Brockamp et al., 2012). Details about score as described below.

i) Trauma Associated Scoring for Hemorrhage (TASH) Score

TASH score was developed and validated from 6044 severe blunt trauma subjects, and establihed on 2006.. This score had been revalidated internally on 2011 based 5834 patient`s data base on TraumaRegister DGU®, with specificity of 98%, sensitivity of 31% with AUC 0.905, that showed better performance then during development period (AUC 0.89) (Maegele et al., 2011). This score comprising of eight variables which are given specific score as shown below:

	Variable	Value	Points
i.	Gender	male	1
ii.	Pelvic fracture (AIS 5 ≥ 5)	clinically unstable	6
	Femur fracture (AIS 5 ≥ 3)	open and/or dislocated	3
iii.	Free IF (FAST) (AIS 4 ≥ 3)	present	3
iv.	Heart rate (bpm)	> 120	2
v.	Systolic blood presure (mmHg)	< 100	4
		< 120	1
		< 7	8
		< 9	6
vi.	Hemoglobin (g/dl)	< 10	4
		< 11	3
		< 12	2
		< -10	4
vii.	Base excess (mmol/L)	< -6	3
		< -2	1

The complexity of this score is that it need to be calculated with formula as shown that make it less ease to use (Calcutt et al., 2013) . Below is TASH calculation formula :

$$p = 1/[(1 + \exp(5.4 - 0.3*TASH)]$$

Cases with score $\geq$ 16, gives 50% prediction for MT and if score is $\geq$ 27, the risk for MT is 100% (Yücel et al., 2006). This score was applied by European Trauma Guideline in their massive hemorrhage protocol (Rossaint et al., 2016).

ii) Assessment of blood consumption (ABC) score

This score consist of four non-weighted variables at patient`s arrival at ED which are:

- Penetrating injury
- SBP $\leq$ 90mmHg
- HR $\geq$ 120mmHg and
- Positive FAST scan

All variables are non-laboratory and non-weighted parameters. This simple and easy to use score been developed using data of 596 level I civillian trauma patients. ABC score of $\geq$ 2 had 75% sensitive and 86% specific for predicting the need of massive transfusion (Nunez et al., 2009). Analysis study by Nunez (2009) in attempt to compare the ABC score with TASH score, showed that ABC score had equal prediction level and the difference between the score was not statiscally significant. By practical, this score is simpler and had comparable accuracy of predicting MT (Nunez, 2009). This score been applied in MTP by number of trauma centre wordwide, ie Singapore and US (Calcutt et al., 2013; Chay et al., 2015).

Massive hemorhage guideline or protocol in trauma is suggested to be implemented based on local evidence-based condition (Rossaint et al., 2016). Among recent study in developing the predictive score is Prince Wales Hospital (PWH) score, that developed in Hong Kong. This score derived from retrospective analysis of 1,891 civilian trauma patient in single level 1 trauma centre. The score included 8 variables with different points as shown below :

	Variable	Value	Points
i.	Displaced pelvic fracture		1
ii.	FAST/Abd CT-positive		2
iii.	HR	≥ 120	1
iv.	SBP	≤ 90	3
v.	Hemoglobin (g/dl)	≤ 7	10
		7.1 to 10	1
vi.	Base deficit	> 5	1
vii.	GCS	≤ 8	1

At score of ≥6, the correct classification in predicting MT requirement was was 96.9%, sensitivity of 31.5% , specificity of 99.7%, with incidence of MT of 82.9%.

Brockamp (2009) had done validation and comparison study between ABC, TASH and PWH score using 5,147 patients was extracted from the TraumaRegister DGU® of the German Trauma Society, with 95% of the cases were blunt trauma. TASH score had highest overall accuracy (AUC 0.889), followed by PWH score (AUC 0.860) and ABC score had AUC of 0.760. The sensitivity and specificity for all the scores is shown below.

Score	TASH	PWH	ABC
AUC	0.889	0.860	0.763
Sensititive	84.4%	80.6%	76.1%
Specific	78.4%	77.7%	70.3%

The author concluded that weighted and more sophisticated systems such as TASH and PWH scores including higher numbersof variables perform superior over simple non-weighted models (Brockamp et al., 2009).

1.6 Injury severity score

Baker (1974) described injury severity score in their article. The Injury Severity Score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned with an Abbreviated Injury Scale (AIS) score (1 to 6) and is allocated to one of six body regions which are (Head, Face, Chest, Abdomen, Extremities (including pelvis), andExternal) and categorized as minor (1), moderate (2), serious (3), severe (4), critical (5) and unsurvivable (6) . Only the highest AIS score in each body region is used. The ISS score takes values from 0 to 75. If an injury is assigned an AIS of 6 (unsurvivable injury), the ISS score is directly assigned to 75. The 3 most severely injured body regions have their score squared and added together to produce the ISS score (Baker et. al., 1974). The score generally represents linear correlation with mortality, morbidity, hospital stay and other measures of severity. The disadvantage of ISS scoring when there is error in initial AIS scoring. Moreover, real injuries may only known after completion of full investigation or after surgery. Thus, the ISS is not useful as a triage tool (Trauma.Org, 2006). AIS is summarized as below :

Score	Severity
1	Minor
2	Moderate
3	Serious
4	Critical
5	Critical
6	Unsurvivable

1.7 Research Justification And Benefit

National Blood Service guideline in trauma and massive transfusion is based on both laboratory and clinical judgement with estimation of blood loss, further expectation of blood loss, and clinical signs and symptoms (National Blood Centre Ministry of Health Malaysia, 2008a). Laboratory results may not be immediately available and coagulopathy states can change rapidly. Massive transfusion is related higher mortality rate and longer length of hospital stay, moreover unguided massive transfusion is tend to cause injudiciously usage of blood (Rainer et al., 2011; Livingston et al., 2014; Mitra et al., 2014). Thus, guidance is needed for blood and blood products administration to optimize patient outcome and improved of blood product management (Malone et al., 2006). Study by Livingston (2014) showed that massive transfusion without protocol does associated with longer hospital stay and increased mortality (Livingston et al., 2014). Protocols are needed to ensure that resuscitation occurs in a coordinated fashion and that patients are given appropriate amounts of blood and blood products (Livingston et al., 2014).

This retrospective study is conducted in Emergency and Trauma Department of Hospital Kuala Lumpur (EDHKL). The purpose of this study is to determine the prevalence and associated factors of massive transfusion among major trauma in adult patient. The associated factors that are taken into account are based on previous studies on predictive factors for likelihood of initiating the massive transfusion, as well as taken account of availability and practice in Emergency and Trauma Department of Hospital Kuala Lumpur (EDHKL). The factors that will be analysed in this study are heart rate ≥120/min, systolic