NORMALISATION OF THE INTERNATIONAL NORMALISED RATIO PRIOR TO INTERVENTIONAL PROCEDURE: IS IT NECESSARY?

BY

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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 not to be sent to any other universities. With that, this research might be used for consultation and can be photocopied as reference.

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TABLE OF CONTENTS

CHAPTER 2: LITERATURE REVIEW

CHAPTER 3: MATERIALS AND METHODS

CHAPTER 4: RESULTS

CHAPTER 5: DISCUSSION

CHAPTER 6: CONCLUSION, RECOMMENDATION AND LIMITATIONS

APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AABB	American Association of Blood Bank
AMDI	Advanced Medical and Dental Institute
APTT	Activated partial thromboplastin time
BBIS	Blood bank informative system
DIC	Disseminated intravascular coagulation
ERCP	Endoscopic retrograde pancreotography
FFP	Fresh frozen plasma
FNHTR	Febrile non-hemolytic transfusion reaction
Hb	Haemoglobin
HKL	Hospital Kuala Lumpur
ICU	Intensive care unit
INR	International normalised ratio
MOH	Ministry of Health Malaysia
OGDS	Oral gastroduodenal endoscopy
PDN	Pusat Darah Negara
PCC	Prothrombin complex concentrate
PRP	Platelet rich plasma
PT	Prothrombin time
RCT	Randomised clinical trial
SPSS	Statistical Package for Social Sciences
SHOT	Serious hazards of transfusion
TACO	Transfusion associated circulatory overload
TRALI	Transfusion related acute lung injury
USM	Universiti Sains Malaysia

ABSTRAK

Latar belakang: Plasma sejuk segar (fresh frozen plasma; FFP) ialah komponen darah yang sering dipohon oleh doktor sama ada bertujuan untuk transfusi terapeutik atau transfusi profilaktik. Transfusi profilaktik FFP di kalangan pesakit yang mempunyai masalah pembekuan darah (*coagulopathy*) adalah untuk mengelakkan episod pendarahan ketika prosedur rawatan invasif. Nilai *international normalised ratio* (INR) melebihi 1.50 sering dijadikan nilai penanda bagi transfusi FFP sebelum prosedur intervensi. Kajian ini berhasrat untuk menilai keberkesanan transfusi FFP dalam menormalkan bacaan INR sebelum prosedur intervensi dijalankan dan menentukan hasil transfusi ini (perbezaan INR, episod pendarahan dan reaksi tindakbalas transfusi).

Kaedah: Kajian prospectif keratan rentas dijalankan dengan data daripada 81 pesakit yang menerima transfusi FFP sebelum prosedur intervensi selama tempoh tiga bulan (Disember 2016 hingga Febuari 2017). Kajian ini telah dijalankan di Hospital Kuala Lumpur dan Pusat Darah Negara. Subjek kajian ini dipilih secara persampelan khusus di mana setiap pesakit yang merekodkan bacaan INR melebihi 1.50 dipilih. Data diperoleh daripada rekod perubatan pesakit dan diisi dalam proforma kajian. Kesemua data demografik dan klinikal berkaitan dengan keberkesanan transfusi FFP dicatatkan dan kemudiannya dianalisa.

Keputusan: Peratusan pesakit yang mencapai nilai INR kurang daripada 1.51 selepas transfusi FFP adalah 30.30% (n=27) dengan seorang pesakit merekodkan bacaan INR

normal iaitu INR < 1.20. Hanya dua pesakit mengalami episod pendarahan selepas menjalani prosedur intervensi (seorang mengalami pendarahan major dan seorang mengalami pendarahan minor). Peratusan reaksi tindakbalas transfusi adalah rendah iaitu 2.50%. Sebahagian besar pesakit menjalani prosedur intervensi dengan bacaan INR melebihi 1.50 selepas transfusi FFP (n=52) tanpa mengalami episod pendarahan. Keseluruhannya, transfusi FFP merekodkan perbezaan median INR yang signifikan daripada 1.89 (IQR, 0.53) kepada 1.60 (IQR, 0.25); $p < 0.001$. Perbezaan median INR yang lebih ketara bagi kumpulan yang merekodkan nilai pra transfusi INR melebihi 2.00 dan kumpulan yang menerima dos transfusi FFP antara 10.00 hingga 20.00 ml kg^{-1} ($p < 0.001$). Perbezaaan INR menunjukkan kolerasi yang signifikan dan positif dengan nilai pra transfusi INR ($r_s = 0.83$, $p < 0.001$) dan dos FFP ($r_s = 0.72$, $p < 0.001$).

Kesimpulan: Prosedur intervensi selamat dijalankan walaupun tanpa normalisasi INR secara keseluruhan selepas transfusi (INR tidak normal). Transfusi profilaktik FFP sebelum prosedur intervensi boleh dielakkan bagi pesakit mengalami *coagulopathy* kurang teruk (INR 1.50 - 2.00). Risiko pendarahan boleh dikurangkan dengan bantuan kemahiran yang bagus dari doktor yang merawat.

Kata kunci: transfusi profilaktik FFP, prosedur intervensi, *international normalised ratio*, dos FFP, *coagulopathy*

ABSTRACT

Background: The fresh frozen plasma (FFP) is frequently prescribed by the clinicians either for therapeutic or prophylactic purpose. Prophylactic FFP transfusion in coagulopathic patient is given to prevent any bleeding complications during invasive procedures. The international normalised ratio (INR) value of 1.50 and above is frequently reported to be a transfusion trigger for FFP prior to interventional procedure. This study aims to evaluate the efficacy of FFP transfusion in normalising the INR prior to interventional procedures. On top of that, it is also to determine the post-transfusion outcomes (INR difference, bleeding episodes and adverse transfusion reactions).

Methods: A prospective cross-sectional study involved 81 patients who received prophylactic FFP transfusion prior to interventional procedures over a period of three months (December 2016 until February 2017). The study was conducted at both Hospital Kuala Lumpur and Pusat Darah Negara. Study subjects with abnormal coagulation laboratory value (pretransfusion INR above 1.50) were selected by purposive (non-probability) sampling. Data retrieved from patient's medical record and were filled in the research proforma. All demographic and clinical data in regards to the outcome of FFP transfusion were captured.

Results: The proportion of patients achieved posttransfusion INR below 1.51 was 30.30% (n=27) with one patient normalised to normal value (INR < 1.20). Only two patients developed bleeding episodes post interventional procedure (one with major bleeding

episode and one with minor bleeding episode). The percentage of adverse transfusion reactions was low with 2.50%. The majority of patients underwent the interventional procedures with posttransfusion INR values of above 1.50 (n=52) without experiencing any bleeding episodes. Overall, FFP transfusion resulted in significant median difference of INR from 1.89 (IQR, 0.53) to 1.60 (IQR, 0.25); $p < 0.001$. The greater median INR difference was observed in group with pretransfusion INR above 2.00 and in group who received FFP doses between 10.00 to 20.00 ml kg^{-1} ($p < 0.001$). The INR difference showed the significant, positive correlation with pretransfusion INR values ($r_s = 0.83$, $p < 0.001$) and FFP doses ($r_s = 0.72$, $p < 0.001$).

Conclusions: The interventional procedures were safely carried out despite abnormal posttransfusion INR (uncorrected INR). The prophylactic FFP transfusions could be avoided in patients with mild coagulopathy (INR 1.50 - 2.00) prior interventional procedures. The risk of bleeding could be minimised by clinicians with the good techniques.

Keywords: prophylactic FFP transfusion, interventional procedures, international normalised ratio, FFP doses, Coagulopathy.

CHAPTER 1- INTRODUCTION

1.1 OVERVIEW

1.1.1 Hospital Kuala Lumpur

Hospital Kuala Lumpur (HKL) is a referral hospital with multi-disciplinary clinical departments and sub-specialties. HKL is considered the largest hospital governed by the Ministry of Health Malaysia (MOH) with the bed capacity of 2300 beds. As one of the leading centres in Malaysia, it receives referral cases from other hospitals, especially from the Klang Valley area. Multiple interventional procedures are performed within the facilities each day such as endoscopic retrograde pancreatography (ERCP), oral gastroduodenal endoscopy (OGDS), lower gastro intestinal endoscopy, bronchoscopy, central vein cannulations, femoral angiography, liver biopsy, kidney biopsy, lumbar puncture, paracentesis, thoracocentesis and drainage of an abscess.

Pusat Darah Negara (PDN) is a blood centre located next to HKL. It is responsible for the planning and development of national blood transfusion services in Malaysia central region and for the national referral. The main services are to begin with blood donor selection, blood collection, blood components processing, laboratory testing and issuing blood components to government hospitals and private health centres in the Klang Valley area including HKL. PDN caters for supplying of blood and components preparation some government hospitals under Ministry of Health Malaysia (central region) such as Hospital Tengku Ampuan Rahimah Klang, Hospital Tuanku Jaafar Seremban, Hospital Temerloh, Hospital Putrajaya, Hospital Sungai Buloh, Hospital Selayang, Hospital Kajang and Institut Kanser Negara.

1.1.2 Fresh Frozen Plasma

Fresh Frozen Plasma (FFP) is processed from whole blood collections and through plasmaphaeresis procedure. FFP prepared from whole blood collection is prepared within 8 hours and subsequently frozen at minus 18°C or below to preserve their coagulation factors activity as well as extend the shelf life. FFP contains normal coagulation factors, including the labile coagulation factors: factor (F) V, FVIII and other haemostasis proteins such as antithrombin and ADAMTS13. Each unit of FFP is about 207 ± 51 ml from whole blood collection and 600 to 800 ml by plasmaphaeresis procedure (AABB Technical Manual, 2014). FFP has the shelf life up to 36 months if stored at colder than - 25°C and shelf life of three months if stored between -18 to -25°C (Europe, 2011). Once FFP is requested for transfusion, it is thawed at 30°C to 37°C in a waterbath to be able to transfuse clinically. For PDN, FFP is only stored at 2 to 6°C for 24 hours post thawing.

FFP is the commonly used blood components besides packed red cell and platelet concentrates in HKL. The National Transfusion Services report of 2013 to 2015 reported a total of 342,228 units of FFP were prepared and a total of 137,744 units were utilised nationwide. The Annual Report of PDN stated for the last 4 years from 2012 till 2015 that HKL have received 9657 units, 7282 units, 7222 units and 7111 units respectively (Annual Report Blood Transfusion Services, 2015).

1.1.3 FFP transfusion and its clinical indication

FFP transfusion was prescribed by clinicians as either for therapeutic or prophylactic transfusion (Stanworth *et al*., 2011; Watson *et al*., 2011). FFP is known to

be effective in correcting multiple coagulation factor deficiencies such as in massive bleeding due to trauma and disseminated intravascular coagulation (DIC) due to many causes. In certain circumstances, FFP is also transfused to non-bleeding patients with coagulopathy to minimise the risk of bleeding as frequently seen in critically ill patients (Walsh *et al*., 2010).

Coagulopathy is defined as an abnormal coagulation laboratory test such as prolonged prothrombin time (PT) or an elevation of international normalised ratio (INR). Early administration of FFP in patients with consumptive coagulopathy have proven to reduce the mortality rate and improved clinical outcomes especially in trauma cases (Brohi *et al*., 2003). However, a few studies reported that FFP transfusions were minimally effective in non-massively bleeding patients with mildly abnormal coagulation tests (Abdel-Wahab *et al*., 2006; Holland and Brooks *et al*., 2006).

1.1.4 Pre interventional procedure of FFP transfusion and rationale to conduct the study

Segal and Dzik (2005) described the three reasons for clinicians to prescribe FFP transfusion: (i) an elevation of the PT or INR as a prediction of bleeding risk, (ii) correction of prolonged or abnormal clotting time and (iii) reduction of overall bleeding events (Segal and Dzik, 2005).

Patients in HKL were given FFP transfusions for bleeding causes as well as prophylaxis prior to a procedure. The prophylactic transfusion was given to patients with elevated INR (INR above 1.50) and expected to correct a targeted INR value prior to an

interventional procedure. The urgent interventional procedures are delayed in order to wait for an acceptable corrected INR value. Subsequently, the longer time required for pre-transfusion testing processes, including the delivery of blood products and a patient will expose too many episodes of blood transfusion before any intervention took place. The practice of prescribing FFP transfusion especially with mildly elevated INR need to be studied and recommendation for an evidence-based indication is necessary.

Transfusion of FFP is not without a risk for adverse transfusion reaction. The common adverse transfusion reactions can be associated with FFP transfusion are allergic reaction, anaphylaxis reaction, febrile non-haemolytic transfusion reaction (FNHTR), transfusion associated circulatory overload (TACO), transfusion related acute lung injury (TRALI) and others. There was evidence that the adverse risk for prophylactic FFP transfusion may outweigh its clinical benefit, especially when the blood component was infused in haemodynamically stable patients with minimal prolongation of PT or INR (West *et al.*, 2011).

1.2 RESEARCH JUSTIFICATION AND BENEFITS

The FFP transfusion is a frequently prescribed by the clinician either for therapeutic or prophylactic purposes. The indication for FFP transfusion in coagulopathic patients was to prevent any bleeding complications when they scheduled for an invasive procedure (Stanworth *et al*., 2011; Watson *et al*., 2011).

The good transfusion practice includes the right indication for each transfusion episode and appropriate use of FFP. This is crucial to ensure patient's benefit is greater than having a transfusion risk. The clinician needs to identify patients with an elevated INR who may clinically benefit from receiving prophylactic FFP transfusions prior interventional procedure. Some patients with mild coagulopathy with hemodynamically stable (no bleeding) may not require the FFP coverage prior to the interventional procedure.

The adequate dosage of FFP transfusion should be calculated according to body weight for an optimum haemostasis process. The recommended dose of FFP is between 10.00 to 20.00 ml per kilogram body weight in each transfusion episode. The reduction of INR post-FFP transfusions was postulated in relation with volume FFP infusions. Inadequate volumes of FFP received by the patient (such as the patient with mild elevated INR or overweight patient) lead to minimal correction of the INR and higher chances for the second episode of FFP transfusion. Delaying undergoing procedures may jeopardise the treatment and management patient indirectly.

The FFP transfusion can be avoided for non-bleeding coagulopathy patients or mildly prolonged PT/INR patients and subsequently, they can undergo a procedure safely without any bleeding. Two previous studies demonstrated no significant risk of bleeding post central line insertions between patients with normal and abnormal coagulation tests (elevated INR or thrombocytopenia). The FFP transfusion to correct coagulation prophylactically was not necessary prior to central venous catheter insertion. It can be avoided in patients with pretransfusion INR values of up to 3.00 (Weigand *et al*., 2009; Carino *et al*., 2012). Minimising the use of FFP transfusions is crucial to reduce the risk of adverse transfusion events as stated earlier. A local study can be conducted to evaluate the outcome:

i) Determine the cut off value of INR before the clinician decided that the FFP transfusion is required prior to an interventional procedure.

ii) Reduction of INR value based on the recommended dose of 10.00 to 20.00 ml per kilogram body weight per transfusion episode and pretransfusion INR value.

iii) The number of adverse transfusion reactions associated with FFP transfusion and bleeding episode reported during or after the interventional procedure.

The outcome of this study will contribute to a reduced use of FFP transfusions in correcting the INR value prior to an interventional procedure, and at the same time increase the awareness among clinicians regarding the judicious use of FFP.

1.3 LIST OF DEFINITIONS

1.3.1 Fresh Frozen Plasma (FFP): A blood component either prepared from fresh whole blood collection or plasma collected by plasmaphaeresis. The FFP will be stored at an appropriate storage temperature to preserve the activity of coagulation factors (Transfusion Practice Guidelines, 2016).

1.3.2 INR value of 1.50: The INR is an expression of the results of a PT in a standardized testing environment. It is calculated by using an international standard that corrects for laboratory variation. In the following calculation, the ISI is the International Sensitivity Index of the thromboplastin reagent used in the assay: INR = (patient PT/control PT)^{ISI} (Malloy *et al*., 2009). INR value 1.50 was chosen based on the clinical practice and what is frequently reported to be the FFP transfusion threshold including for patients scheduled for any interventional or invasive procedures (Lauizer *et al*., 2007; Stanworth *et al*., 2011; Hall *et al*., 2012; Muller *et al*., 2015).

1.3.3 Abnormal Coagulation Test: The coagulation test comprises measurements in vitro coagulation processes and the parameters of testing are the PT, INR and activated partial thromboplastin time (APTT). The abnormal coagulation test defined as an APTT is measured more than 38 seconds and/or INR is measured more than 1.20 or PT is prolonged more than 13 seconds (Abdel-Wahab *et al*., 2006).

1.3.4 Normalised prothrombin time and international normalised ratio: PT is less than 13 seconds and INR is less than 1.20 (Abdel-Wahab *et al*., 2006).

1.3.5 Mild elevation of prothrombin time and international normalized ratio: The PT is less than 17 seconds or INR is less than 2.00 (Abdel-Wahab *et al*., 2006).

1.3.6 **Fresh frozen plasma dose**: The dose will be calculated by volume in millilitre (ml) divided to patient's body weight in kilogram (kg) and ranged from 10.00-20.00 ml FFP per kilogram for adult transfusions.

1.3.7 **Interventional procedures**: endoscopic retrograde pancreotography (ERCP), oral gastroduodenal endoscopy (OGDS), lower gastrointestinal endoscopy, bronchoscopy, central vein cannulation, femoral angiography, liver biopsy, kidney biopsy, lumbar puncture, paracentesis, thoracocentesis and drainage of abscess (Muller *et al*., 2015).

1.3.8 **Bleeding episode in relation with the procedure**: The bleeding episode categorised into major and minor bleeding. **Major bleeding** is defined as bleeding associated with either:

a) Haemoglobin reduction by more than 2 g/dL in the absence of another cause of bleeding.
b) No increment of haemoglobin measurement after two or more units packed cells transfusion.

Meanwhile, **minor bleeding** is defined as any bleeding incidence at the site of insertion such as oozing or increase in the size of subcutaneous haematoma (Muller *et al*., 2015).

1.4 RESEARCH OBJECTIVES

1.4.1 General Objective

To evaluate the efficacy of FFP transfusion in normalising the INR prior to interventional procedures

1.4.2 Specific Objectives

i) To determine the percentage of INR ≤ 1.50 post-FFP transfusion.

ii) To determine the transfusion outcomes (INR difference, bleeding episode and adverse transfusion reaction)

iii) To compare INR difference within the following groups :

a) pretransfusion INR value

b) FFP dose

iv) To evaluate the correlation between INR difference and:

a) pretransfusion INR value

b) FFP dose

1.5 Alternative Hypothesis

i) There is a significant difference of median INR difference between groups of pretransfusion INR value and groups of FFP dose.

ii) There is a positive correlation between the INR difference with pretransfusion INR value and FFP dose.

1.6 CONCEPTUAL FRAMEWORK

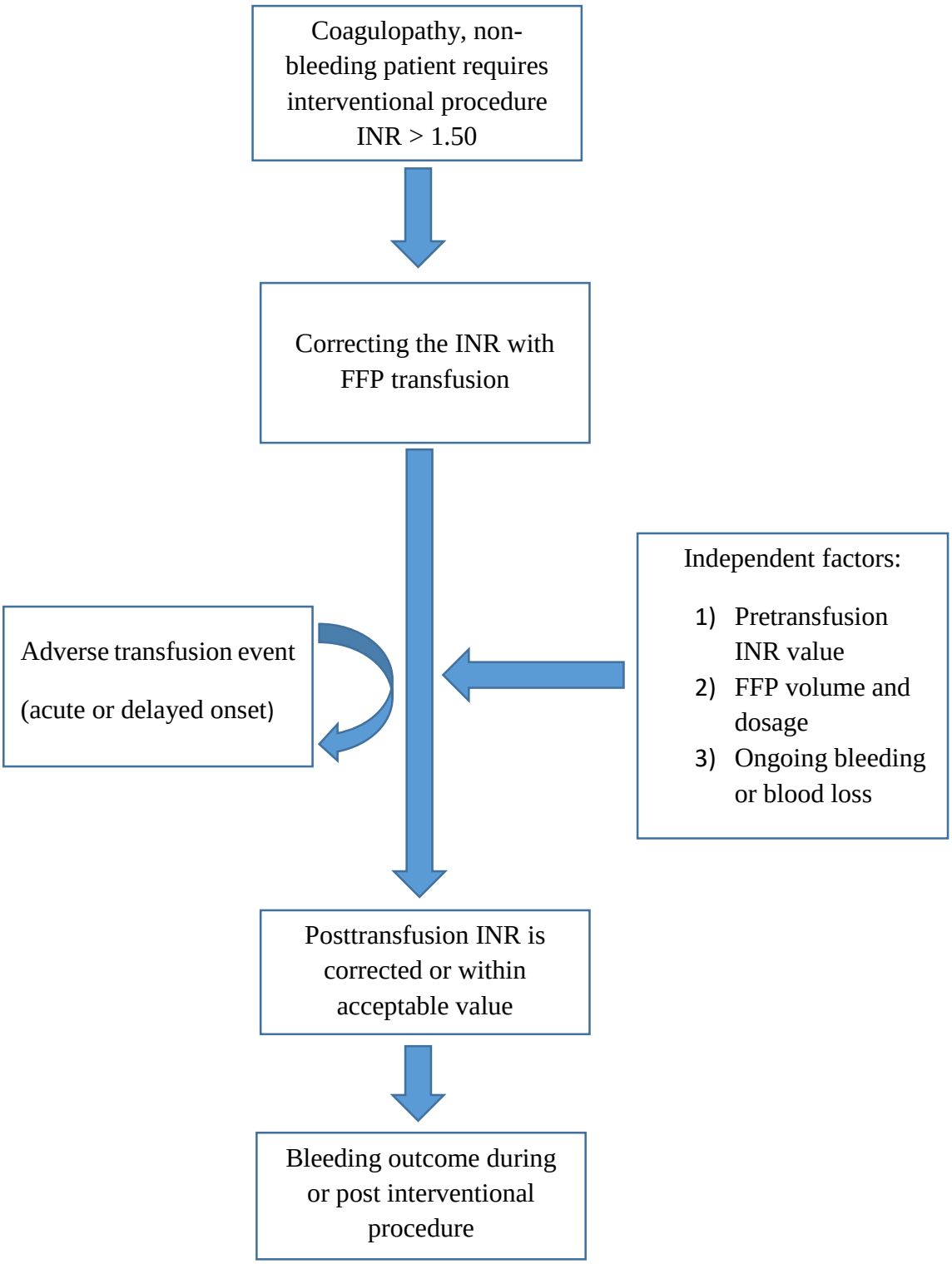

Figure 1.1 The clinical practice of prophylactic FFP transfusion for INR normalisation prior to interventional procedures.

CHAPTER 2- LITERATURE REVIEW

2.1 Preparation and clinical guidelines of FFP

FFP is one of the blood components collected from whole blood donation or by aphaeresis blood donation. It should be processed within 8 hours after blood collection by using the specific blood centrifuge machine. In PDN, if whole blood collected from the double bag, it will undergo hard spin centrifugation to separate red cells from plasma. Meanwhile, the triple bag whole blood unit will undergo soft spin in order to separate red cells from platelet rich plasma (PRP). PRP will be processed to separate FFP and platelet concentrate by using hard spin centrifugation at 20 to 24 °C. Following that, the processed FFP is frozen using the blast freezer and is stored at minus 18°C or below. This is necessary to preserve all the coagulation factors, including the labile coagulations factors such as factors V and VIII. Most FFP units contain 225 ± 25 ml from single whole blood donation and plasmaphaeresis derived units may contain up to 600 ml in volume (Labarinas *et al*., 2013). Upon request, FFP needs to be thawed for 15 to 30 minutes at 37°C for clinical usage. The thawed FFP has the shelf life of 24 hours if kept at 2 to 6 °C. In addition, in United State, it can be stored for another 4 days if stored at 2 to 6 °C and labelled as Thawed Plasma (AABB Technical Manual, 2014).

After thawing, FFP will contain almost near normal levels of pro-coagulant plasma protein, inhibitory protein of the coagulation system, immunoglobulin, albumin and others acute phase proteins. Prior blood administration, the transfusion services must ensure the FFP should be safe and meet the standard production quality set by international and national requirement. The standard FFP with the volume of 200 to 250 ml contain at least 0.7 IU/ml of factor VIII in at least 75% of the FFP units

(O'Shaughnessy *et al*., 2004). In line with United Kingdom guideline, PDN quality control requirement for factor VIII level is more than 0.7 IU/ml and 10 units FFP tested in every 3 months (Transfusion Practice Guidelines, 2016). FFP transfusion for surgical and traumatic bleeding should be guided by coagulation testing**.**

The usage of FFP has grown steadily over past two decades in the United Kingdom. Prophylactic FFP transfusion accounts for almost 50% and was given prior an invasive procedure or surgery (Stanworth *et al.*, 2011). There was a local guideline available regarding the indications of FFP transfusion. The FFP can be transfused for the immediate reversal of overwarfarinisation in the presence of potentially life-threatening bleeding, if the prothrombin factor concentrate (PCC) is not available. It is clinically used for the treatment of multiple coagulation factor deficiencies associated with acute bleeding in disseminated intravascular coagulation (DIC) and abnormal coagulation parameters following cardiac bypass surgery, massive transfusion or in patient with liver disease (Rational Use of Blood and Blood Products, 2007). Multiple international guidelines proposed the FFP transfusion can be considered prior to invasive procedure or surgery in patient with clinical coagulopathy. The cut off value for FFP transfusion was PT greater than 1.5 times the midpoint of the normal range (usually >18 seconds or INR 1.5) or aPTT greater than 1.5 times the top of the normal range (Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines, 1994; Liumbruno *et al*., 2009; Michelle *et al*., 2007; Blood transfusion: summary of NICE guidance , 2015).

Besides, FFP also can be used to treat for single factor deficiency when specific human plasma based or recombinant factor concentrate is unavailable. It is be used to treat the bleeding or as the prophylactic infusion in the patient with underlying factor II,

V, XI, XIII, Fibrinogen and Protein C deficiency (Benjamin and McLaughlin, 2012). Blombery and Scully (2014) suggested the plasma exchange is the first line treatment for thrombotic thrombocytopenic purpura. It will provide the source of ADAMTS 13 protein and the autoantibody in blood circulation will remove via plasma exchange (Blombery and Scully, 2014). Early administration of FFP in trauma patient resuscitation will prevent the early-trauma induced coagulopathy and increased initial survival rate with higher ratio packed cells: FFP transfusion (Mitra *et al*., 2010).

The effects of FFP transfusion were more beneficial in the correction of multiple clotting factor deficiencies such as massive bleeding and consumptive coagulopathy such bleeding DIC (O'Shaughnessy *et al*., 2004). A few studies reported that FFP was also frequently administered prophylactically in critical illness, non-bleeding patients with coagulopathy as evidenced by prolonged PT or elevated INR (Dara *et al*., 2005; Lauzier *et al*., 2007; Vlaar *et al*., 2009; Tinmouth *et al*., 2013). In a prospective study conducted by Stanworth *et al* in 2011, about 15% of FFP transfusions (out of 388 treatment episodes) were given to non-bleeding patients prophylactically prior to undergoing any procedures (Stanworth *et al.*, 2011).

Despite multiple guidelines regarding the clinical indication of FFP published, there were variable percentages of FFP appropriateness or misused FFP usage based on their local clinical transfusion guidelines (Yang *et al*., 2012). A study conducted in Singapore by Chng *et al.* (2003) showed only 27% transfusion episodes were deemed appropriate and 73% of inappropriate requests (such as non-bleeding DIC and INR ≤ 1.50 without any bleeding episode) were similar across clinical specialties (Chng *et al*., 2003). Stanworth *et al*. (2011) reported in the United Kingdom, 43% of FFP transfusions were

given to the non-bleeding patient and as prophylactic transfusion prior procedures or surgery for both adults and children. About 56% of plasma was transfused to reverse the overwarfarinisation without any underlying bleeding. For FFP dosing, they found 40% of adults, 24% of children and 20% of infants were transfused with FFP dose of less than 10.00 ml kg^{-1} (Stanworth *et al.*, 2011). Meanwhile, an audit study of FFP utilisation in Canada found 28.6% were inappropriate transfusions as FFP were administered to patients with an INR below 1.50 and in the absence of bleeding (Tinmouth *et al*., 2013). A prospective study was conducted among 100 patients who received FFP transfusions from June 2013 to June 2014 at Vinayaka Mission's Kirupananda Variyar Medical College & Hospital. They found 74% transfusion episodes were appropriate based on National Health And Medical Research Council and the Australasian Society for Blood Transfusion fresh frozen plasma (Jayanthi and Pitchai, 2015). Another recent study conducted by Alcon *et al.* (2017), compliance of FFP transfusion based on institution-specific guidelines was at the higher rate (90% of 3018 transfusion events) (Alcon *et al.,* 2017). Pratiba *et al*. (2001) retrospectively analysed on the practice of FFP transfusions in the University Hospital, Kuala Lumpur. The authors have found that 60% of the total FFP units were inappropriately transfused across the multiple clinical departments. The causes of inappropriate FFP usage were as a volume expansion, no coagulation blood testing available prior to transfusion, INR less than 1.5 and in cardiac-bypass surgery post operative bleeding (Pratiba *et al*., 2001).

2.2 Correcting the INR with FFP transfusion

There were studies that reported on the effectiveness of FFP transfusions on normalising the INR in the hospitalised coagulopathy patient. The INR of at least 1.50

was frequently reported to be the transfusions trigger for prophylactic FFP transfusion prior procedures (Lauzier *et al*., 2007; Stanworth *et al*., 2011; Hall *et al*., 2012 and Muller *et al*., 2015). Muller *et al.* (2015) conducted a multicentre randomised control trial (RCT) in the Netherlands on prophylactic FFP transfusion. The selected study subject was critically ill patients with coagulopathy (INR 1.50 to 3.00) underwent an invasive procedure. However, the clinical trial was terminated early due to slow inclusion of study subjects. Even though the prophylactic FFP transfusion resulted in a reduction of INR, only 54% of transfused patients had a corrected INR of less than 1.50. The efficacy of FFP transfusion on INR normalisation varied widely. Patients with the higher pretransfusion INR values recorded the largest INR difference ($r = 0.68$, $p < 0.01$). Their findings showed an INR reduction posttransfusion and however, it was not a complete normalisation of INR after FFP transfusion (Muller *et al*., 2015).

In a prospective audit of all FFP transfusions at the Massachusetts General Hospital (September 2004 until September 2005), Abdul-Wahab *et al*. (2006) analysed 121 patients with mild coagulopathy (INR ≤ 1.85). FFP transfusion resulted in the normalisation of posttransfusion PT/INR in only 0.8% of patients and decreased the PT/INR halfway toward normal values in only 15% of patients. The median INR difference was 0.07 post-FFP transfusion. The authors found no significant relationship between pretransfusion PT value and 50% correction of the PT post-FFP transfusion. A minority of patient achieved partial normalisation of posttransfusion PT with 99% of study subject recorded uncorrected PT post-FFP transfusion (Abdul-Wahab *et al*., 2006).

A retrospective cohort study was done by Dara *et al*. (2005) on the effectiveness of FFP transfusion in the critically ill patient with coagulopathy. They found that the INR

was corrected to less than 1.50 in only 36% of patients (16 out 44 patients with median pretransfusion INR 2.70) post-FFP transfusion. The risk-benefit ratio of FFP transfusion in critically ill medical patients with mild coagulopathy may not be favourable (Dara *et al*., 2005). The subsequent year, Holland and Brooks (2006), reported that FFP treatments were minimally effective in correcting mild elevation in INR (INR less than 1.70). There were significant changes in the posttransfusion INR values if pretransfusion INR above than 1.70. The authors concluded that minimally elevated INR cannot be corrected with FFP administration at currently accepted dosages and INR normalisation was correlated with the pretransfusion INR value (Holland and Brooks, 2006).

2.3 Association between posttransfusion INR values with FFP dose.

There was an association between the volume and doses of FFP with reduction values of posttransfusion INR. In a small cohort study of 22 critically ill patients, a dose of 33.00 ml kg^{-1} was more effective in achieving target levels of coagulation factors compared to 12.00 ml kg^{-1} (Chowdhury *et al*., 2004). Dara *et al.,* (2005) retrospectively reported the median dose of FFP was higher in the group (17.00 ml kg^{-1} vs 10.00 ml kg^{-1} with *p*-value 0.018) whose INR decreased to 1.50 post-transfusion (Dara *et al*., 2005). However, a multicentre RCT done in Netherlands found that the INR was partially corrected with a dose of 12.00 ml kg^{-1} in patients with coagulopathy (Muller *et al*., 2015).

Hall *et al.* (2012) evaluated the FFP dose with reduction of INR post transfusion. This was a prospective cohort among patients with coagulopathy who underwent vascular catheterisation. They found more than half of patients received FFP dose less than 10.00 ml kg^{-1}, which was unlikely to reliably correct coagulation factor defects

(Hall *et al*., 2012). A multicentre, prospective observational study by Stanworth *et al.* (2011) concluded the posttransfusion corrections of INR in critical care patients were consistently small unless the pretransfusion INR value greater than 2.50. The median volume FFP given prior to the invasive procedure was 560 ml and the median FFP dose given was 9.80 ml kg^{-1}. In relation to the FFP dose and pretransfusion INR value, the authors confirmed there was a larger dose given for higher pretransfusion INR value in order to achieve targeted posttransfusion INR value. The median reductions in posttransfusion INR were greater when the pre-FFP transfusion values were higher. There was no significant relationship between the degree of change of INR and dose of FFP used with a *p*-value of 0.86 (Stanworth *et al*., 2011).

2.4 Bleeding outcome

Bleeding is a common complication during and after any interventional procedure. The risk of bleeding is greater in patients with coagulopathy. Numerous retrospective studies reported the low incidence (less than 1%) of major bleeding after an invasive procedure in patients with a prolonged INR (Mumtaz *et al*., 2000; Fisher *et al*., 1999; Goldfarb *et al*., 1982). A multicentre RCT was done by Muller *et al*. (2015) found occurrences of bleeding complications after an invasive procedure did not differ between transfused and non-transfused patients. There were six patients in the non-transfused group had bleeding episode compared to eight patients in the FFP group with *p*-value 0.77. They suggested the invasive procedures can be safely carried out without prophylactic FFP transfusion (Muller *et al.*, 2015).

Foster *et al.* (1992) reported 202 percutaneous central venous catheter insertions performed in patients with coagulopathy without any major bleeding episodes. The INR values more than 5.00 (n = 137) or platelet counts less than 50,000/μL (n = 146) was associated with a higher incidence of superficial hematomas or site oozing, respectively (Foster *et al*., 1992). Another study by Fisher *et al.* (1999) reported 658 central venous cannulations in patients with advanced liver disease and coagulopathy. The median INR was 2.40 (range: 1.00 - 16.00) and the median platelet count was 81,000/μL (range: 9000 to 1,088,000/μL). Preprocedure FFP or platelets transfusions were not administered routinely. They found only one patient had bleeding complications (superficial skin hematomas and mild oozing at the puncture site) attributed to the technical mishap. This paper reveals that technical mishaps remain the main contributing factors for haematoma formation. Others bleeding complications are rare regardless of the coagulation test results (Fisher *et al*., 1999).

A retrospective study was done at the University of Pennsylvania Medical Center on the outcomes of 567 central venous catheterisations. The procedures were carried out in patients with platelet counts below 50,000/μL and/or an INR > 1.50. There were no haemorrhagic complications occur in the group with abnormal laboratory parameters. Meanwhile, three bleeding complications (1 in 1057) reported even with platelet counts above 50,000/μL and INR < 1.50. Despite these very abnormal laboratory test results, the complication rate in this group with abnormal laboratory results (without correction by plasma infusion) was identical to that of patients with more normal laboratory numbers (Haas *et al*., 2010). The subsequent study by Carino *et al*. (2012) showed no benefits of prophylactic FFP observed in a retrospective cohort study in patients with post central line insertion. Out of 27 transfused patients, only one patient with INR 3.90 had a bleeding episode post-procedure. The occurrence of bleeding episodes post central line

insertion was 0.03% in both transfused and non-transfused patients. The results suggested that the prophylactic plasma transfusion can be avoided when the INR is less than 3.00 and used highly selectively in patients with higher INR values (Carino *et al*., 2012).

A prospective study conducted by Mac Donald *et al*. (2003) evaluated ten patients with end-stage liver disease (INR above 1.50) underwent cardiac catheterisation. Only one patient developing a haematoma post-procedure. The retrospective studies suggested that commonly performed invasive procedures in the critically ill, such as thoracocentesis, central venous catheter insertion and percutaneous tracheostomy, carry a low bleeding risk (Segal and Dzik, 2005; Hibbert *et al*., 2013; Rosseland *et al*., 2011). Hibbert *et al.* (2013) conducted a retrospective study to assess haemorrhagic complications post ultrasound-guided thoracentesis. They found only 0.4% out of 1009 patients have haemorrhagic complication post-procedure. All patients with haemorrhagic complications had received FFP transfusion prior to the procedure. The haemorrhagic complications were infrequent and attempting to correct abnormal INR or platelet level before the procedure was unlikely to confer any benefit (Hibbert *et al*., 2013). In the earlier study done in 1991 by McVay and Toy showed no significant risk of bleeding in mild coagulopathy patients compared to normal patients. Apart from that, they reported the overall frequency of clinically significant bleeding complications was very low (0.2%, 1/608 events). The prophylactic blood component transfusion was not recommended for paracentesis and thoracentesis in non-bleeding patients with mild coagulopathy (McVay and Toy, 1991).

In a prospective study by Makris *et al.* (1992) evaluated the bleeding incidences for 104 patients underwent liver biopsy. The INR, aPTT, thrombin time, fibrinogen,

bleeding time, and platelet count were measured before the procedure. More than half of patients recorded one or more abnormalities of laboratory testing results. The highest INR value was 2.00 and platelet counts were above than 50,000/μL. They reported two patients experienced procedure-related bleeding and eventually, both of patients had normal pre-procedure coagulation parameters (Makris *et al*., 1992). Diette *et al.* (1999) reported a retrospective review of 720 fiberoptic bronchoscopies performed over a 12-month period at Johns Hopkins Hospital. They concluded that bleeding complications were poorly correlated with coagulation parameters or platelet count. On top of that, transbronchial biopsy can be safely performed without an increase the risk of bleeding (Diette *et al*., 1999).

2.5 Complications of FFP transfusion

The FFP transfusion carries a risk for adverse transfusion reactions. It can cause morbidity and mortality to the recipient. Plasma transfusion complication can be either divided as acute or delayed transfusion reactions. Others classification, It also can be divided into infectious or non-infectious transfusion complications. Acute transfusion reaction occurs less than 24 hours from the onset of transfusion (AABB Technical Manual, 2014). Among the transfusion reactions for plasma were include TRALI, TACO, allergic/ anaphylaxis reactions, FNHTR, post transfusion purpura (PTP) and transfusion-associated graft versus host disease (TA-GVHD). As for other complications, plasma transfusion reported having a higher risk to develop multiple organ failures (2.1% increases for every FFP unit transfusion) and acute respiratory distress (2.5% increases for every unit of FFP) (Watson *et al.*, 2009). As such, clinical justification of FFP transfusion of whether the benefit is far greater than the risk of any adverse transfusion reactions is very crucial.

An allergic or anaphylactic reaction is commonly associated with FFP and platelet transfusions with percentages of 80% and 60% out of the total allergic/anaphylaxis incidences respectively, reported in the year 2015 (Serious Hazards of Transfusion Annual Report, 2015). The incidence of allergic transfusion reactions has been estimated less than 3% of all transfusions with most of them presented with mild symptoms such as to urticaria, pruritus and/or flushing (Domen *et al*., 2003; Vamvakas *et al*., 2007). Meanwhile, Karim *et al.* (2014) reported allergic reaction was one of the most common adverse transfusion reaction accounting for 57.8% of all transfusion reactions (Karim *et al.*, 2014). It is due to the presence of plasma allergens such as IgA and haptoglobin. A patient may experience urticaria, pruritus, facial puffiness, and oral-pharyngeal oedema. In severe form of allergic reactions, patient may experience hypotension, bronchospasm and stridor. Pretransfusion medication with antipyretics and antihistamine are widely used to prevent this reaction. In the patient who has the deficiency in IgA (serum IgA < 0.5 mg/L) or haptoglobin, transfusion with IgA free plasma components are necessary to reduce the risk of severe allergy transfusion reaction (Hirayama, 2012). The incidences of anaphylaxis secondary to plasma transfusion are very uncommon and happened in only 1% to 3% of total plasma transfusions (O'Shaughnessy *et al*., 2004).

Apart from allergy, FNHTR is another most commonly encountered transfusion reaction. Usually, it is mild in severity, self-limiting and documented fever more than 1°C increment from baseline body temperature, chills, and rigors. The mechanism involved in FNHTR is recipient's anti-leukocyte antibody that is directed against donor's HLA antigen, or against granulocyte-specific antigen and due to the accumulation of cytokines in the blood components (Arewa, 2012). Universal

leukoreduction or leucodepletion of RBCs had proven to reduce the incidence of FNHTR from 0.37% to 0.19% (King *et al.,* 2004). FFP administration is associated with acute lung injury and the incidence increased up to 30% of transfused critically ill patients (Dara *et al*., 2005). Sarani *et al.* (2008) reported retrospectively that FFP transfusion was associated with increased risk of infectious complications such as ventilator associated pneumonia and bacteraemia shock in critically ill patients (Sarani *et al.,* 2008).

CHAPTER 3 – MATERIALS AND METHODS

3.1 INTRODUCTION

HKL is the biggest tertiary hospital in Malaysia. HKL has various facilities and a substantial number of clinical experts in various specialties and sub specialties. Hence, numerous interventional procedures carried out by many disciplines in the hospital.

Among all patients that were scheduled for interventional procedures, a proportion of them were having abnormal coagulation profiles secondary to the underlying medical diseases. These patients may require the FFP transfusion as a precautionary measure to minimise bleeding complications during or after the procedure.

3.2 STUDY DESIGN

This prospective cross-sectional study was composed of data from 81 patients who received FFP transfusions prior to interventional procedures within the data collection period.

3.3 PERIOD OF STUDY

This study was conducted at both PDN and HKL. The period of study was from 1st June 2016 until 31st March 2017. The period of data collection started from December 2016 to February 2017.

3.4 SAMPLING METHOD

Study cases were chosen using purposive (non-probability) sampling according to the inclusion and exclusion criteria stated in section 3.7.

3.5 STUDY POPULATION

Our source population were all patients with abnormal coagulation laboratory values (INR above 1.50) and received FFP transfusions from December 2016 until February 2017. Then, the patient underwent the interventional procedure post-FFP transfusion as part of the clinical management. The study cases were selected based on the inclusion and exclusion criteria. The sample size calculation is as shown in section 3.6.

3.6 SAMPLE SIZE

The sample size was calculated using a computer software, PS: Power and Sample Size Calculation version 3.0, 2009 (Dupont and Plummer, 1997). The sample size estimation based on RCT by Muller *et al.* (2015); only 54% of patients had a corrected INR to less than 1.50 in 38 patients who underwent the interventional procedure. The study precision was set to be 12% with 95% confidence interval (CI) and 0.54 of study proportion. The estimated sample size was to be 67 subjects.

For the correlation of pretransfusion INR with median INR reduction posttransfusion, the sample size was calculated based on the study done by Muller *et al.* (2015), with the r = 0.68 and a *p*-value less than 0.01. The correlation sample size estimation was calculated based on the correlation sample from the computer