A RETROSPECTIVE AUDIT OF THE USE OF FRESH FROZEN PLASMA AT A TERTIARY CARE HOSPITAL

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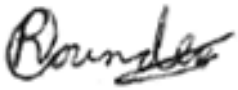
A research report (in the format of a "submissible" paper) submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine (Haematology)

Johannesburg, 2019

Declaration

I, **Reenelle Gounden**, declare that this research report (in the format of a "submissible" paper) is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(signature of candidate)

17 April 2019, in Johannesburg

The contribution of the candidate to the Paper

Declaration: Student's contribution to article(s) and agreement of co-author(s)
I, Reenelle Gounden, student number 0002503N declare that this Research Report is my own work and that I contributed significantly towards the research findings presented in the paper intended for publication below.

Signature of Student
Date: 05/12/2018

Name of Supervisor: Professor JN Mahlangu

Signature of Supervisor
Date: 11/12/2018

Dedication

This research is dedicated to my husband, Kumaren Chetty, my son and my parents Barry and Rose Gounden.

Presentations arising from this study

Reenelle Gounden, Johnny Mahlangu. A Retrospective Audit of the Use of Fresh Frozen Plasma at A Tertiary Care Hospital. PathCape Congress of the Federation of South African Societies of Pathology, 16-18 August 2018, Cape Town (poster presentation).

Abstract

Background:

Blood transfusions reduce morbidity and mortality in hospitalized patients. Fresh Frozen Plasma (FFP) is one of the most commonly used blood products in many clinical settings as well as the one least understood in its indications for use. While guidelines on the use of FFP have been published by the South African National Blood Service (SANBS), there is a paucity of data on how well these are followed.

Objectives:

This study assessed the indications and appropriate use of FFPs in a tertiary care hospital.

Method:

A retrospective audit was conducted over six months from March to August 2015 at the CMJAH. The study was reviewed and approved by the University of the Witwatersrand and SANBS Human Research Ethics Committees. Study participants included all recipients of FFP at the CMJAH during the study period. Data on indications for FFP, volumes of FFPs transfused, clinical units transfusing the FFPs, were collected and analysed.

Results:

There was a total of 1233 FFP transfusions to 736 patients during this study period. 53.8% of these transfusions were appropriate following the SANBS blood transfusion guidelines while 39.4% were inappropriately transfused and a further 6.8% of FFP transfusions were indeterminate. The appropriate indications for FFP transfusions included multiple factor deficiencies, reversal of warfarin and thrombotic thrombocytopenic purpura. The inappropriate indications involved; bleeding without a coagulopathy, abnormal coagulation studies in a non-bleeding patient and prophylactic use before invasive procedures.

Conclusion:

In this retrospective audit, half FFP transfusions were appropriate while 40% were inappropriate according to current guidelines. This study highlights the need for education on the use of FFP in our institution.

Acknowledgements

I want to thank my supervisor Professor JN Mahlangu for his guidance and support for the duration of this project.

I am grateful to the South African National Blood Services, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital for allowing me to conduct this research.

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List of Abbreviations

AABB	American Association of Blood Banks
ACT	Activated Clotting Time
APH	Antepartum Haemorrhage
aPTT	activated Partial Thromboplastin Time
ASBT	Australian Society of Blood Transfusion
BCSH	British Committee for Standards on Haematology
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DIC	Disseminated Intravascular Coagulopathy
FFP	Fresh Frozen Plasma
HELLP	Haemolysis, Elevated Liver enzymes, Low Platelet count
ICU	Intensive Care Unit
INR	International Normalised Ratio
ITP	Immune Thrombocytopenic Purpura
NHMRC	National Health Medical Research Council
PCC	Prothrombin Complex Concentrates
PPH	Postpartum Haemorrhage
PT	Prothrombin Time
SA	South Africa
SANBS	South African National Blood Service
SISET	Society of Thrombosis and Haemostasis
TACO	Transfusion Associated Cardiac Overload
TRALI	Transfusion Related Acute Lung Injury
TTP	Thrombotic Thrombocytopenic Purpura

A research report in the the format of a “submissible” paper

Introduction

South Africa has a population of approximately 57.7 million people who are reliant on only a small pool of 484 606 regular blood donors for blood and blood products (1, 2). The use of various blood products varies according to clinical indications with fresh frozen plasma (FFP) the most commonly used product in haematology, oncology, intensive care and trauma interventions (3, 4). The FFP is collected from the plasma of donors from whole blood and apheresis technology followed by subsequent centrifugation. To preserve clotting factors, the plasma processing has to be within eight hours of collection followed by freezing below -18 degrees Celsius. A typical unit of FFP is approximately 280ml in volume and contains all clotting factors, electrolytes, plasma proteins, and plasma pseudocholinesterase at physiological levels(5, 6)

There are many well-established indications for clinical use of FFP, and these have been summarised by the South African National Blood Transfusion Service (SANBS) in their guideline for the appropriate use of FFP shown in Table 1. The SANBS guidelines are in line with those published by many national and international organizations including British Committee for Standards on Haematology (BCSH) (7), National Health Medical Research Council (NHMRC) (8, 9) and the Australasian Society of Blood Transfusion (ASBT). The prophylactic use of FFP in a non-bleeding patient is not recommended in any guidelines and FFPs are only recommended for the reversal of warfarin for massive bleeding or emergency surgery.

Table 1: Indications for the use of FFP (5)

• Replacement of inherited single factor deficiencies (if single factor concentrate is not available)
• Multiple coagulation factor deficiencies (DIC, massive blood transfusion, liver disease) in the presence of active bleeding and abnormal coagulation screening tests.
• Thrombotic thrombocytopenic purpura (TTP)
• Reversal of warfarin effect if active bleeding: preferable to use Prothrombin Complex Concentrate.
• Vitamin K deficiency associated with active bleeding.
• Scoline Apnoea
• Paediatric use: Haemorrhagic disease of the Newborn: use FFP and intravenous Vitamin K

Established contra-indication for the use of FFPs are many and include previous allergic/anaphylactic reaction to blood or blood products as well as patient preference such as religious reasons for refusing a blood transfusion. Use of FFP is associated with some adverse events including transfusion reactions and potential for transfusion-transmitted infections, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO).

Globally, FFP utilization has been steadily increasing over the past decades. In the United States, there was an 11,8% increase in the use of FFP since 2006 with approximately 30-50% being transfused prophylactically (10). The most frequent reasons for transfusions in different countries included; non-bleeding patients with abnormal coagulation profiles (10, 11), prophylactic use following invasive procedures (12, 13), high risk of bleeding combined with coagulopathy in neonates (14) and chronic liver disease resulting in DIC (15). A neonatal unit in South Africa was recently audited their use of FFPs and deemed 75% of their transfusions appropriate by national guidelines and 25% inappropriate (14). The cost to the state for the improper use of FFPs was thirteen thousand nine hundred and sixty-eight rands. Kakkar et al. felt that the most frequent reason for the inappropriate use of FFPs was the misconceptions by clinicians with regards to its effectiveness as a haemostatic agent and inadequate knowledge on appropriate situational use (16).

The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a quaternary care academic centre which used 9278 units of FFP in an audit conducted in 2014. Most of the FFP use was in the Internal Medicine Department. However, the indications and appropriateness of these transfusions have not been established at the CMJAH. There is also a lack of data on the use of FFPs in the South Africa health care system. The purpose of this audit is to determine the indications for the use of FFPs at CMJAH and correlate this with the SANBS blood transfusion guidelines.

Aim

This audit was performed to assess the indications and appropriate use of Fresh Frozen Plasma (FFP) at a tertiary care hospital in SA.

Materials and methods

Study setting and approvals

This study was undertaken at the CMJAH over six months from March to August 2015. CMJAH is a quaternary care academic hospital with 1088 beds and approximately 4000 professional and support staff. This study was reviewed and approved by the University of Witwatersrand Human Research Ethics Committee as well as the SANBS Human Research Ethics Committees. Permission to conduct the investigation was granted by the CMJAH management.

Study design

This is a retrospective observational study.

Study population

The target population included patients of all ages admitted at the CMJAH over the study period. The key inclusion criterion was patients receiving FFP while managed at CMJAH; We excluded patients with contraindications to receiving FFP, those given FFP in other facilities before transfer to CMJAH and those with incomplete records on the use of FFP at the hospital.

Data collection methods

The data collection sheet was used for collecting data from SANBS blood bank as well as the wards at the CMJAH. The data collected from the SANBS included a list of all patients from the blood bank to whom FFPs were dispensed during the study period. Data collected from the medical records included the demographics (ethnicity, age and gender) of the patients, wards of admission, diagnosis, screening coagulation profiles and indications for FFP transfusions. Collected data was transferred to an excel spreadsheet and anonymized.

Data analysis

Quantitative data were summarised as means and tabulated or presented as graphs. Qualitative data were described and interpreted.

Results

Over a six month study period from March to August 2015, 1233 FFP transfusions were transfused in 736 patients admitted at the CMJAH. The demographic information of the study population is shown in table 2.

Table 2: Demographic data of study participants (N=736)

Demographic Parameter	**Values**
• Age median, years (range)	35 (1- 84)
• Gender, n (%)	
Male	348 (47.2)
Female	388 (52.7)
• Race, n (%)	
White	89 (12.1)
Non-white (Black, Coloured, Indian)	647 (87.9)

The use of FFP was appropriate in 53.8% of the study population and inappropriate in 39.4% and not clear 6.8% of FFP use. (see figure 1).

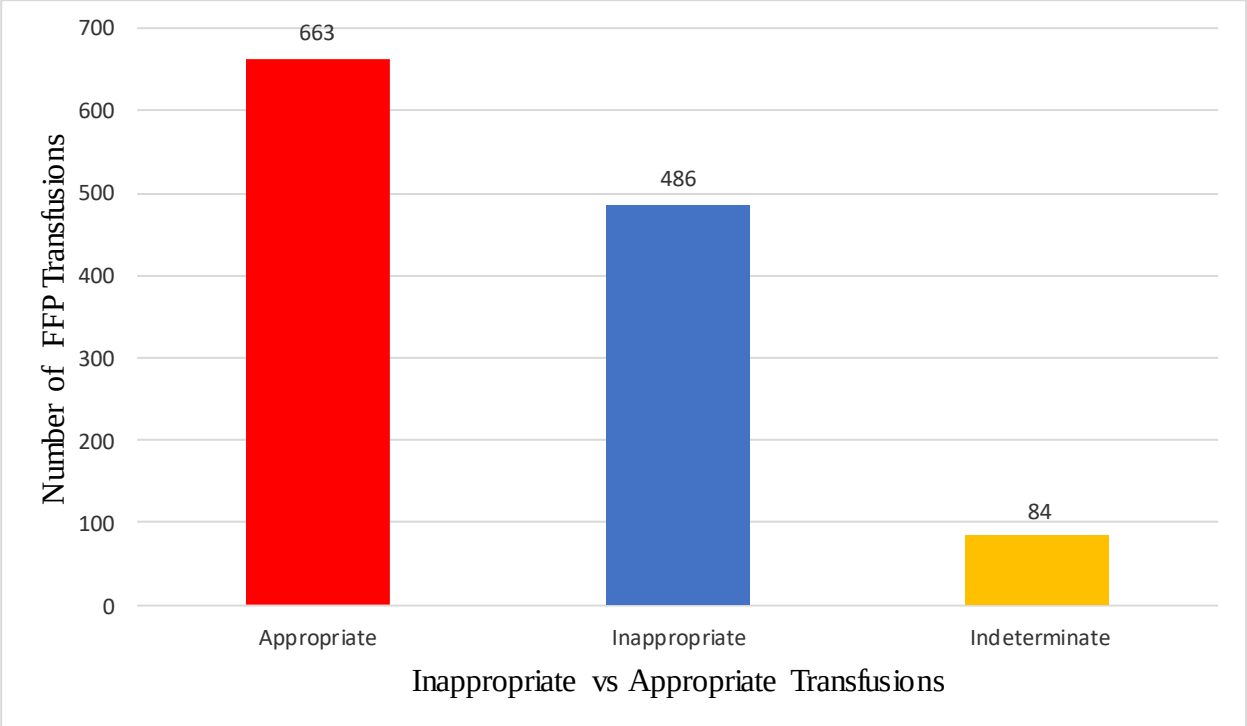

Figure 1: Number of transfusions for appropriate and inappropriate usage

Results by specialty/ward

The patients were admitted in the following wards; trauma, cardiothoracic surgery, surgery, intensive care, paediatrics, haematology, medicine, obstetrics, and gynaecology (see Table 3 for patient distribution).

Table 3: Recipients of FFP by hospital Departments

Ward	Number of Patients (n)(%)
Cardio-Thoracic	128 (17.3)
Gynaecology	69 (9.3)
Haematology	29 (4.0)
Intensive Care Unit	28 (4.0)
Medicine	134 (18.2)
Obstetrics	48 (6.5)
Orthopaedics	9 (1.2)
Paediatrics	10 (1.3)
Surgery	102 (14.0)
Trauma	113 (15.2)
Incomplete Records	66 (9.0)
Total	**736 (100)**

Medicine department comprised the largest number of patients requiring FFP transfusions, patients from medical disciplines including gastrointestinal, oncology, infectious diseases, renal, cardiology, radiation oncology, and respiratory wards. The majority of the medical

patients were admitted in the gastrointestinal ward and suffering from chronic or acute liver failure (secondary to numerous pathologies) with an overt coagulopathy. Patients in the oncology ward and infectious diseases accounted for the second and third highest transfusions respectively. The majority of these patients presented with DIC secondary to sepsis.

There were a total of 29 haematology patients, the patient population for haematology included; 12 Thrombotic Thrombocytopenic Purpura (TTP) patients, 11 overwarfarinised patients (7 DVTs and four atrial fibrillation), 3 ITP (Immune Thrombocytopenic Purpura) patients and one patient with iron deficiency.

The surgical discipline encompassed patients from general surgery, orthopaedics, neurosurgery, and vascular surgery. The cardiothoracic patients comprised 17.3% of the total patient population and included both paediatric and adult patients. Most of the paediatric cardiac patients suffered from congenital cardiac lesions requiring repair and the adults suffered from ischaemic heart disease or valvular disease.

Intensive Care Unit ICU encompassed a small percentage of the total patient population (4.0%) these patients were predominantly treated for sepsis. Patients included both paediatric and adult patients admitted to the respective ICUs. The obstetrics and gynaecology patients (a total of 117 patients) presented with bleeding from antepartum or postpartum haemorrhage or incomplete abortions.

Results by clinical indication of FFP transfusions

There was a total of 1233 FFP transfusions administered, of which 663 were appropriate, and 486 were inappropriate in accordance to the SANBS transfusion guidelines. See Figure 2 for results of specific indications and Table 4 for distribution of these transfusions within the different wards**.**

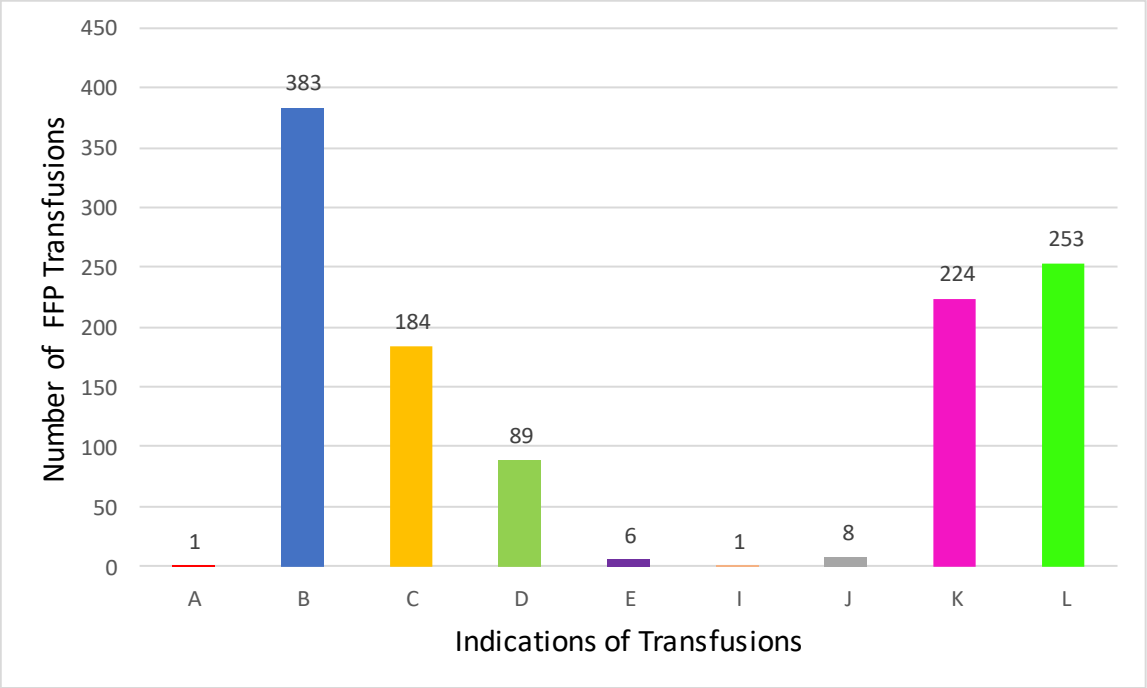

Figure 2: Indications for FFP transfusions: A=single factor deficiencies, B= multiple factor deficiencies with bleeding, C= Thrombotic thrombocytopenic purpura, D= Warfarin reversal, E= Vitamin K deficiency, I= Volume expansion, J= Abnormal coagulation studies in a non-bleeding patient, K= prophylactic use following invasive procedures, L= Bleeding without a coagulopathy.

Table 4: FFP use by hospital transfusion requested per department

Ward	**Total No. of Transfusions**	**Appropriate**	**% Appropriate**	**Inappropriate**	**% Inappropriate**
C/T (Cardio Thoracic	163	12	7,4%	151	92,6%
Gynaecology	75	19	25,3%	56	74,7%
Haematology	206	201	97,6%	5	2,4%
ICU (Intensive Care Unit)	58	50	86,2%	8	13,8%
Medicine	236	210	89,0%	26	11,0%
Obstetrics	70	32	45,7%	38	54,3%
Orthopaedics	14	8	57,1%	6	42,9%
Paediatrics	11	10	90,9%	1	9,1%
Surgery	149	92	61,7%	57	38,3%
Trauma	167	29	17,4%	138	82,6%
Incomplete Records	84				
Total	**1233**				

Transfusion of FFPs in the Medical wards

The medical ward patients received the highest number of FFP transfusions. The predominant indications involved multiple factor deficiencies secondary to sepsis and DIC or synthetic liver dysfunction. Majority of the FFP transfusions were deemed appropriate per the SANBS transfusion guidelines. The inappropriate transfusions included prophylactic use before invasive procedures and bleeding without a coagulopathy. See Figure 3 for the distribution of transfusions in the medical wards.

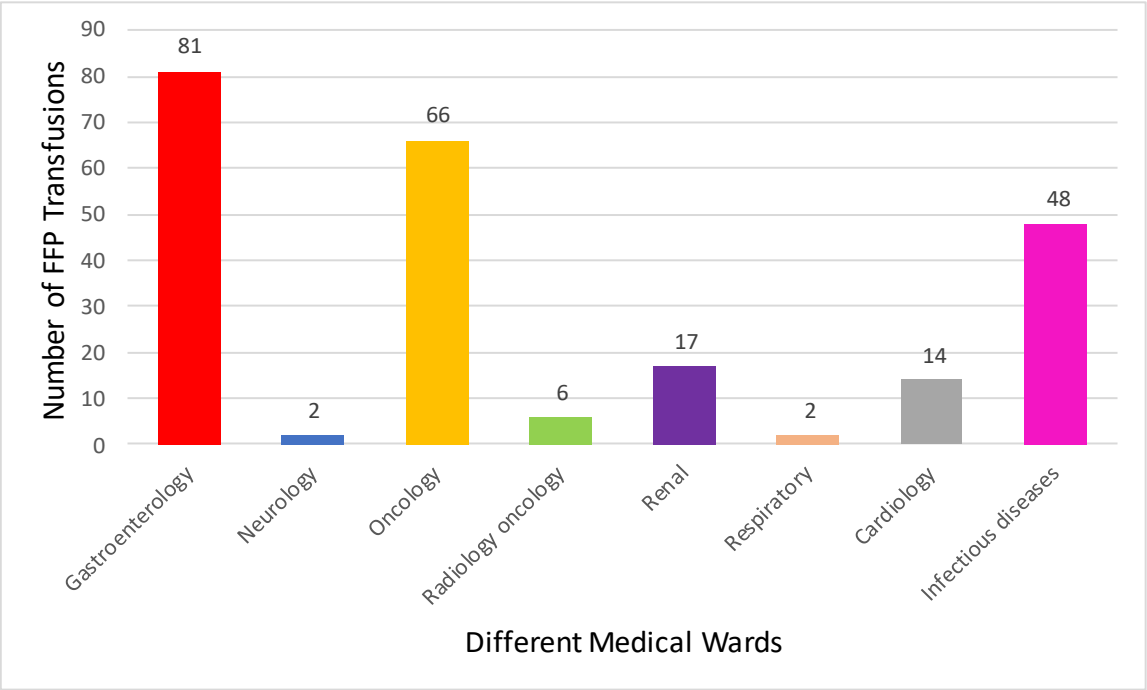

Figure 3: Distribution of FFP transfusions in the different medical wards

Haematology FFP transfusions

Haematology administered the second largest number of FFP transfusions where most of these patients suffering from TTP. TTP requires an average of 10 days of plasma exchange with plasma products. The TTP patients received 88.7% of the FFP transfusions in the haematology ward with an average hospital stay of ~15 days. Additional 9% of transfusions were used for warfarin reversal. Inappropriate transfusions accounted for 2.5% for bleeding without a coagulopathy and prophylactic use before an invasive procedure.

Paediatric FFP Transfusions

Paediatric ward administered the least number of FFP transfusions. The majority of the FFP transfusions (90.9%) were appropriate following sepsis with multiple coagulation factor deficiencies and vitamin K deficiencies. 9.1% of the transfusions were inappropriate, the inappropriate indications included, bleeding without coagulopathy and prophylactic use before invasive procedures.

Obstetrics and gynaecology FFP transfusions

The obstetric ward (45.7% appropriate transfusions) faired better than gynaecology ward (25.3%) with respect to the number of appropriate transfusions. The majority of the FFP transfusions in the gynaecology involved bleeding without coagulopathy. These included patients with incomplete abortions and abnormal uterine bleeding however on admission no blood was drawn for a coagulation screen (including INR or PTT). The appropriate transfusions (25.3%) included multiple factor deficiencies (secondary to septic incomplete abortions (ICA)) and warfarin reversal (cervical malignancy on oral anticoagulants).

The appropriate obstetric transfusions (32 transfusions) included, bleeding with a coagulopathy secondary to eclampsia with HELLP syndrome and postpartum haemorrhage (PPH). The inappropriate transfusions (38 transfusions) predominantly consisted of bleeding without a coagulopathy (PPH and APH without coagulopathy). A single haemophilia carrier patient was given an FFP transfusion for bleeding without a coagulopathy.

Trauma FFP transfusions

In trauma, the majority of transfusions were deemed as inappropriate. Indications for these inappropriate transfusions included, bleeding without a coagulopathy and prophylactic use before invasive procedures. Pre-transfusional coagulation screening (INR, aPTT) were not routinely performed.

Cardiothoracic FFP transfusions

The minority of FFP transfusions were deemed appropriate and the majority (92.6%) inappropriate. The inappropriate transfusions were primarily due to prophylactic use before invasive procedures, i.e. cardiothoracic surgery. Appropriate indications included warfarin reversal and multiple coagulation factor deficiencies (following sepsis). Most FFP transfusions were deemed inappropriate since no primary coagulation screening was requested as part of the pre-operative work-up. In theatre the coagulation parameters on and off cardiac bypass were monitored with an activated clotting time (ACT) and treated accordingly.

Surgical FFP transfusions

The majority of these transfusions were appropriate and these indications included; multiple coagulation factor deficiencies (92 transfusions) and warfarin reversal (14 transfusions). There were 57 inappropriate transfusions which involved; bleeding without a coagulopathy (17 transfusions) and prophylactic use before invasive procedures (40 transfusions).

Intensive care unit FFP transfusions

Transfusions administered in the intensive care unit were overall appropriate and were secondary to multiple coagulation factor deficiencies (sepsis/DIC). The inappropriate

transfusions accounted for 13.8% for procedures which included, prophylactic use before invasive procedures, bleeding without a coagulopathy and a single transfusion for volume expansion.

Unknown FFP transfusions

There were also 84 transfusions (6.8%) that involved 66 patients that were unaccountable, reasons being that the medical files were incomplete, the medical files for that person did not match the patient hospital number, or there were no records found for that patient name/ hospital number.

Discussion

This audit of the FFP use at CMJAH over the six-month study period revealed that the majority (53.8%) of the FFP transfusions administered to patients were deemed appropriate and 39.4% were deemed inappropriate as per the SANBS blood transfusion guidelines.

The findings of this audit are similar to those of previous audits which showed that the majority of FFP transfusions were appropriate although there are still a significant number of inappropriate transfusions (8, 17, 18). Additionally, other studies have shown a majority of FFP transfusions being inappropriate (7, 9, 19). The appropriate indications for transfusions included; multiple factor deficiencies, reversal of warfarin and TTP. Wards that largerly transfused appropriately included; medicine, haematology, ICU, surgery and paediatrics where as those that largerly transfused inappropriately included; trauma, gynaecology, and cardiothoracic surgery. The latter wards in our audit were deemed inappropriate in their transfusion practices due to the lack of pre-transfusional coagulation screening, bleeding without evidence of coagulopathy and prophylactic transfusion before invasive procedures. Our trauma casualty manages daily incidences of high impact polytrauma, e.g., gunshot wounds, penetrating and blunts assaults and pedestrian/motor vehicle accidents. National and international resuscitation protocols in the trauma casualties for blood transfusions include a 1:1:1 ratio of red blood cells: plasma: platelets for life-threatening bleeds (20). Several studies have also found a lower mortality risk with a higher plasma to RBC ratio in the blood (21). This is however in contrast to Bhananker et al.who suggesed that only massively transfused patients could potentially benefit from a higher FFP: RBC ratio and that increased transfusion of FFPs to routinely transfused patients could be potentially wasteful (22). Most institutions concur and maintain 1:1:1 ratio of RBC: platelets: plasma blood transfusion protocol for their high impact trauma patients (20, 23).

Cardiothoracic surgery predominantly involves placing patients on cardiopulmonary bypass (CPB). The anaesthetist in theatre uses an activated clotting time (ACT) to assess haemodynamic status and the need for FFP transfusion. A Cochrane review by Desborough et al in 2015 (24) analyses 14 clinical trials that investigated the prophylactic use of FFP in elective cardiac surgeries and found no beneficial effect on mortality with FFP transfusions. In contrast a long-term (7.5 years) retrospective study (25) that followed patients post-CABG showed a reduced overall survival for those patients that received FFP transfusions. In a

recent study by anaesthetists, compared FFP to prothrombin complex concentrate (PCC) for the intraoperative reversal of anticoagulation on patients undergoing heart surgery with CPB and found that PCC was safer, faster and resulted in less bleeding than FFPs (26).

This audit found that the gynaecology ward frequently transfused FFPs without an initial coagulation screen and hence was deemed as inappropriate transfusions with bleeding without a coagulopathy. In contrast to our audit, an Australian audit of FFP usage showed obstetric and gynaecology requiring the highest usage and deemed these transfusions to be appropriate secondary to acute DIC with excessive bleeding and an elevated INR and volume depletion (17). There are no national or international guidelines that advocate for or against the use of FFP in the initial management of early pregnancy loss (27, 28). Management is decided solely on the judgment of the clinician about the need for FFP transfusions before definitive management (medical or surgical evacuation of the uterus).

The guidelines regarding the assessment of bleeding risk, with pre-transfusional coagulation screening, appear contradictory. The British Committee for standards on haematology (BSCH) guidelines advocated that a patient with a negative bleeding history requires no initial pre-transfusion screening (29) while the Italian Society of thrombosis and haemostasis (SISET) (30) considers an aPTT, PT and platelet count appropriate in adults and children even with a negative bleeding history. The latter, however, is based on consensus guidelines and not evidence-based. The American guidelines (American Association of Blood Banks-AABB) stated that there is no clinical data to support the correlation of FFP transfusions with coagulation testing (31).

Recent audits from different countries have shown variable findings on the appropriate and inappropriate usage of FFPs. A Turkish study by Emektar et al. (7) showed an overall appropriate use of FFPs (59.6%) predominantly due to warfarin overdose. In contrast to our audit, the rarest indications were secondary to DIC and TTP. A retrospective audit by Bhagwat et al. (9) in 2017 of 627 FFP transfusions to 109 patients revealed an overall amount of inappropriate transfusions (53.4%) with the highest transfusions administered in cardiothoracic surgery (27.9%). Medicine appropriately transfused their patients (70.5% of all FFP transfusions) which is similar in findings to our audit. They also found that surgery transfused the most inappropriately to patients with mildly elevated PT in a non-bleeding patient, hypoalbuminemia and acute leukaemia with no bleeding. In the South of India, Lingegowda et al. (8) found appropriate usage (59.3%) for massive transfusion and therapeutic plasma exchange. Inappropriate uses included volume replacement, mildly abnormal coagulation parameters with no active bleeding and prophylactic transfusions. A long-term audit over twenty-two years by Gader et al. (19) showed significant inappropriate use of FFPs. This study also found a high level of compliance with regards to pre-transfusional screening with PT and aPTT in obstetrics, gynaecology and trauma casualty. This differed with our audit which specifically lacked screening tests in the stated wards. An Australian audit in 2018 (18) revealed 60% appropriate use which is similar to this audit. The appropriate applications similar in most audits revealed abnormal coagulation profiles with

massive bleeding and DIC with an increased INR and inappropriate uses included, volume expansion, overwarfarinisation in a non-bleeding patient and prophylactic use.

The reasons for the inappropriate use are not clear but may include; a lack of awareness of the guidelines, poor consultation between guideline developers and the practitioners, complex pathology managed inappropriately with FFPs and poor interface between users of blood products and haematologists (32).

Study limitations

The limitations in this study may possible include a degree of bias with the interpretation of the medical files, the retrospective nature of the study, incomplete records although this was only a small percentage and unlikely to bias the results, number of FFP dispensed but not used in the wards and the fact that this is an uncontrolled audit.

Conclusion

This retrospective audit revealed that the majority of patients at our hospital were appropriately transfused with FFPs, however, there remains a significant number of patients that were unnecessarily transfused. It has also highlighted several important issues most importantly a disconnection between the SANBS transfusion guidelines and clinical practice. The current South African blood transfusion guidelines requires further discussions with clinicians to establish a cost-effective yet safe therapeutic practice for the transfusion of FFP. An introduction of patient blood management as a hospital policy may also further reduce the misuse of FFP and other blood products.

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Appendix A - Research Protocol

A RETROSPECTIVE AUDIT OF THE USE OF FRESH FROZEN PLASMA AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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MMED HAEMATOLOGY

RESEARCH PROTOCOL

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Introduction

South Africa has an estimated population of 54,9 million people according to Statistics South Africa (1). Of these, less than 1% of the eligible South African people are regular blood donors. It has been proposed that eight out of ten people in our country will need a blood transfusion or some form of blood products during their life (2). These statistics are alarming since there seem to be much fewer blood donors than there are recipients, a situation resulting in a regular shortage of blood and blood product in South Africa.

In 2014, the SANBS received 802 807 units of whole blood from voluntary non-remunerated donors. These were separated into various cellular blood components which included 3850 red cell products, 27 371 apheresis products and 29 267 pooled platelet products. During this period the SANBS released 197 092 red blood cell issues, 56 638 platelet issues and 164 658 litres of plasma which was used to produce various plasma derived products. The plasma products included Fresh Frozen Plasma, cryoprecipitate, albumin, immunoglobulin, vaccines and other products.

Review of Fresh Frozen Plasma

Fresh Frozen Plasma (FFP) is a product derived from the plasma of whole blood by centrifugation or apheresis technology. Separation of the plasma from whole blood must be within eight hours of donation and must after that be frozen below -18 degrees Celsius. One unit of FFP is approximately 280ml of plasma that is collected in a citrate containing the anticoagulant solution. The end product of FFP has physiological levels of clotting factors and electrolytes which include all clotting factors, electrolytes, plasma proteins and plasma pseudocholinesterase. The term Fresh Frozen Plasma refers to the fact that Factor V and Factor VIII which are labile, have been preserved in the FFP product which has been appropriately collected and processed. Table 1 below shows the composition of one unit of locally produced FFP.

Table 1: Composition of FFP (3)

Factor	**Average Levels**
Fibrinogen	200mg per unit FFP
Factor II	1.03 IU/ml
Factor V	0.64 IU/ml
Factor VII	1.21 IU/ml
Factor VIII	0.85 IU/ml
Factor IX	0.95 IU/ml
Factor X	1.25 IU/ml
Factor XI	0.79 IU/ml
Antithrombin	104 IU/ml
Plasma pseudo-cholinesterase	3000-10 000 IU/ml

Before use, FFPs are thawed at 37 degrees Celsius in a water bath for approximately 35-45mins. (4). Heating at elevated temperatures can induce clotting factor activation resulting in a Disseminated Intravascular Coagulopathy (DIC) which may precipitate Systemic Inflammatory Response Syndrome (4). Therefore once correctly thawed, FFP should be transfused as rapidly as possible at approximately 15-20 minutes per unit (3). The dosage is dependent on the medical indication averaging between 15-60 ml per kg. Lower doses are needed in paediatric patients.

Indications for the use of Fresh Frozen Plasma

Although there are several guidelines established by many countries, Fresh Frozen Plasma use remains controversial and highly dependant on the experience of the treating clinician, complexity of diseases managed and the institutional guidelines. In South Africa, guidelines for the use of FFP are often a consultative process involving SANBS, haematologists and end-user clinicians. Indications and guidance on the use of FFP have been well defined by the SANBS and are shown in Table 2.

Table 2: Indications for the use of FFP (3)

Indications
Replacement of inherited single factor deficiencies (if single factor concentrate is not available)
Multiple coagulation factor deficiencies (DIC, massive blood transfusion, liver disease) in the presence of active bleeding and abnormal coagulation screening tests.
Thrombotic thrombocytopenic purpura (TTP)
Reversal of warfarin if active bleeding: preferable to use Prothrombin Complex Concentrate.
Vitamin K deficiency associated with active bleeding.
Scoline Apnoea
Paediatric use: Haemorrhagic disease of the Newborn: use FFP and intravenous Vitamin K

Replacement of inherited single factor deficiencies

Haemophilia is the most common inherited bleeding disorder. Its inheritance is X-linked, and the prevalence is worldwide. Factor VIII , Factor IX and Von Willebrands disease comprise ~95% of all inherited deficiencies of coagulation (5). The management of haemophilia has been extensively researched and the mainstay of treatment is replacement with factor VIII or IX or vWF clotting factor concentrates (6). If clotting factor concentrates are not available then FFPs are recommended for use. Approximately 20-30% of patients with severe haemophilia A have developed alloantibodies or inhibitors which neutralize the activity of factor VIII replacement (7).

Other plasma coagulation factor deficiencies are and occur in ~1:500000 to 2 million individuals (8). These deficiencies include fibrinogen, prothrombin and factors II, VII, X, XI, XIII deficiencies which are primarily autosomal recessive conditions. Their rarity lies in the fact that they are recessively inherited.

Until the 1970s, the haemophiliacs were treated with plasma replacement or cryoprecipitate in large volumes (8) with the additional risk of transmission of viral infections. In the late 1980s, recombinant factor concentrates were developed (5). They are now the gold standard

for haemophilia treatment because of their increased safety and small volume of infusion. For the rare inherited factor deficiencies (RICD) there is not as much progress on treatment options. Recombinant activated Factor VII (Novo Seven) is available however Factors XI, XIII, V and combined FV and FVIII deficiencies can only be treated with FFPs. Prothrombin and FX deficiencies are often treated with Prothrombin Complex Concentrates (PCC) containing the Vitamin K dependent factors other than those actually deficient. PCC has the added risk of increasing FVII, IX and X to very high plasma levels, especially with repeated infusions, which may increase the risk of thrombosis. Therefore the mainstay of treatment for rarely inherited coagulation factor deficiencies is single-donor fresh frozen plasma (contains all coagulation factors) at 15-20ml/kg (5).

Although FFPs are the most appropriate form of treatment of RICD they do result in numerous complications. These include volume overload following repeated transfusions, thrombosis with an increase in the vitamin K dependent factors and the development of allo-antibodies following FFPs and factor concentrates. A phase III clinical trial comparing native rV11a and Vatreptocog alfa (recombinant factor VIIa with three amino acid substitute) resulted in 11% of patients developing Vatreptocog alfa-binding antibodies (9).

Disseminated Intravascular Coagulopathy (DIC)

DIC is the systemic activation of coagulation in response to local injury initiated by various factors including infections, inflammation and malignancy. It is characterised by the occurrence of wide-spread thrombi, compromising blood supply to various organs contributing to organ failure (8) injury results in the release of tissue factors which initiates the clotting cascade. This eventually results in increase thrombin generation which leads to consumption and depletion of the anticoagulation regulatory proteins. Blood products should only be administered to patients that are bleeding, have a risk of bleeding or undergoing an invasive procedure. Treatment of the underlying cause is recommended however FFPs are the treatment of choice for the bleeding patient with a prolonged INR and activated partial thrombin time (>1.5 the upper limit of normal) (10). FFPs should be administered as 15-20 ml/kg or higher doses in severely bleeding patient without the risk of volume overload (10). Cryoprecipitate is indicated when the fibrinogen levels are <1.5g/L and the patient is bleeding. The use of PCCs lack Factor V and have the added risk of thrombosis. Therefore FFP is the best choice of treatment for DIC.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is an acquired or inherited syndrome consisting of fever, renal impairment, abnormal neurology, microangiopathic haemolytic anaemia and thrombocytopenia (11). Most commonly caused by an acquired or inherited ADAMTS13 deficiency, other causes include; drugs (clopidogrel, cyclosporine, tacrolimus), following HSCT (haemopoietic stem cell transplant), pregnancy and autoimmune disorders (SLE). Treatment involves plasma exchange therapy which has been proven better than plasma infusion therapy (12). The benefit of plasma exchange is that it removes an IgG inhibitor of ADAMTS13 and replaces the deficient protein. However plasma infusions are recommended when exchange transfusions are not readily available. Daily plasma exchange (60ml/kg) until neurological symptoms have resolved, normal platelet count achieve, the LDH is within normal and fragments have disappeared. FFP remains the most commonly used replacement product. As

yet there is no advantage to the use of cryopoor plasma compared to FFP (13). Rock et al showed no differences in one month survival in TTP patients comparing both products (13). Daily plasma exchange with FFP is the appropriate treatment of TTP.

Reversal of warfarin for active bleeding and vitamin K deficiency associated bleeding

Warfarin is the most commonly used, anti-coagulant drug in the treatment of thromboembolic events. Its benefit outweighs the risk of bleeding. However warfarin therapy can prove challenging, it has a narrow therapeutic range, and there can be numerous individual compounding variables. This hinders achieving accurate control of the drug. Vitamin K antagonist-associated bleeding has an in-hospital mortality rate of 7.6%, and the 90 day mortality was 14% (14).The management of warfarin reversal depends on the severity of the bleeding and an abnormal INR. Significant bleeding can be treated with Vitamin K orally or intravenously, and major bleeding requires rapid reversal of warfarin effect with 20-50U/kg PCC and 5mg Vitamin K given intravenously (14). FFP is recommended as an alternative only when PCC is unavailable. Vitamin K takes 24 hours to become fully affective therefore FFPs and PCCs may be used for immediate reversal. PCC is available as a three or four factor concentrate containing factors II, IX and X but low levels of factor VII. Recombinant FVIIa has been suggested as an alternative to warfarin reversal. However studies have shown that it may result in excessive thrombin formation culminating in thromboembolic complications (15). Its safety has not yet been established.

Scoline Apnoea

Muscle paralysis resulting in apnoea following the administration of the drug succinylcholine. This is due to atypical plasma cholinesterase activity which is found to occur in 1:2800 patients (16). These patients may remain paralysed for a long period of time following an average dose of succinylcholine. The plasma concentration of cholinesterase in the blood bank falls by 85% within two days however FFP showed no decrease for 7 weeks (16). Replacement of FFP apparently increases the cholinesterase activity and reverses the neuromuscular block.

Paediatric Indications

Neonates presenting with significant bleeding should be promptly investigated. Intraventricular haemorrhage is the most severe complication associated with an increased mortality and permanent disability (17). Maternal factors including drugs (anticonvulsants, warfarin and antibiotics), medical illnesses and maternal deficiency of Vitamin K should be eliminated. In ill looking neonates, DIC or liver disease may result in acquired factor deficiencies (8). This may result in diffuse bleeding. Well looking newborns are more likely to experience localised bleeding from thrombocytopenia, Vitamin K deficiency or rarely inherited factor deficiency. Liumbruno G et al concur with South African guidelines that FFPs are indicated in neonates when the bleeding is as result of Vitamin K deficiency, DIC or congenital single factor deficiencies when specific concentrate in unavailable (18). Coagulation parameters are longer in neonates than adults. Therefore, abnormal coagulation tests in the absence of bleeding is not an indication for neonates (19). A South African study in neonatal ICU showed that 75% of neonates received appropriate transfusions of FFPs (in keeping with SA guidelines) due to high risk of bleeding combined with a coagulopathy (19).

For all the above indications, understanding the need for the appropriate transfusion of FFPs is extremely important in preventing complications associated with the unnecessary transfusion of FFPs.

Complications following Fresh Frozen Plasma transfusion

As with transfusion of any other blood product, plasma transfusions also carry the risk of transfusion reactions, transfusion transmitted infections and allergic reactions. Plasma transfusion has an increased association with certain complications e.g. transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO) and allergic/anaphylactic reactions (20). As standard rule associated with testing of all blood products at the SANBS, every unit of blood is screened for HIV, Hepatitis and transfusion transmitted infections using nucleic acid testing (NAT) molecular techniques.

A study conducted by Watson, G et al in 2009 evaluated the independent risk factors for mortality, multi-organ failure (MOF), acute respiratory distress syndrome (ARDS) and nosocomial infection following the transfusion of plasma (FFP), platelets and cryoprecipitate in bluntly injured adults in haemorrhagic shock. They found that FFP was independently associated with an associated 2.1% increase in MOF and 2.5% increase in ARDS (21).

Murad et al compared several studies and found that overall plasma transfusion was associated with a significant increase risk of pulmonary complication (acute lung injury) (22). By this study TRALI has emerged as a leading cause of transfusion related mortality (5-25% cases are fatal), risk per component was 6.9% higher in FFPs than red blood cells (20). In another study conducted in intensive care units (ICU), TRALI was reported as the most worrying effect of FFP transfusion, followed by TACO and allergic reactions respectively (23). For these reasons intensivists would choose to omit FFP transfusions unless necessary.

TACO found to the second most commonly occurring complication of FFP transfusions is also associated with respiratory distress and pulmonary oedema secondary to hydrostatic not permeability oedema (20). Greater plasma volumes are a risk factor to developing TACO and possible alternative such as PCC should instead be considered especially with the extremes of age and those with pre-existing cardiac and renal co-morbidities.

Allergic reactions are estimated at <1% of transfusion reactions (20, 22) and most exhibit mild symptoms of urticaria, pruritus and flushing. Anaphylactic reactions are more severe and occur 1: 18000-172000 patients (20). IgA antibodies are responsible for causing reactions mediated by complement activation to small amounts of plasma containing IgA proteins.
Other less likely risks include infection related transmitted disease (HIV, Hepatitis), febrile non-haemolytic reactions, RBC allo-immunization and haemolytic transfusion reaction. Therefore the benefits must undoubtedly outweigh the risks when a patient is transfused with FFPs.

Findings of Previous Fresh Frozen PlasmaAudits

Across the globe, FFP utilisation has been steadily increasing over the past decades. In the United States there was an 11,8% increase in the use of FFP since 2006 with approximately 30-50% being transfused prophylactically (20) The most frequent reason for transfusion was non-bleeding patient with abnormal coagulation studies. Muller et al surveyed ICU and found that FFPs was administered prophylactically to reduce the risk of bleeding before conducting invasive procedures (23). However the actual risk of bleeding was an only significant concern in the minority of respondents (15%). A randomised control trial conducted in 2015 also in the ICU setting showed that there was no difference in bleeding complications to those that were administered FFPs prophylactically and those critically ill patients that were not given FFPs (24). Clearly more evidence based medicine is needed on the appropriate use of FFPs in critically ill coagulopathic patients in the ICU.

A neonatal unit in South Africa was recently audited their use of FFPs and deemed 75% of their transfusions appropriate by national guidelines and 25% inappropriate (19). The cost to state for the inappropriate use of FFPs was thirteen thousand nine hundred and sixty eight rands. The most common and appropriate reason for transfusion was a high risk of bleeding combined with a coagulopathy. However of note, pre-transfusion coagulation profiles compared to the post-transfusion coagulopathy profiles showed no statistical difference in the <28 week and>34 week age groups (19). The inappropriate reasons for use included transfusing FFPs as volume expander, low risk of bleeding with abnormal coagulation profile and prophylactic to non-coagulopathic infants.

Kappar et al felt that the most frequent reason for them in the appropriate use of FFPs was the misconceptions by clinicians with regards to its effectiveness as homeostatic agent and inadequate knowledge on proper situational use (25). They audited and then performed an educational intervention on the prescribing clinicians and then re-audited. Their re-audit found a 23% reduction in the inappropriate use of FFPs (25). They found inappropriate uses; for nutritional supplementation in patients suffering from burns and sepsis, anaemia, volume expander and bleeding without a coagulopathy. Following their intervention, the clinicians no longer used FFPs to treat anaemia, however continued to request them in hypoproteinemic states. Shinagre et al also concurred that uncertainty among clinicians was the reason for inappropriate usage of FFPs (26). Therefore clinicians allowed to be requesting FFPs should have a clear understanding of the product and the desired effects with an understanding of the potential hazardous effects.

From the United Kingdom, Jones and company audited the FFP use at Morrison Hospital and found that 66% of transfusions were appropriate. They also found that 15% of the patient had no abnormalities in their coagulation profiles and <50% actually showed prolongation of the coagulation tests (i.e. > two times over the control value) to support haemostatic instability (27). Palo found that more than 60% of FFP transfusion was used on surgical patients, the typical FFP transfused patient in Finland is a middle age male undergoing cardiac surgery (28). They found it was used inappropriately and in incorrect dosages. In southern Taiwan in a thousand bed teaching hospital they found a monthly usage 9693 units of FFP from which 70.4% was used inappropriately; for volume expansion, nutritional supplementation or wound healing (29). According to the British Committee for Standards in Haematology (BCSH) an audit in Parkistan showed 42% appropriate use of FFP (30). It was most commonly appropriately used for chronic liver disease resulting in DIC and inappropriately used as a volume expander, hypoproteinemia and bleeding with no coagulopathy.

From the many audits performed across the globe, much can be learnt and much is still to be corrected. The most appropriate indication for FFP use in adults and paediatric patients is a bleeding patient or high risk of bleeding with a coagulopathy. The majority of audits show an overwhelming misappropriation of FFP use especially as a volume expander and prophylactically. There is also evidence to show that education interventions to clinicians have not proven entirely successful in reducing the wastage and inappropriateness of the use of FFPs. The different demographics in the various continents also reveals different medical needs however the clinical guidelines across all continent are similar in their indications for the use of FFPs.

CMJAH is an accredited quarternary care hospital situated in Johannesburg in the province of Gauteng. It is a 1088 bed hospital with approximately 4000 professional and support staff. This hospital offers care at a quaternary level as well as providing undergraduate and postgraduate training in all health professions. It includes paediatric and adult care across all medical and surgical disciplines, nursing and allied health care. Also, the hospital serves as referral hospital within its referral chain. In 2014, CMJAH used a total of 9278 units of plasma with the greatest usage recorded by the Internal Medicine wards. The indications and appropriateness of these transfusions have not been established.

Aim

To assess the indications and appropriate use of Fresh Frozen Plasma (FFP) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over a six months from March 2015 to August 2015.

Objectives

- To document the number of FFP units ordered and the clinical units using the FFP
- To track how the FFP is handled and administered in the clinical units
- To document the indications for FFP use
- To document the outcome of FFP use
- To compare the use of FFP at the CMJAH to published guidelines
- To make a recommendation on the optimal use of FFP at the CMJAH.

Methodology

Study Design

This is a retrospective observational study.

Study Population and setting

The target population will be the clinical data of patients of any age admitted at the CMJAH over the six month study period from March 2015 to August 2015. In particular that patient enrolled in this study will have to havereceived FFP as part of their routine management plan

during their admission, as prescribed by the treating clinical physician. CMJAH manages paediatric and adult patients across all medical and surgical disciplines.

Eligibility Criteria

Inclusion Criteria

- Any patient admitted to CMJAH during the study period from March 2015 to August 2015
- Patients receiving FFP as part of their routine management
- Includes both paediatric and adult patients requiring FFPs
- FFP use must be prescribed by staff based at the CMJAH which includes both inpatient and outpatient use of FFP

Exclusion Criteria

- Known allergies or previous transfusion reactions to FFP
- Patients are given FFP in theatres because of inaccessibility of theatres
- Patients are given FFP in other facilities before transfer to CMJAH as it will not be possible to verify what was given, how it was given and how much was given
- Where records of use of FFP is not complete

Procedure to be followed by the Investigator in collecting data

1. The investigator will contact the blood bank to obtain a list of all patients that had received FFPs during the study period.
2. The researcher will then try to obtain all relevant patient medical records/files from the medical records department, respective clinics or wards.
3. The researcher will then use the information available from the clinical notes to collect the data for the study using the data collection sheet.
4. This data will then be uploaded onto an Excel spreadsheet.
5. The data will be anonymized and analysis performed on the anonymized data.

Interpretation of results

- The appropriateness of the use of FFPs as administered by the prescribing clinicians at CMJAH will be decided upon by the SANBS national guidelines on the use of FFPs.
- The outcome of the use of FFP will be documented whenever possible.

- Additional data about demographics and clinical diagnosis will be collected on the data collection sheet (see appendix A) and interpreted as necessary.

Data Analysis

The data derived from this study will be captured on Microsoft Excel spreadsheets. Quantitative data of the study participants will be tabulated and presented using means and ranges for continuous values and percentages for discrete values. Qualitative data will be interrogated to address the objectives.

Also, assistance from the University statisticians will be sought. The STATA statistical package, version12, will be used to perform all analyses (Stata Corp LP, Texas, USA). The data will be analysed using linear and multiple regression models as indicated,

Possible Limitations of the study

If at any point during the six month study period, FFP is not available or if there is a shortage in supply to the patients at CMJAH. It will hinder accurate interpretation of this audit. If the medical records are incomplete and the data is not available, this will also hinder results of the audit.

Study Timeline

	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collection data												
Data Analysis												
Writing up - thesis												
Writing up - paper												

Study Budget

Budget for study	
Action funded	**Amount(Rands)**
Photocopying, binding of thesis	1000
Biostatiscian	3000
Publication	1000
Local Conference attendance	10000
Total	15 000

Ethics considerations

There is no patient intervention in this study therefore informed consent is not required. Permission to conduct this study has been granted from the SANBS Human Research Ethics Committee for using the local SANBS Branch information and from the CMJAH CEO as well as the Gauteng Protocol Review Committee. All patients involved in the study will have full anonymity and their details will be known only to the study researchers with no publications of their identities. The investigation will only commence once the appropriate ethics and approval have been obtained.

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Appendix B - Data Collection Sheet

DATA COLLECTION SHEET FOR FFP AUDIT

Date	Age	Sex	Study no	Ward	No. FFP	Appropriate	Inappropriate	Diagnosis

Appropriate Indication		Inappropriate indications	
A	Single factor deficiency	H	Hypoproteinaemia-nutritional supplementation
B	Multiple coagulation factor deficiencies	I	Volume expansion
C	Thrombotic thrombocytopenic purpura (TTP)	J	Abnormal coagulation studies in non-bleeding patient
D	Warfarin reversal	K	Prophylactic use before invasive procedures
E	Vitamin K deficiency	L	Bleeding without a coagulopathy
F	Scoline apnoea	M	Wound healing
G	Paediatric use-HDNB		

Appendix C - Ethics Clearance Certificates

C1: Blood Bank

C2: Witwatersrand University

C1: Blood Bank

SOUTH AFRICAN NATIONAL BLOOD SERVICE NPC

Human Research Ethics Committee

SANBS
South African National Blood Service

Association Incorporated Under Section 21
Registration No. 2000/026390/08

OHRP Number : IORG0006278
FWA Registration Number : IRB00007553
SA NHREC Registration Number : REC-270606-013

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E-mail:reenellegounden@yahoo.co.uk

Dear Dr Gounden

DATE OF COMMITTEE MEETING:	**8 September 2015**
PROJECT TITLE:	**A prospective audit of the use of Fresh Frozen Plasma at Charlotte Maxeke Johannesburg Academic Hospital**
DECISION OF THE COMMITTEE:	**Approved**
CLEARANCE CERTIFICATE NO:	**2015/26**

- Execution of the study must be compliant with applicable guidelines and policies.
- Any amendment, extension or other modifications to the protocol must be submitted to this Ethics Committee for approval prior to implementation.
- The Committee must be informed of any serious adverse event, planned and unplanned termination of the study.
- A progress report should be submitted yearly for long-term studies and a final report at completion of both short term and long term studies.
- Kindly refer to the SANBS HREC clearance certificate number on all future correspondence on this study to the HREC secretariat.
- This approval is valid for 5 years from the date stated above.

COMMITTEE GUIDANCE DOCUMENTS:

- International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guideline (ICH, 1996), Ethics in Health Research: Principles, Structures and Procedures (SA Department of Health, 2004); Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (SA Department of Health, 2006); Ethical Principles for Medical Research Involving Human: Declaration of Helsinki (World Medical Association, 2013); Reviewing Clinical trials: A Guide For Ethics Committees (Karlberg and Speers, 2010)

CHAIRPERSON: Prof J.N. Mahlangu

22 September 2015
DATE

C2: Witwatersrand University

R14/49 Dr Reenelle Gounden

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150974

NAME: (Principal Investigator)	Dr Reenelle Gounden
DEPARTMENT:	Molecular Medicine and Haematology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Prospective Audit of the Use of Fresh Frozen Plasma at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	02/10/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/12/2015

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 Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 07/12/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

12 January 2016
Person No: 0002503N
PAG

Miss R Gounden
44 The Meridian
291 AG De Witt Drive
Solheim
Germiston
1401
South Africa

Dear Miss Gounden

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *A retrospective audit of the use of fresh frozen plasma at Charlotte Maxeke Johannesburg Academic Hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix D - Turn-it-in Report

0002503n:Turb-it-in_v4-7-12-18.doc

ORIGINALITY REPORT

10%	7%	9%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	2%
2	www.sanbs.org.za Internet Source	1%
3	www.wpbtsmedical.org.za Internet Source	1%
4	"Abstracts", Vox Sanguinis, 2017 Publication	1%
5	"Poster Abstracts", Vox Sanguinis, 07/2011 Publication	1%
6	Mirzamani, N.. "Evaluation of appropriate usage of fresh frozen plasma: Results of a regional audit in Iran", Transfusion and Apheresis Science, 200904 Publication	<1%
7	jid.oxfordjournals.org Internet Source	<1%
8	Anticoagulation and Hemostasis in Neurosurgery, 2016.	<1%

	Publication	
9	www.transfusionontario.org Internet Source	<1%
10	www.j3.jstage.jst.go.jp Internet Source	<1%
11	www.dovepress.com Internet Source	<1%
12	www.jcmr-online.com Internet Source	<1%
13	Bulent Ozgonenel. "Warfarin reversal emerging as the major indication for fresh frozen plasma use at a tertiary care hospital", American Journal of Hematology, 12/2007 Publication	<1%
14	"Principles of Adult Surgical Critical Care", Springer Nature, 2016 Publication	<1%
15	open.uct.ac.za Internet Source	<1%
16	www.scribd.com Internet Source	<1%
17	Francesco Dentali, Chiara Marchesi, Matteo Pierfranceschi, Mark Crowther et al. "Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K	<1%

antagonists", Thrombosis and Haemostasis, 2017
Publication

18	air.unimi.it Internet Source	<1%
19	Robert L. Crookes, Christopher D. Hillyer. "Fresh Frozen Plasma and Related Products", Elsevier BV, 2007 Publication	<1%
20	intjem.springeropen.com Internet Source	<1%
21	H. H. Phan. "Should we increase the ratio of plasma/platelets to red blood cells in massive transfusion: what is the evidence?", Vox Sanguinis, 04/2010 Publication	<1%
22	"Poster abstracts", Vox Sanguinis, 7/2007 Publication	<1%
23	M. Shukri Raban, Michael C. Harrison. "Fresh Frozen Plasma Use in a Neonatal Unit in South Africa", Journal of Tropical Pediatrics, 2015 Publication	<1%
24	Cosmi, B.. "Assessment of the risk of bleeding in patients undergoing surgery or invasive procedures: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)",	<1%

Thrombosis Research, 200911
Publication

25	Raban, M. S., and M. C. Harrison. "Fresh Frozen Plasma Use in a Neonatal Unit in South Africa", Journal of Tropical Pediatrics, 2015. Publication	<1%
26	"Hemostasis and Thrombosis", Springer Nature, 2017 Publication	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Appendix E - Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Reenelle Gounden (Student number: 0002503N) am a student registered for the degree of Master of Medince (MMed) in the academic year 2018.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 05 December 2018

Appendix F - Statement of principles for postgraduate supervision

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

STATEMENT OF PRINCIPLES FOR POSTGRADUATE SUPERVISION

IN A CONTEXT OF ACADEMIC FREEDOM AND WITHIN A FRAMEWORK OF INDIVIDUAL AUTONOMY AND THE PURSUIT OF KNOWLEDGE THIS STATEMENT IS WRITTEN IN THE BELIEF THAT THERE IS A RECIPROCAL RELATIONSHIP AND MUTUAL ACCOUNTABILITY BETWEEN SUPERVISOR AND STUDENT.

THE SUPERVISOR AND THE STUDENT:

1. Will establish agreed roles and clear processes to be maintained by both parties. In the case of join supervision everybody's role needs to be clarified.
2. Will meet regularly and as frequent as is reasonable to ensure steady progress towards the completion of the proposal, research report, or dissertation or thesis. This time varies but the normal minimum requirement for face-to-face contact spread across each year of registration is: 10 contact hours for an Honours project, 15 contact hours for a Masters by a research report and 24 contact hours for a Masters by dissertation and a PhD.
3. Will keep appointments, be punctual and respond timeously to messages.
4. Will keep one another informed of any planned vacations or absences as well as changes in his/her personal circumstances that might impact on the work schedule. Unplanned absences or delays should be discussed as soon as possible and arrangements should be made, to catch up lost time.
5. Will ensure that research on animal or human subjects is concluded according to the procedures and the requirements of the relevant University Ethics committee.
6. Will together complete progress reports on the research project, as requested by each Faculty Graduate Studies Committee.

THE SUPERVISOR

1. Undertakes to provide guidance for the student's research project in relation to the design and scope of the project, the relevant literature and information sources, research methods of data analysis.
2. Has a responsibility to be accessible to the students.
3. Will be prepared for the meeting with student. This includes being up to date on the latest work in his/her area of expertise.
4. Will expect written work as jointly agreed, and will return that work with constructive criticism within a timeframe (a suggestion of 2-4 weeks) jointly agreed at the outset of the research.
5. Will provide advice that can help the student to improve his/her writing. This may include referrals for language training and academic writing. The supervisor will provide guidance on technical aspects of writing such as referencing as well as on the discipline specific requirements. Detailed correction of drafts and instruction in aspects of language and style are not the responsibility of the supervisor.

6. Will support the student in the production of a research report, dissertation or thesis. Provision should be allowed for adequate, mutually respectful, discussion around recommendations made.
7. Will assist with the construction of a written time schedule, which outlines the expected completion dates of successive stages of the work.
8. Will ensure the student has the opportunity to present work at postgraduate/staff seminars/national/international conferences as appropriate.
9. Will assist with the publication of research articles appropriate.
10. Will discuss the ownership of research conducted by the student in accordance with the University guidelines and rules on intellectual property, co-authorship and copyright.
11. Will ensure that the research is conducted in accordance with the University's policy on plagiarism.
12. Will ensure that the student is made aware in writing of the inadequacy of progress and/or of any work where the standard is below par. Acceptability will be according to criteria previously supplied to the student.
13. Has a duty to refuse to allow the submission of sub-standard work for examination, regardless of the circumstances. If the student chooses to submit without the consent of the supervisor, then this should be clearly recorded and the appropriate procedures followed.

THE STUDENT

1. Undertakes to work independently under the guidance of the supervisor. This includes reading widely to ensure that the literature pertinent to his/her chosen topic has been identified and consulted.
2. Is obliged to make appointments to see the supervisor and will arrange meeting times well in advance.
3. Will think carefully about how to get maximum benefit from these contact sessions by planning what s/he wants in these sessions.
4. Should submit written work for discussion with the supervisor well in advance of a scheduled meeting. The kind and frequency of written work should be agreed with the supervisor at the outset of the research.
5. Written work that is submitted should be relatively free from basic spelling mistakes, incorrect punctuation and grammatical errors. Responsibility for the accuracy of language, the overall structure and coherence of the final research report, dissertation or thesis rests with the student.
6. Undertakes to heed the advice given by the supervisor and to engage in discussion around suggestions made. Ultimately the student has to take responsibility for the quality and presentation of the work.
7. Should strive, within reasonable bounds, to maintain a focus on his/her research area and to work within the agreed time schedule.
8. Will prepare material for presentations at seminars and conferences.
9. Undertakes to submit papers for publication.
10. Agrees to honour agreements about ownership of the research and in accordance with the University's guidelines and rules in relation to co-authorship, copyright and intellectual property.
11. Will ensure that the work contains no instances of plagiarism and that all citations are properly referenced and that the list of references is accurate, complete and consistent.
12. Agrees to work in accordance with the criteria of acceptability as supplied by the supervisor.
13. Undertakes not to place the supervisor under undue pressure to submit work for examination until the supervisor is satisfied that it has reached an acceptable level of quality. We confirm that we have read and understood this statement and agree to be guided by its principles for as long as we continue to work together.

Please note: The University and Faculty endorse the **Singapore Statement** on research integrity. The principles of the Singapore Statement include honesty, accountability, professionalism and stewardship. Our responsibilities as researchers (i.e. both as students and supervisors) are as pledged in the Singapore Declaration: the assurance of appropriate "data integrity, data sharing, record keeping, authorship, publication, peer review, conflict of interest, reporting misconduct and irresponsible research, communicating with the public, complying with regulations, education, and social responsibilities (World Conference on Research Integrity, 2010)". These principles and responsibilities are important in training our postgraduate students and in promoting global research integrity. Ref: Resnik, DB and Shamoo AE (2011). The Singapore Statement on Research Integrity.Account Res. 18:71-75.

Name of student: _____Reenelle Gounden_____ Student's signature: _____

Name of Supervisor: ___Professor JN Mahlangu_____ Supervisor's signature: _____

REVIEWED AND SUPPORTED
By Prof Johnny Mahlangu at 12:36, 11/12/2018

The broad area of study is: _____Blood banking_____

Provisional submission date is: ___December 2018_____ Degree: ____Master of Medicine_____

School: ____School of Pathology_____ Faculty: ___Health Sciences_____

Date: _____

Specific agreement pertaining to: ownership and joint publication, funding, may be attached and signed.

GRIEVANCE PROCEDURES: It should be acknowledged that during the course of the research that both students and supervisors can feel aggrieved. In this event, these should be dealt with as swiftly as possible by the parties involved and, if necessary, the Postgraduate Coordinators and Committees. There is, in addition, a University Grievance Policy to help guide deliberations.