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Freeze-Dried Plasma and Adverse Events

A retrospective study evaluating the frequency of adverse events in trauma patients in correlation to the ratio of freeze-dried plasma and erythrocytes transfused

Author:

Johannes Forsberg
Medical Student
Sahlgrenska Academy
University of Gothenburg
gusforjol@student.gu.se

Supervisors:

Timothy Craig Hardcastle
MBChB, MMed. and Ph.D.
Chief Trauma Surgeon
Trauma Service and Trauma ICU
Inkosi Albert Luthuli Central Hospital
hardcastle@ukzn.ac.za

Per Nellgård
M.D. and Ph.D.
Section Chief
AnOpIVA
Sahlgrenska University Hospital
per.nellgard@vgregion.se

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Abstract

Degree project in Medicine

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Johannes Forsberg

Programme in Medicine, Sahlgrenska Academy, Gothenburg, Sweden, 2019

Introduction: Freeze-dried plasma (FDP) is a pulverized form of blood plasma. FDP has many advantageous characteristics and can be used to correct coagulopathy or as a volume expander. Packed red blood cells (PRBC) are erythrocytes used for transfusions and common indications are haemorrhage and anaemia. FDP and PRBC are crucial components for treatment of coagulopathic and haemorrhagic patients.

Aim: The aim of this study was to investigate how different ratios of FDP and PRBC transfused to trauma patients during the initial patient care affect mortality, the number of days treated and the frequency of transfusion related complications, i.e. Acute Kidney Injury (AKI), Acute Respiratory Distress Syndrome (ARDS), Multiple Organ Dysfunction Syndrome (MODS) and Transfusion Related Acute Lung Injury (TRALI).

Methods: The study was a retrospective descriptive analytical chart review for patients treated between 2018-01-01 to 2019-08-15 at the resuscitation unit and the trauma ICU at Inkosi Albert Luthuli Central Hospital, Durban, South Africa. Data was collected from a local database and electronic medical records. Fisher's Exact Test and Pearson's Chi-Squared Test was used to analyse the research questions.

Results: 73 patients were included in the study and divided into two groups with 35 patients in group A (FDP ≤ PRBC) and 38 patients in group B (FDP > PRBC). The number of patients that expired during the first two weeks in group A were 8 (7 patients during day 0-7 and 1 patient during day 8-14) and 10 patients group B (5 patients during day 0-7 and 5 patients during day 8-14), resulting in a p-value of 0.152. In group A, the number of patients treated for 1-7 days were 4, the number of patients treated between 8-14 days were 9 and the number of patients treated for 15 days or more were 11. The corresponding number of patients in group B for the three different categories in the same succession were 10, 8 and 9 patients respectively, resulting in a p-value of 0.277. Regarding transfusion related complications that occurred more than 24 hours after arrival, 4 patients developed AKIN, 0 patients developed TRALI, 1 patient developed ARDS and 5 patients developed ARDS. The number of patients who developed transfusion related complications were too small in order to perform analytical statistics.

Conclusions: No significant differences between the groups were found regarding the three research questions. Additional studies with greater number of patients will be required to further evaluate the impact of different ratios of PRBC and FDP.

Key words: Freeze-dried plasma, packed red blood cells, transfusions, trauma, adverse events

Abbreviations

AIS:	Abbreviated Injury Scale
AKI:	Acute Kidney Injury
AKIN:	Acute Kidney Injury Network
ARDS:	Acute Respiratory Distress Syndrome
FDP:	Freeze-Dried Plasma
FFP:	Fresh Frozen Plasma
FLYP:	French Lyophilized Plasma
IALCH:	Inkosi Albert Luthuli Central Hospital
ISS:	Injury Severity Score
MODS:	Multiple Organ Dysfunction Syndrome
PRBC:	Packed Red Blood Cells
ROTEM:	Rotational thromboelastometry
TIC:	Trauma-induced coagulopathy
TICU:	Trauma Intensive Care Unit
TRALI:	Transfusion Related Acute Lung Injury
VAP:	Ventilator-Associated Pneumonia

Background

Introduction to the study

This study was conducted in South Africa, which is one of the countries in the world which has highest injury burdens and highest injury-related mortality (1). In year 2017, the homicide rate in South Africa was 35.9 per 100,000 inhabitants, which in absolute numbers generates high quantities of homicides considering the approximately 58.7 million inhabitants (2, 3). Since FDP has been used since 1996 in considerable proportions in South Africa, there is wide experience and a great scientific foundation which promotes research on FDP. Considering the great numbers of trauma patients, the need for appropriate blood products, such as FDP, is therefore indispensable. The South African Blood Service has for a long time faced great challenges recruiting sufficient numbers of blood donors to fulfil the need for blood products (4, 5). The combination of the above-mentioned factors therefore demands optimal usage of blood products. Further knowledge about FDP and its effect could possibly optimize its usage and improve the treatment of trauma patients. Under the following subheadings in the backgrounds section, important physiological and pathological processes in trauma patients will be presented, as well as crucial components and factors in the treatment of trauma and their possible consequent complications.

Haemostasis

Haemostasis is the physiological process responsible for both clot formation and prevention of bleeding. Both *procoagulant* and *anticoagulant* processes are involved in the haemostasis. When the vascular system is intact, maintenance of blood fluidity is prioritized. If vascular damage occurs, clot formation is triggered in order to prevent loss of blood (6). These functions are elementary components for adequate physiological function and survival. Inadequate function of the haemostasis may therefore lead to disease or death (7). The formation of blood

clots is a complex mechanism involving both primary and secondary haemostasis. *Primary haemostasis* alludes to the cellular activity of the haemostasis, while the secondary haemostasis alludes to the activity of the coagulation cascade (8). In the primary haemostasis the platelets play a very central roll. If a vessel injury appears, platelets adhere to molecules on the exposed subendothelial extracellular matrices, thereby circumscribing blood loss. *Adhesion*, *activation* and *aggregation* are involved in the primary haemostasis. Aggregation which is the final step, signifies that a clot containing platelets and fibrinogen forms. (9, 10). The *secondary haemostasis* pathway consists of the coagulation cascade which leads to the formation of fibrinogen and fibrin (7). The different coagulation factors in the coagulation cascade are zymogens, inactive precursors, that can be activated and catalyse the activation of other coagulation factors. The coagulation cascade is divided into the *intrinsic* pathway, *extrinsic* pathway and *common* pathway. The intrinsic pathway is activated by damaged surfaces and the extrinsic pathway is activated by tissue factor. Both these pathway leads to the common pathway where the end product is fibrin. Fibrin finally integrates with platelets in a process called crosslinking which strengthens the clot and consequently prevents haemorrhage (6, 11). *Anticoagulation* is a process which inhibits coagulation and prevents thrombosis. *Protein C* which can be converted into activated protein C (APC), is one of many proteins involved in anticoagulation. *Fibrinolysis* is the process where blood clots are being broken down to enable normal blood flow. Fibrinolysis is activated by tissue plasminogen which converts plasminogen to plasmin. Plasmin then splits fibrin which resolves the fibrin clot (7).

Coagulopathy and haemorrhage

Coagulopathy is defined as the lack of normal coagulation function. Trauma itself is a risk factor for coagulopathy, which the term *trauma-induced coagulopathy* (TIC) refers to (12). Chemically and physiologically, several pathological components like bleeding and tissue injury in the initial phase of trauma, contributes to inadequate balance of both procoagulant processes, anticoagulant processes and fibrinolysis. Multiple studies have suggested that protein C is involved in the development of TIC (12). Insufficient perfusion and bleeding cause exaggerated activation of protein C. As a result, excessive fibrinolysis and fast consumption of factors regulating haemostasis occurs (13). TIC is a clinical syndrome and multiple clinical factors can contribute to the arising of TIC (14). Five of these clinical factors that increase the risk for TIC are *treatment with intravenous fluids*, *blood dilution*, *hypothermia*, *acidosis* and *insufficient perfusion* (12). *The lethal triad* is a phenomenon which refers to *hypothermia*, *acidosis* and *coagulopathy* and how each of these factors affect and worsen the other factors. Hypothermia and acidosis respectively worsen coagulopathy. If both hypothermia and acidosis are present simultaneously, the deterioration of coagulation is more profound than the deterioration of each factor summed up (15). *Rotational thromboelastometry* (ROTEM) is a method that can be used to analyse coagulation status and detect coagulopathy. Different parts of the coagulation cascade can be analysed. INTEM is a test which screens the intrinsic pathway whereas EXTEM is a test that screens the extrinsic pathway. The results of different tests can be used as guidance for administration of fluids and blood products like platelets, plasma, cryoprecipitate or tranexamic acid (12). TIC can also contribute to haemorrhage and haemorrhagic shock. Haemorrhagic shock causes more than 500,000 deaths per year globally. Except for aiming to quickly control the bleeding source, transfusions with fluids or blood components are the preferred treatments for uncontrolled haemorrhage and haemorrhagic shock (16).

Injury Severity Score

In trauma, a grading system called *injury severity score* (ISS), can be used to assess the severity of the injuries. The score is based on *abbreviated injury scale* (AIS). AIS grades injuries from 0-6 (17). The ISS is calculated by using the square of the AIS and adding the square values from the three most seriously injured regions out of six specified body regions. A score of 6 on AIS in one of the 6 regions, by definition generates an ISS of 75 which is the highest possible ISS. Each body region can generate an injury severity score between 0-25, consequently generating a possible total injury severity score between 0-75, where a higher score correlates with more serious injuries (17, 18).

Freeze-dried plasma

Plasma is a blood product which contain all clotting factors (19). Freeze-dried plasma (FDP) is pulverised form of blood plasma (20). FDP was developed during the 1930s and was used by the British and American forces during World War II. The blood plasma used for FDP can be obtained through separation or apheresis from whole blood and can be prepared through *lyophilization* or *aerosolization*. Lyophilization is the most common of the two processes and implies that plasma first is being frozen, whereupon the pressure is reduced and the temperature is slowly increased, resulting in pulverization of the plasma (4, 20, 21). FDP has many *advantageous characteristics* in military settings and harsh conditions. FDP is shelf stable for up to two years, can be stored in ambient temperatures, is easily transported and is ABO-universal (21-23). FDP is easily rehydrated with sterile water and then stirred for three to five minutes to enable administration (20, 23). FDP can be used as a volume expander or to treat coagulopathy through substitution of depleted coagulation factors (24, 25). The production of FDP was for a period discontinued since transmission of viral diseases such hepatitis and HIV occurred too frequently (4, 21). Since the early 1990s and after however new methods have enabled FDP to be produced with considerably higher safety profiles. This led to re-establishment of the FDP within the military (23), but also increased the interest to use FDP within the health care. In some parts of South Africa FDP has been used within the healthcare since 1996 (4), and in Bergen (Norway) and Gothenburg (Sweden) FDP has been used within the air medical service in the last few years (26). Currently there are at least three different producers globally who produce FDP with their own product names. The French Military Blood Institute produces the French lyophilised plasma (FLYP), the German Red Cross produces LyoPlas N-w and National Bioproducts Institute in Pinetown, South Africa, produces Bio plasma FDP (4).

Comparison of freeze-dried plasma and fresh frozen plasma

FDP has traditionally mostly been associated with military use, whereas fresh frozen plasma (FFP), another form of plasma, has been more regularly used within the health care (4, 20, 21). FFP is obtained through separation or apheresis from the whole blood and is then within 8 or 24 hours frozen and stored at -18 °C or colder for maximally one year. Regarding handling of FFP, this product must be stored frozen and has to be thawed in a water bath for at least 15 to 20 minutes before administration is possible. Once thawed the FFP can be stored refrigerated for maximally 5 days before it expires (21, 23, 27). For FFP, these factors entail continuous access to storage in freezers and therefore contribute higher demands for storage than for FDP. Studies have tried to evaluate the effect of FDP compared to FFP and it has been shown that FDP is functionally equivalent compared to FFP (4, 21). FDP has equal levels of clotting factors and proteins compared to FFP after storage at ambient temperature for two years (23). In both in vitro and porcine injury models, FDP has shown equal coagulation profile compared to FFP as single treatment but also when combined with packed red blood cells in ratio 1:1 (21). The clotting factor activity however is slightly lower for FDP than for FFP, but it does not seem to contribute to clinical ineffectiveness or lose its coagulative effect in animal models. The risks of FDP are equal to them of FFP, namely allergic reactions and overtransfusion with side effects such as lung oedema. The prevalence of transfusion reactions is not considered higher for FDP than for FFP (20, 28). In a big study where FFP was compared towards LyoPlas N-w, the frequencies of transfusion reactions were 0.023% for FDP and 0.018% for FFP.(4).

Blood products, fluids, calcium and magnesium

Packed red blood cells (PRBC), or red blood cells, or, are erythrocytes separated from whole blood intended for transfusion (29, 30). PRBC can be used to increase the oxygen carrying capacity, to treat anaemia and haemorrhage, as part of treatment for TIC and as part of massive transfusions (more than 10 units of PRBC during 24 hours) (19, 31-35). A single unit of PRBC

can raise the haemoglobin levels 1 g/dl. For in-ICU patients with stable organ dysfunction, many studies have found beneficial aspects when the threshold for transfusions is set to haemoglobin levels of 7 g/dl (30), while for trauma patients undergoing resuscitation or being planned for surgery, the threshold for transfusions is set to haemoglobin levels of 10 g/dl (36). The patient's clinical status and signs of anaemia are also important factors to consider. *Platelets* can be obtained from whole blood or apheresis (30). Platelets can be used in patients with thrombocytopenia or functional defects in the thrombocytes (19). Platelets can also be used as part of massive transfusions (31, 32). A single unit of platelets typically raise the platelet count 30 to 60 x 10^9/L. *Cryoprecipitate* is obtained from plasma or apheresis and contain high levels of fibrinogen and factor VIII. Cryoprecipitate can be used to replace low levels of fibrinogen (hypofibrinogenemia). Hypofibrinogenemia is regularly caused by coagulopathy and massive bleeding. If administration of cryoprecipitate is indicated, 10 units are typically transfused. The aim is to preserve the fibrinogen levels at minimally 100 mg/dL. A single unit of cryoprecipitate typically increase the fibrinogen levels from 5 to 10 mg/dL (19, 30). *Calcium* (Ca^{2+}) is a metal ion which is essential for adequate thrombosis (7). For instance, calcium, and also the cation *magnesium* (Mg^{2+}), are important for normal physiological function of factor IX. During massive blood transfusion, citrate consumes both calcium and magnesium, which can lead to hypomagnesemia and hypocalcaemia (37-39). Calcium gluconate and magnesium sulphate can be infused to treat hypocalcaemia and hypomagnesemia respectively (31). *Voluven* is a synthetic colloid composed of hydroxyethyl starch and can be used to prevent and treat hypovolemia (40). *Ringers Lactate* and *normal saline* are the most frequently utilized resuscitation crystalloids. These crystalloids can be used as maintenance or replacement fluids (31).

Transfusion ratios

Many studies have investigated how different ratios of plasma and PRBC affect haemorrhagic patients (4, 13, 31, 32). It appears that high ratios of plasma to PRBC correlate to enhanced outcomes (4, 13). A ratio approaching 1:1 of plasma and PRBC has been proved to be associated with increased survival among seriously injured with traumatic bleeding in combat (4). Other studies have shown that ratios higher than 1:2 are correlated to increased survival and reduced mortality due to haemorrhage in patients receiving massive transfusions or suffering significant haemorrhage (24). A study from 2008 showed that a ratio of FFP:PRBC $\geq$ 1:1.5 compared to <1.5 in patients treated with massive transfusions correlated to reduced mortality risk but a higher frequency of acute respiratory distress syndrome (ARDS) (41). Regarding massive transfusions, the evidence for the ratio 1:1:1 for PRBC:FFP:Platelets increases (31, 32). However, many of the studies proposing high ratios of plasma:PRBC are exclusively based on patients treated with massive transfusions which represent a small patient group in trauma centres. Although the data is convincing enough to confidently prove that high ratios from 1:2 to 1:1 increase survival, a big share of the studies were retrospective and observational, and faced methodical and analytical difficulties. Lack of data and survival bias are some of the issues that contributed to aggravating circumstances. (32). It seems like many of the studies evaluating the effect of different plasma:PRBC ratios focus on FFP rather than FDP as plasma product (4, 13, 31, 32, 41). The usage of blood products like FDP and PRBC within the military has been studied, though the usage of FDP and PRBC within the emergency medical services has been studied in a limited extent (42).

Transfusion related complications

Transfusions can be the difference between life and death, though blood transfusions are not performed without risk. Transfusion related complications can be divided into infectious and non-infectious, acute and delayed (19). One of the complications that can occur due to transfusions of blood products (especially apheresis platelets and plasma), is transfusion-related acute lung injury (TRALI) (24, 43, 44). TRALI is an acute complication and can be described as a "non-cardiogenic pulmonary edema causing acute hypoxemia that occurs within six hours of a transfusion and has a clear temporal relationship to the transfusion". The oedema is caused by immune system activation. TRALI is a lethal complication and in the year of 2006 it contributed to more than 50 % of the deaths related to transfusion complications (19). Another condition that can occur due to multiple transfusions is acute respiratory distress syndrome (ARDS). ARDS can be described as a condiction which "is characterized by acute lung injury, noncardiogenic pulmonary edema, and severe hypoxia". The oedema is caused by injury on the pulmonary epithelium and endothelium. ARDS is also a lethal complication and can lead to reduced lung function (45). Multiple organ dysfunction (MODS) is another transfusion related complication and can be caused by PRBC-transfusions (33). Sequential Organ Failure Assesment (SOFA) is one of many models that can be used to evaluate organ failure (46). Acute kidney injury (AKI) is a potential complication from transfusions and can be described as "a common clinical syndrome defined as a sudden onset of reduced kidney function manifested by increased serum creatinine or a reduction in urine output". There are many different definitions for AKI and there are also different classification systems, where acute kidney injury network (AKIN) is one of them. AKIN is categorized into stage 1-3 depending on the severity where stage 3 is the most severe. AKIN stage is based on creatinine levels, urine output and need for renal replacement therapy (47, 48).

Inkosi Albert Luthuli Central Hospital

Inkosi Albert Luthuli Central Hospital (IALCH), located in Durban, South Africa, is a highly specialized tertiary and quaternary governmental regional referral hospital. IALCH is the only quaternary facility in KwaZulu-Natal and the apex unit for a province covering an area of 94,000 km^2, with a population of 11.5 million inhabitants. The hospital is a specialised referral centre for complex patients requiring sub-specialist care and holds multiple surgical, medical, peri-operative, and mother and child domains with totally 864 beds. South Africa's solely dedicated burns unit with 46 beds is also situated here. There are 6 intensive care units (ICU's) in IALCH, namely: neonatal, paediatric, cardiothoracic, renal, neuro and trauma. The trauma ICU (TICU) is a level 1 trauma centre and has a total of 16 beds, half of them are ICU beds and the other half are high-care beds. The TICU and resuscitation unit at IALCH, two linked and cooperating trauma departments, are both tertiary health departments. These departments receive both paediatric and adult patients with serious and complex traumatic injuries via referral from surrounding hospitals or directly from scene in the entire region of KwaZulu-Natal. The other regional hospitals all have small ICU's but there is no other trauma specific ICU elsewhere than on IALCH.

Since the TICU and resuscitation unit at IALCH are tertiary departments, exclusively patients with severe injuries are admitted. If a person in the region of KwaZulu-Natal is exposed to trauma, there are typically two ways the patient can be admitted to the resuscitation unit and TICU at IALCH. The first way is that the patient first is taken to a primary or secondary hospital (base hospital) or an out-patient clinic. If the patient is transported to this first care institution by ambulance, Ringers lactate, Saline and sometimes Voluven are used. At the arrival to the this first care institution the patient's status is evaluated. If the injuries are too extensive or severe at this care institution, or if too severe complications occur, the patient will be

transported the by road ambulance or helicopter to IALCH. At the first care institution and during the transport to IALCH, FDP, PRBC, Ringers lactate, Saline and Voluven can be transfused. It is the first care institution that provide the road ambulance or helicopter with FPD and PRBC. Smaller health care institutions might only possess two to four units of blood for the entire institution. Except for referrals, the second way that patients can be admitted to the resuscitation unit and TICU at IALCH is directly from scene, which can occur if the severity of the injuries initially are considered to be too serious to be treated at a primary or secondary hospital. Regarding transfusions, haemorrhagic patients are typically transfused with FDP and PRBC in the ratio 1:1, but since the supply of FDP and PRBC often is limited, haemorrhagic patients sometimes will be transfused with other ratios than 1:1.

At arrival to IALCH the patient first enters the resuscitation unit where the patient's status is evaluated using ATLS. At the resuscitation unit the patient's coagulation status is typically analysed by rotational thromboelastrometry (ROTEM) and blood samples in order to evaluate the need for further transfusions. For ROTEM the standard measurement method used is EXTEM. Depending on the patient's circulation status, coagulation status, ROTEM results and blood samples, further administration with FDP, PRBC, thrombocytes, cryoprecipitate, calcium, magnesium, Ringers lactate, saline and/or Voluven can be carried through. Local memos based on guidelines like ATLS 10 are used to guide the transfusions and administrations. After management in the resuscitation unit the patient is referred to the TICU or the operation theatre if acute surgery is needed.

Since March 2007, when this specialised unit opened, information about the patients admitted to the TICU at IALCH is recorded into a local database called the Medicom Databank. The database includes all trauma admissions to the TICU at IALCH and is hosted by the mentioned

health care institution. Approximately 250 patients are treated at the TICU at IALCH and recorded into the database annually. At IALCH, MEDITECH is the system used for electronical medical records. Patient information recorded before the arrival to IALCH can be stored in MEDITECH in the form of a short summary, a referral consultant form, scanned medical records and/or an ambulance form. Information about the treatment at IALCH is recorded in MEDITECH. The most relevant information is compiled into the database when the patient has been discharged from the trauma ICU at IALCH.

Indications for transfusions at Inkosi Albert Luthuli Central Hospital

Under this subheading the indications for transfusion at the resuscitation unit and trauma ICU at IALCH will be presented. If TEG is pathological, FDP is primarily used as treatment and secondarily platelets or cryoprecipitate. The indications for transfusion of FDP, PRBC and platelets at IALCH are illustrated in table 1. The FDP is produced by and purchased from Natal Bioproducts (NBI). Since the availability of platelets occasionally is limited and sometimes has to be transported long distances, FDP is intermittently administered instead of platelets when platelets are indicated. Cryoprecipitate shall be administered to patients with fibrinogen levels lower than 1 g/L and the aim is to reach fibrinogen levels of 2 g/L. Administration of calcium is indicated when the serum levels of ionized calcium are lower than 1 mmol/L. Finally, administration of magnesium is indicated when the plasma levels of magnesium is lower than 0.75 mmol/L.

Table 1 Indications for transfusion of FDP, PRBC and platelets

Indications for transfusion of FDP
1. As a component in massive transfusions
2. As an expander
3. As a supplement when 2 litres of other fluids have been administered
4. Present coagulopathy on ROTEM
4a. Prolonged clotting time
4b. Increased alpha-angle
4c. Increased maximum clot firmness
Indications for transfusion of PRBC
1. As a component in massive transfusions
2. Noted or suspected extensive bleeding
3. Specific Hb-levels
3a. Stable patients are transfused when Hb drops to 6-7 g/dL
3b. For patients planned for surgery the aim is an Hb-level of approximately 9 g/dL
3c. Throughout resuscitation during the first 24-48 h the aim is a Hb-level as close to 10 g/dL as possible
3d. Patients treated with dialysis are transfused when Hb drops to 5
Indications for transfusion of platelets
1. As a component in massive transfusions
2. Present coagulopathy on ROTEM
2a. Decreased maximum amplitude
2b. Decreased alpha-angle (if FDP has been transfused previously)
3. Decreased platelet count
3a. $< 100 \times 10^9$ for neurosurgery
3b. $< 50 \times 10^9$ for other surgery than neurosurgery
3c. $< 20 \times 10^9$ in ICU if no active bleeding

Aim

The aim of the study is to investigate how different ratios of freeze-dried plasma and erythrocytes transfused to trauma patients during the initial patient care affect mortality, the number of days treated and transfusion related complications.

Research questions

How do different ratios of FDP and PRBC transfused to trauma patients until 24 hours after admission to the trauma ICU affect *mortality*, *the number of days treated at the trauma ICU at IALCH* and *the frequency of the following transfusion related complications*: Acute Kidney Injury diagnosed with AKIN, Transfusion Related Acute Lung Injury (TRALI), Acute Respiratory Distress Syndrome (ARDS), and Multiple Organ Dysfunction Syndrome (MODS)?

Theory

As mentioned in the introduction section, it seems like no optimal ratio for FDP and PRBC has yet been confirmed. Higher ratios of plasma compared to PRBC seem to have benefits compared to lower ratios. In many hospitals, for example at the Sahlgrenska University Hospital in Gothenburg, Sweden, PRBC is administered before plasma in trauma patients. A theory is that early administration of FDP and higher ratios of FDP:PRBC transfused to trauma patients might correlate to more beneficial outcomes.

Material and methods

The study was a retrospective exploratory observational longitudinal descriptive analytical chart review conducted at the resuscitation unit and the trauma ICU at Inkosi Albert Luthuli Central Hospital, Durban, South Africa. Patients who had been treated at the resuscitation unit and/or TICU at IALCH between 2018-01-01 to 2019-08-15 and were transfused with FDP and PRBC were included. The patient data was collected from a local database (the Medicom Databank) and the electronic medical records system MEDITECH. Both the database and MEDITECH contained information written in English. The collected data was stored anonymised in an encrypted excel document. Eight weeks of time were dedicated to collect data for as many patients as possible. The data was collected along with David Karlsson, a

fellow medical student, who did research on the same topic but on different research questions. Before patients could be included, they were reviewed regarding the inclusion and exclusion criteria shown in table 2.

Table 2 Inclusion & exclusion criteria

Inclusion criteria
Trauma patients admitted to the resuscitation unit at IALCH within 24h after injury
Patients who at admission were between 18-80 years of age
Patients treated at the resuscitation unit and/or trauma ICU between 2018-01-01 to 2019-08-15
Patients transfused with FDP and PRBC before arrival to the resuscitation at IALCH or within the first 24 hours after admission to IALCH
Exclusion criteria
Non-trauma patients
Patients with thermal injuries covering 1 % or more of the total body surface area
Patients with known diseases that affect coagulation (for example haemophilia and Von Willebrands disease)
Patients who prior the trauma had been regularly treated with anticoagulants
Patients with known pregnancy
Patients declared brain dead before arrival at IALCH
Patients with ISS 75 who expired due to other conditions than bleeding and coagulopathy
Patients who are known to have been treated for another trauma within 2 weeks before current trauma injury
Patients who expired within 72 hours after arrival where bleeding and coagulopathy were not present and did not contribute to the death

The included patients were divided into 2 groups depending on the ratio of FDP and PRBC that had been transfused from injury until 24 hours after admission to IALCH, or alternatively the ratio of FDP and PRBC transfused from injury until the moment of expiration at IALCH if expiration occurred within 24 hours after admission to IALCH (table 3).

Table 3 Grouping

Group number	**A**	**B**
Ratio	FDP ≤ PRBC	FDP > PRBC

Except for data specific for the research questions, the standard trauma variables for exploratory retrospective trauma studies were included. The following data was extracted from the database and the electronic medical records and then recorded in the encrypted excel

document/proforma: sex, age, injury severity scale, date and time for injury and admission, survival and date for death or discharge. Also, the following laboratory measurements and vital parameters taken both at admission to IALCH and earliest possible subsequently to 24 hours after admission to IALCH were recorded in the excel document: pH, base excess, lactate, ionized calcium (only routinely recorded at arrival), body temperature, haemoglobin and platelets. Body temperature and pH was used to conclude if the patients had acidosis ($pH \leq 7,2$ was considered acidosis) and hypothermia (body temperature $\leq$ 36.0 °C was considered hypothermia). Furthermore, transfusions and treatment of the following products from injury until admission to IALCH and during the first 24 hours after admission to IALCH were recorded: FDP, PRBC, platelets, cryoprecipitate, calcium, magnesium, Ringers lactate (boluses but not maintenance treatment was recorded), Saline and Voluven. Whereas different notes in the medical records regarding amounts of transfused FDP and PRBC contained conflicting information or were defective, the amounts of FDP and PRBC that were considered most reasonable after reviewing and comparing the notes were recorded into the excel document. If no quantifiable amount or details were mentioned, no administrations were recorded and the corresponding cell was left empty in the proforma. If no information about transfusions prior to admission, no referral letters or no ambulance forms could be found, it was considered that no transfusion had been carried through before arrival to IALCH. Finally, presence of the following conditions stated in the database or medical records and the day the conditions occurred were recorded in the proforma: AKI diagnosed with AKIN, TRALI, ARDS, MODS, Ventilator Associated Pneumonia (VAP) and Sepsis. For the number of days treated and the day the conditions occurred, the day of admission is recorded as day 0. If necessary, additional information about the patients could be added in a comment column.

Statistical methods

The acquired data was analysed through SPSS v 26.0 for Mac (IBM, Armonk NY, USA) to draw conclusions about how the different ratios of FDP and PRBC affect adverse events. The significance level was set to Significance level $p < 0.05$. The null hypothesis was stated as followed: there is no significant difference in mortality, the number of days treated or the frequency of transfusion related complications between the two groups. Further, the alternative hypothesis was stated in this way: there is a significant difference in mortality, the number of days treated or the frequency of morbidities between the three groups. Categorization of the number of days treated and the days of survival was made. Fisher's Exact 2-Sided Test was used to analyse the mortality Pearson's Chi-Squared Test was used to analyse the number of days treated. Analytical statistical tests were not applied on the transfusion related complications since the number of positive outcomes were too few to fulfil the tests' assumptions. Fisher's Exact 2-Sided Test and Independent-samples Mann-Whitney U test were used to analyse characteristics of the two ratio groups. No other subgrouping was made since only severe trauma cases were admitted to the resuscitation unit and TICU at IALCH which entailed that the studied population could be considered quite homogenous.

Ethical considerations

The study was conducted according to the UN's declaration on human rights and the ethical principles of the Declaration of Helsinki. The local database (Medicom Databank) has been approved for retrospective observational studies by the Ethics Committee of the University of KwaZulu-Natal (BCA207-09). An application for approval of this study as a BCA207-09 substudy was sent to The Research Committee of the University of KwaZulu-Natal and the approval was authorised. The data was stored anonymously in encrypted excel documents.

Results

Sample statistics

Under this subheading, characteristics of the two ratio groups and the entire study population will be demonstrated. Under the following subheadings in the result section, descriptive and analytical statistics related to the research questions will be illustrated. As described in the methods section, the study population was divided into two groups. Group A was administered with fewer or equal units of FDP compared to PRBC, while group B was administered with more units of FDP than PRBC. In total 73 patients were included. The distribution of the patients, gender and age characteristics among the two ratio groups are illustrated in table 4. Fisher's exact 2-sided test showed no significant difference of the gender distribution between the two groups ($p = 0.782$). Independent-samples Mann-Whitney U test showed no significant difference in distribution of age across group A and group B ($p = 0.795$).

Table 4 Characteristics of the study population

Group descriptions		**Group**	**A**	**B**
		Ratio	FDP ≤ PRBC	FDP > PRBC
		Nr of patients	35	38
Gender		Female	7 (20.0%)	9 (23.7%)
		Male	28 (80.0%)	29 (76.3%)
Age	Continuous data	Mean	35.86	36.18
		Median	34	34
		Minimum	18	18
		Maximum	65	73
	Categorised data	18 – 29	12 (34.3%)	14 (36.8%)
		30 – 39	11 (31.4%)	8 (21.1%)
		40 – 49	8 (22.9%)	14 (36.8%)
		≥ 50	4 (11.4%)	2 (5.3%)

In the grouped bar chart in figure 1, the patients are categorised according to age and gender.

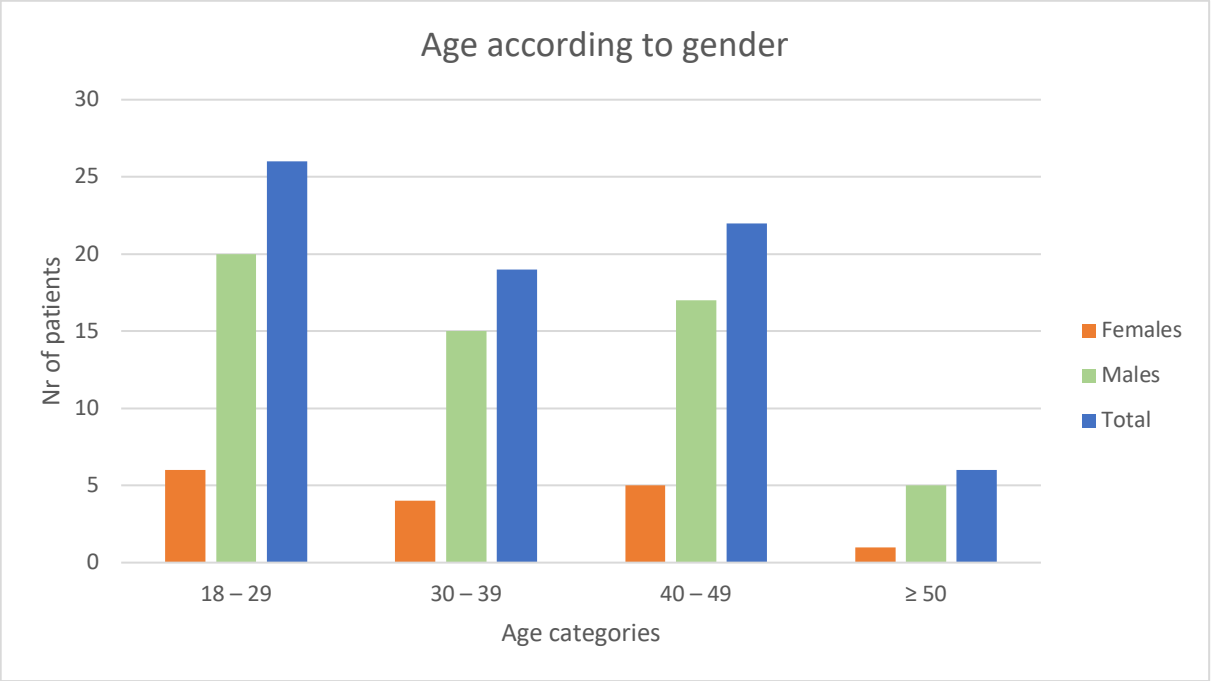

Figure 1 Age according to gender

In the grouped bar chart in figure 2, the patients are categorised according to ISS and gender.

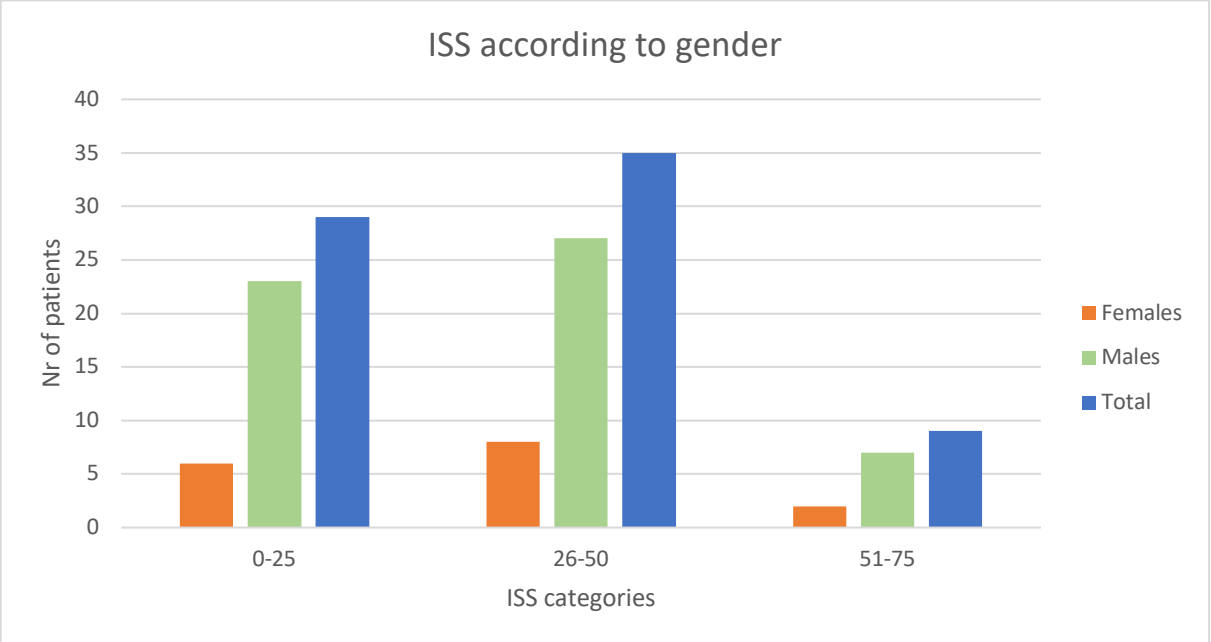

Figure 2 ISS according to gender. ISS = Injury severity score.

In the box plot in figure 3, ISS for the two ratio groups are illustrated. For group A there are three outliers, two with ISS 75 and one with ISS 64. Independent-samples Mann-Whitney U test showed no significant difference in distribution of ISS across group A and group B (p = 0.619).

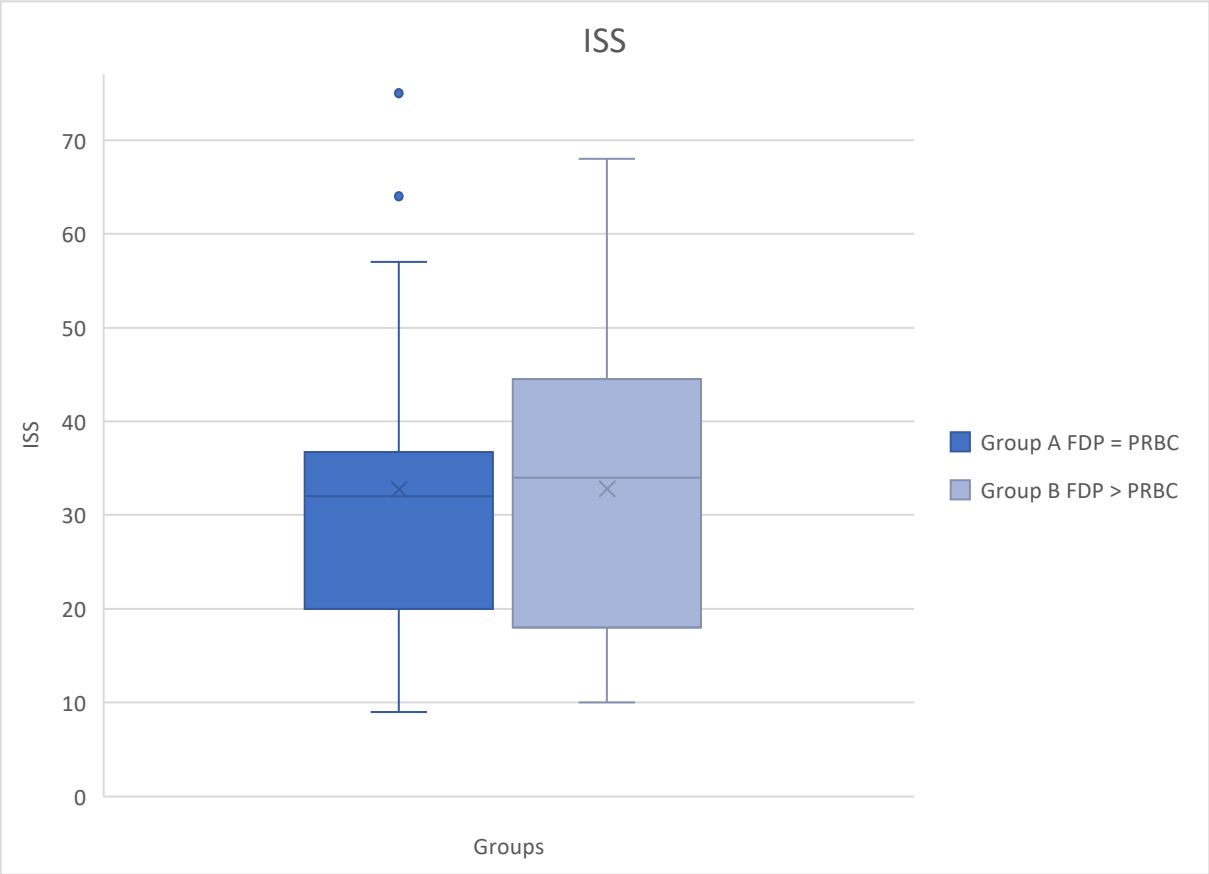

Figure 3 ISS according to sample groups. ISS = Injury severity score.

In table 5 below, blood parameters at arrival are illustrated. All blood parameters were missing for 2 patients in group A.

Table 5 Blood parameters at arrival

Group descriptions	Group nr	A	B	Units
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of patients	33	38	
Base Excess	Mean	-6.155	-6.926	mmol/L
	Minimum	-24.0	-22.3	
	Maximum	7.3	2.7	
	25th percentile	-9.250	-10.700	
	50th percentile	-7.000	-7.250	
	75th percentile	-2.150	-2.350	
Lactate	Mean	5.388	5.200	mmol/L
	Minimum	0.9	0.7	
	Maximum	18.9	18.0	
	25th percentile	3.150	2.125	
	50th percentile	5.000	4.250	
	75th percentile	6.600	7.425	
pH	Mean	7.3052	7.2703	
	Minimum	6.98	6.87	
	Maximum	7.52	7.45	
	25th percentile	7.2450	7.2200	
	50th percentile	7.3200	7.2900	
	75th percentile	7.3900	7.3525	
Ionized calcium	Mean	1.0626	1.0730	mmol/L
	Minimum	0.73	0.68	
	Maximum	1.23	1.23	
	25th percentile	1.04	1.01	
	50th percentile	1.09	1.09	
	75th percentile	1.12	1.15	
Haemoglobin	Mean	8.767	10.242	g/dL
	Minimum	5.5	4.9	
	Maximum	12.4	16.2	
	25th percentile	7.25	8.10	
	50th percentile	8.90	10.35	
	75th percentile	9.95	12.20	
Platelets	Mean	173.47	176.84	10^9/L
	Minimum	32	39	
	Maximum	336	313	
	25th percentile	127.75	113.25	
	50th percentile	172.00	177.00	
	75th percentile	205.50	227.25	

Table 6 demonstrates the first blood parameters taken 24 hours after admission. The number of patients in table 6 are lower than in table 5 due to expiration of patients. Ionized calcium could not be found other than at arrival except for a few patients and is therefore not illustrated in table 6.

Table 6 Blood parameters 24 hours after arrival

Group descriptions	**Group nr**	**A**	**B**	**Units**
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of patients	30	36	
Base Excess	Mean	0.800	2.331	mmol/L
	Minimum	-8.0	-16.8	
	Maximum	7.9	9.2	
	25th percentile	-1.700	0.275	
	50th percentile	1.650	2.700	
	75th percentile	3.700	5.375	
Lactate	Mean	1.987	2.408	mmol/L
	Minimum	0.5	0.5	
	Maximum	5.3	19.4	
	25th percentile	1.200	1.025	
	50th percentile	1.750	1.700	
	75th percentile	2.325	2.625	
pH	Nr of patients	30	35	
	Mean	7.3870	7.4157	
	Minimum	7.21	7.19	
	Maximum	7.52	7.59	
	25th percentile	7.3525	7.3800	
	50th percentile	7.3950	7.4300	
	75th percentile	7.4325	7.4600	
Haemoglobin	Mean	8.820	8.717	g/dL
	Minimum	5.5	2.7	
	Maximum	12.4	12.3	
	25th percentile	7.775	7.825	
	50th percentile	8.450	8.750	
	75th percentile	9.650	9.600	
Platelets	Mean	119.77	122.39	10^9/L
	Minimum	50	26	
	Maximum	271	252	
	25th percentile	95.50	99.25	
	50th percentile	115.00	114.00	
	75th percentile	144.00	143.00	

In table 7 below, administered products from injury until arrival at IALCH are illustrated. In the medical records and the database, no records of administration of autotransfusion or administration of tranexamic acid, calcium and magnesium before arrival were found, therefore this was not presented in table 7. The minimum amount of each administered products in each group was 0.

Table 7 Administered products from injury until arrival on IALCH

Group descriptions	**Group nr**	**A**	**B**	**Units**
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of patients	35	38	
FDP	Nr of patients administered	9 (25.7%)	17 (44.7%)	Units (1 unit = 200 ml)
	Mean	0.66	1.82	
	Maximum	6	13	
PRBC	Nr of patients administered	12 (34.3%)	17 (44.7%)	Units (1 unit = 300 ml
	Mean	0.93	1.47	
	Maximum	6	9	
Platelets	Nr of patients administered	1 (2.9%)	2 (5.3%)	Units (1 unit = 250 ml)
	Mean	0.03	0.08	
	Maximum	1	2	
Cryoprecipi-tate	Nr of patients administered	1 (2.9%)	1 (2.6%)	Units
	Mean	0.23	0.26	
	Maximum	8	10	
Ringers Lactate	Nr of patients administered	18 (51.4%)	24 (63.2%)	Units (1 unit = 1 000 ml
	Mean	1.557	1.829	
	Maximum	5	10	
Voluven	Nr of patients administered	10 (28.6%)	10 (26.3%)	Units (1 unit = 500 ml)
	Mean	0.486	0.539	
	Maximum	3.0	4.0	
NaCl	Nr of patients administered	1 (2.9%)	2 (5.3%)	Units (1 unit = 1 000 ml)
	Mean	0.006	0.066	
	Maximum	0.2	1.5	

In table 8, administered products during the first 24 hours after admission to IALCH are illustrated. The minimum amount of each administered products in each group was 0. For one patient, there was a note in the medical records informing that the patient had been administered with crystalloids. The amount and type of crystalloids transfused were not registered, therefore no data for Ringers Lactate and NaCl was recorded for this patient, thereby resulting in missing data regarding Ringers Lactate and NaCl for this patient. For this reason, percentage for the number of patients administered is not illustrated for Ringers Lactate and NaCl. Percentiles for the administered products are only demonstrated when at least 50 % of the patients in both ratio groups have been administered with the product.

Table 8 Administered products during the first 24 hours after admission to IALCH

Group descriptions	**Group nr**	**A**	**B**	**Units**
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of patients	35	38	
FDP	Nr of patients administered	29 (82.9%)	35 (92.1%)	Units (1 unit = 200 ml)
	Mean	2.60	4.55	
	Maximum	7	14	
	25th percentile	2.00	2.00	
	50th percentile	2.00	4.00	
	75th percentile	4.00	6.00	
PRBC	Nr of patients administered	30 (85.7%)	27 (71.1%)	Units (1 unit = 300 ml)
	Mean	2.843	1.842	
	Maximum	7	8	
	25th percentile	2.00	0.00	
	50th percentile	2.00	1.00	
	75th percentile	4.00	3.00	
Platelets	Nr of patients administered	10 (28.6%)	13 (34.2%)	Units (1 unit = 250 ml)
	Mean	0.31	0.39	
	Maximum	2	2	
Cryoprecipi-tate	Nr of patients administered	7 (20.0%)	7 (18.4%)	Units
	Mean	1.77	1.55	
	Maximum	10	10	

Calcium	Nr of patients administered	16 (45.7%)	22 (57.9%)	Ampoules (1 ampoule = 10 ml 10 % Ca)
	Mean	1.54	2.42	
	Maximum	6	12	
Magnesium	Nr of patients administered	21 (60.0%)	16 (42.1%)	Ampoules (1 Ampoule = 2 ml 50% Mg)
	Mean	1.63	1.53	
	Maximum	4	6	
Ringers Lactate	Nr of patients administered	25	29 (76.3%)	Units (1 unit = 1 000 ml
	Mean	1.2176	1.4316	
	Maximum	7.50	4.00	
	25^{th} percentile	0.000	0.375	
	50^{th} percentile	1.000	1.000	
	75^{th} percentile	2.000	2.125	
Voluven	Nr of patients administered	16 (45.7%)	18 (47.4%)	Units (1 unit = 500 ml)
	Mean	0.760	0.816	
	Maximum	3.0	4.0	
NaCl	Nr of patients administered	1	1 (2.6%)	Units (1 unit = 1 000 ml)
	Mean	0.06	0.03	
	Maximum	2	1	

In table 9, administration of tranexamic acid and autotransfusion during the entire length of stay is illustrated.

Table 9 Autotransfusions and administration of tranexamic acid at IALCH

Group descriptions	**Group nr**	**A**	**B**
	Ratio	FDP ≤ PRBC	FDP > PRBC
	Nr of patients	35	38
Autotransfusion	Nr of patients administered	2 (5.7%)	3 (7.9%)
Tranexamic acid	Nr of patients administered	6 (17.1%)	3 (7.9%)

In table 10, the number of units of FDP and PRBC transfused from injury until 24 hours after admission to IALCH, are illustrated.

Table 10 Administered FDP and PRBC from injury until 24 hours after admission

Group descriptions	Group nr	A	B	Units
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of patients	35	38	
FDP	Mean	3.26	6.37	Units (1 unit = 200 ml)
	Maximum	7	15	
	25th percentile	2.00	4.00	
	50th percentile	2.00	5.50	
	75th percentile	5.00	8.00	
PRBC	Mean	3.771	3.316	Units (1 unit = 300 ml
	Maximum	7.0	11.0	
	25th percentile	2.00	1.00	
	50th percentile	4.00	3.00	
	75th percentile	6.00	5.00	

Illustrated in table 11 below are the frequencies of consequences of trauma and complications due to trauma care among the two ratio groups during the entire length of stay. Fisher's Exact significance 2-sided test generated the p-value 0.60 when analysing hypothermia at arrival.

Table 11 Consequences of trauma and complications due to trauma care during the entire length of stay

Group descriptions	Group nr	A	B
	Ratio	FDP ≤ PRBC	FDP > PRBC
	Nr of patients	35	38
Hypothermia at arrival	Yes	13 (37.1%)	6 (15.8%)
	No	22 (62.9%)	32 (84.2%)
Hypothermia after 24 h[a]	Yes	0 (0%)	3 (8.3%)
	No	30 (100%)	33 (91.7%)
Acidosis at arrival[b]	Yes	7 (20.6%)	8 (21.1%)
	No	27 (79.4%)	30 (78.9%)
Acidosis after 24 h[a]	Yes	0 (0%)	1 (2.9%)
	No	30 (100%)	34 (97.1%)
VAP[c]	Yes	6 (17.1%)	4 (10.5%)
	No	29 (82.9%)	34 (89.5%)
Sepsis	Yes	7 (20.0%)	8 (21.1%)
	No	28 (80.0%)	30 (78.9%)

a. Patients missing because of death or missing data in medical records
b. Patients missing because of missing data in medical records
c. VAP = Ventilator associated pneumonia

Mortality

In this section, descriptive and analytical statistics related to the following research question will be demonstrated: how do different ratios of FDP and PRBC transfused to trauma patients until 24 hours after admission to the trauma ICU affect mortality. In group A, 11 (31.4%) of the 35 patients expired. In group B, 11 (28.9%) of the 38 patients expired. In table 12, descriptive analytical statistics of expired patients are presented. Independent-samples Mann-Whitney U test showed no significant difference in distribution of ISS among expired patients across group A and group B (p = 0.171). As mentioned in the text describing figure 3, two patients in group A had ISS 75. Both these patients expired at the day of arrival. Fischer's Exact 2-sided Test was used to compare the two mortality time intervals 0-7 days and 8-14 days between for the two group ratio groups. This test generated the p-value 0.152.

Table 12 Mortality

Group descriptions	**Group nr**	**A**	**B**	**Fischer's Exact Test (2-sided)**
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of expired patients	11	11	
ISS[a]	Minimum	26	18	
	Maximum	75	51	
	25th percentile	27.00	18.00	
	50th percentile	43.00	35.00	
	75th percentile	64.00	50.00	
Days of survival	Mean	9.82	6.91	
	Minimum	0	1	
	Maximum	51	19	
	25th percentile	1.00	2.00	
	50th percentile	5.00	8.00	
	75th percentile	16.00	9.00	
24-hour mortality	Expired (<24 h[b])	5 (45.5%)	2 (18.2%)	
	Expired (>24 h[c])	6 (54.5%)	9 (81.8%)	
Days of survival (Categorised)	0-7	7 (63.6%)	5 (45.5%)	0.152
	8-14	1 (9.1%)	5 (45.5%)	
	≥15	3 (27.3%)	1 (9.1%)	

a. ISS = Injury Severity Score
b. Expired within 24 hours after arrival
c. Expired 24 hours after arrival or later

The number of days treated

In this section, descriptive and analytical statistics related to the following research question will be demonstrated: how do different ratios of FDP and PRBC transfused to trauma patients until 24 hours after admission to the trauma ICU affect the number of days treated at the trauma ICU at IALCH. All the results presented in this section are based on surviving patients only. In table 13, descriptive and analytical statistics for surviving patients are presented. Independent-samples Mann-Whitney U test showed no significant difference in distribution of ISS among surviving patients across group A and group B ($p = 0.151$). Pearson's Chi-Squared Exact Significance (2-sided) Test was used to analyse the number of days treated with categorised time intervals. This test generated the p-value 0.277.

Table 13 Number of days treated for surviving patients

Group descriptions	**Group nr**	**A**	**B**	**Pearsons Chi-Squared Exact Significance (2-sided) Test**
	Ratio	FDP ≤ PRBC	FDP > PRBC	
	Nr of patients	24 (100%)	27 (100%)	
ISS[a]	Minimum	9	10	
	Maximum	41	68	
	25th percentile	16.25	18.00	
	50th percentile	25.00	30.00	
	75th percentile	35.50	43.00	
Number of days treated	Mean	20.08	15.04	
	Minimum	2	2	
	Maximum	130	47	
	25th percentile	8.25	4.00	
	50th percentile	11.00	11.00	
	75th percentile	24.50	24.00	
Number of days treated (Categorised)	1-7	4 (16.7%)	10 (37.0%)	0.277[b]
	8-14	9 (37.5%)	8 (29.6%)	
	≥15	11 (45.8%)	9 (33.3%)	

a. ISS = injury Severity Score
b. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.59.

The number of days treated for all surviving patients in the study population are illustrated in the histogram in figure 4. Among the surviving patients, the lowest number of days treated were 2 days and the highest number of days treated were 130 days.

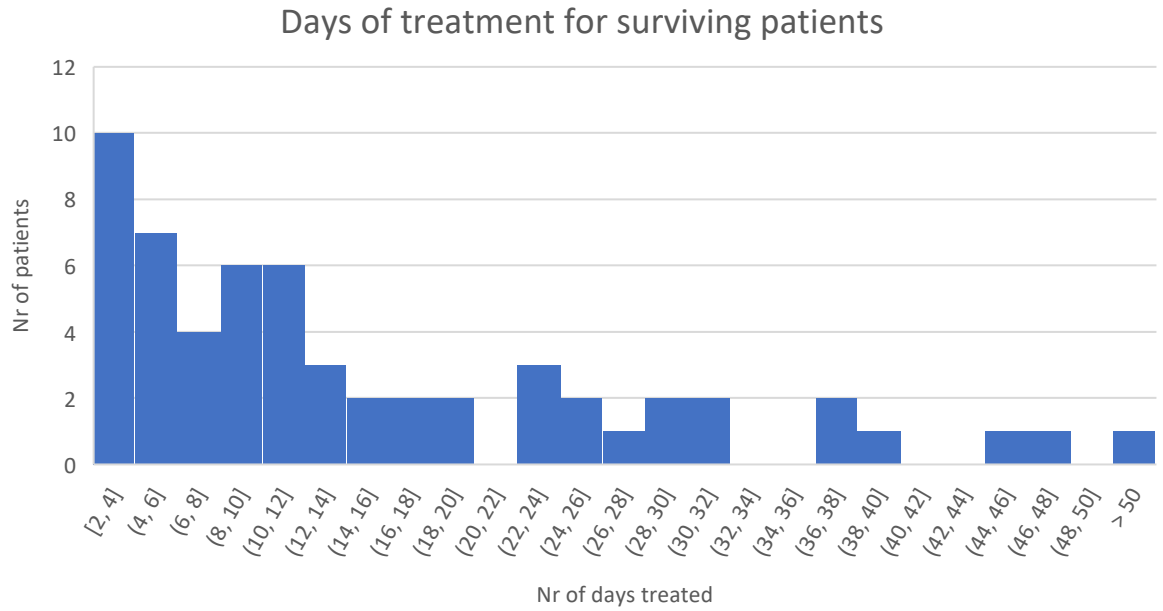

Figure 4 Number of days treated for surviving patients

The box plot in figure 5 illustrates ISS for surviving patients depending on the number of days treated categorised into time intervals.

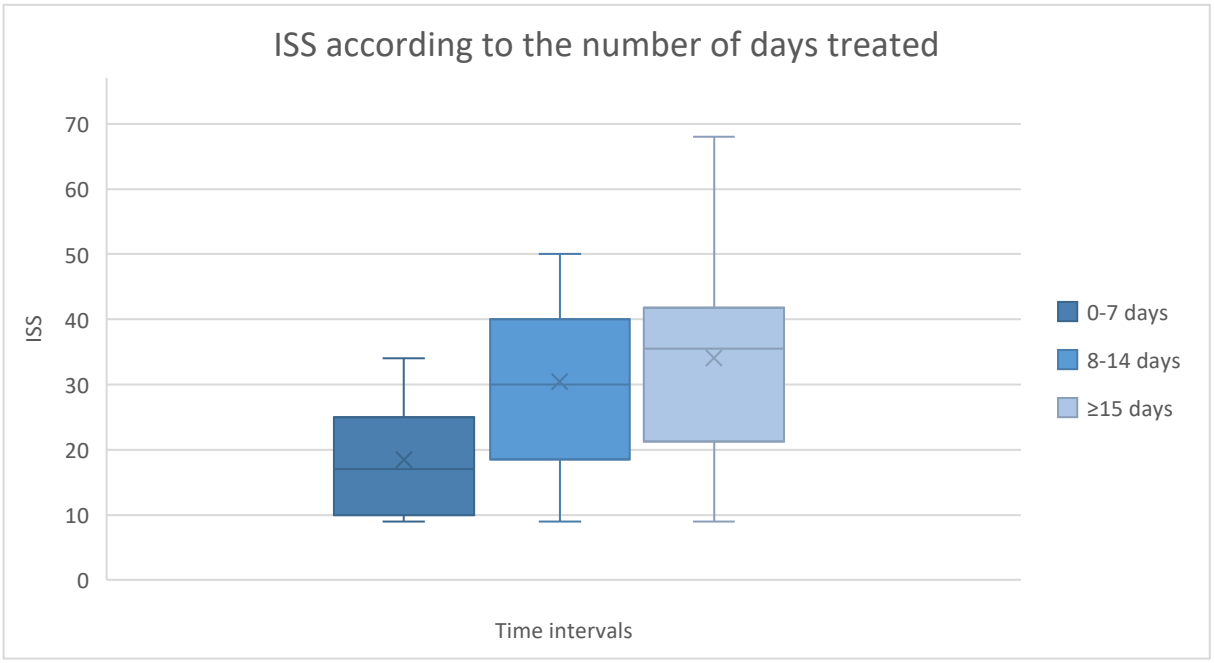

Figure 5 ISS for surviving patients according to the number of days treated. ISS = Injury severity score

Transfusion related complications

In this section, descriptive and analytical statistics related to the following research question will be demonstrated: how do different ratios of FDP and PRBC transfused to trauma patients until 24 hours after admission to the trauma ICU correlate to the frequency of AKI, TRALI, ARDS and MODS. In table 14, transfusion related complications that occurred 24 hours after arrival or later among patients that survived more than 24 hours are presented. Multiple patients developed AKI within 24 hours after admission and therefore they are not included in this chart. No patients developed TRALI, ARDS or MODS within 24 hours after admission. The frequencies of the transfusion related complications were too few in order to apply analytical statistic tests. One case of TRALI was suspected and considered likely and therefore registered, however TRALI was not definitely confirmed.

Table 14 Transfusion related complications that occurred 24 hours after arrival or later among patients that survived >24 hours

Group descriptions	**Group nr**	**A**	**B**
	Ratio	FDP ≤ PRBC	FDP > PRBC
AKIN	Yes	3 (13.0%)	1 (3.6%)
	No	20 (87.0%)	27 (96.4%)
TRALI	Yes	0 (0%)	0 (0%)
	No	30 (100%)	36 (100%)
ARDS	Yes	1 (3.3%)	0 (0%)
	No	29 (96.7%)	36 (100%)
MODS	Yes	2 (6.7%)	3 (8.3%)
	No	28 (93.3%)	33 (91.7%)

AKIN = Acute Kidney Injury Network
TRALI = Transfusion Related Acute Lung Injury
ARDS = Acute Respiratory Distress Syndrome
MODS = Multiple Organ Dysfunction Syndrome

Discussion

Result oriented considerations

Introduction to discussion and discussion of sample statistics

In this section, the most important findings will be mentioned and the characteristics of the samples will be discussed. As shown in the result section, there were no significant differences regarding how the two different ratios of FDP and PRBC affect mortality and the number of days treated. The number of transfusion related complications were too few in order to perform analytical statistical tests. Under the following sections below, each research question will be discussed further. Regarding the sample characteristics, an important factor is that the two sample groups should be quite homogenous. The reason for this line of argument is that many other factors than the ratio of FDP and PRBC might affect the outcomes investigated. Slighter differences were found in some of the collected variables. These variables and other important variables will accordingly be discussed. Regarding *ISS*, there was no significant difference between the two ratio groups ($p = 0.619$). Figure 2 (ISS according to gender) shows that most patients, namely 35 patients, had ISS 26-50 and fewest patients, namely 9 patients, had ISS 51-75. This figure also shows that the distribution of gender among the different ratio groups is quite equal. As described for figure 3 (ISS according to sample groups), two patients in group A had ISS 75, the highest ISS possible, which correlates to increased risk for mortality. Concerning *age* and *gender*, no significant difference in analytical statistical tests were found ($p = 0.782$ respectively $p = 0.795$). Figure 1 (Age according to gender) shows even distribution of gender among different age categories.

Regarding *haemoglobin* at arrival, table 5 (Blood parameters at arrival) shows that the mean value for group A is 8.767 g/dL while the mean value for group B is 10.242 g/dL. In addition to the mean value, all percentiles are also higher for group B than for group A. This might

reasonably be a contributing factor to the division of the ratio groups. In group A, a bigger share of the patients most likely fulfilled the indications for transfusion of PRBC, thereby contributing to more or equal units of transfused PRBC compared to FDP. Table 6 (Blood parameters 24 hours after arrival) shows that both mean values and percentiles of haemoglobin 24 hours after arrival are equalized, likely due to greater shares of PRBC transfusions in group A compared to group B. Concerning administration of *tranexamic acid*, which can contribute to decreased haemorrhage, table 9 (Autotransfusions and administration of tranexamic acid at IALCH) shows that 6 patients in group A were administered with tranexamic acid while 3 patients in group B were administered. Accordingly, twice as many patients were transfused in group A compared to group B, however the absolute numbers were too few to apply analytical statistical tests. Finally, regarding *hypothermia*, table 11 (Consequences of trauma and complications due to trauma care during the entire length of stay) shows that 13 patients in group A and 6 patients in group B had hypothermia at arrival. Fisher's Exact significance 2-sided test showed no significant difference between the two ratio groups regarding hypothermia at arrival ($p = 0.60$). Regarding hypothermia after 24 hours, 0 patients in group A and 3 patients in group B were positive. As described, there sometimes were trends pointing towards differences in relevant factors, however none of these trends showed statistical significance. This fact therefore enables comparison of the two ratio groups regarding the research questions.

Mortality

The results related to mortality are illustrated in table 12 (Mortality). As previously mentioned, there was no significant difference regarding how the two different ratios of FDP and PRBC affect mortality. The number of expired patients in group A was 11 (31.4 %) out of 35, and in group B the number of expired patients was 11 (28.9 %) out of 38. Regarding ISS for the expired patients, all percentiles and the maximum value were higher for group A than for group B. In group A, two patients had ISS 75, and both these patients expired at the day of arrival. In group

A, totally 5 patients (45.5 % of the expired patients) expired within the first 24 hours after arrival, compared to 2 patients (18.2 % of the expired patients). As shown in table 12, for group A, 7 patients expired within 0-7 days, 1 patient within 8-14 days and 3 patients after 15 days or more. For group B, the number for the different intervals enumerated in the same order are 5, 5 and 1. Since expiration related to or affected by coagulopathy, haemorrhage and transfusion was considered unlikely ≥ 15 days after admission, the patients that expired ≥ 15 days after arrival were not included when Fischer's exact test was used to analyse mortality. Seen to the descriptive statistics, a bigger share of the patients in group A expired early (within 0-24 hours after admission and during the first 7 days after admission) compared to group B. A possible explanation to this might be the two patients with ISS 75 in group A with poor survival prognosis.

As mentioned in the background, most of the studies investigating plasma:PRBC ratios are based on data from patients receiving massive transfusion and FFP as the choice of blood plasma. Therefore, articles that focus on FFP:PRBC ratios are applied in the discussion. A meta-analysis published 2013 investigated how different ratios of plasma:PRBC in trauma patients receiving massive transfusions affect 30-day mortality. This study showed that plasma:RPBC ratios of 1:2 or higher significantly reduced the mortality in relation to ratios lower than 1:2. However, ratios of 1:1 were not more advantageous than 1:2 ratios (49). Zink *et al.* also showed that ratios of FFP:PRBC higher than 1:2 correlated to higher survival rates compared to ratios lower than 1:2 (50). Many studies have shown similar results as those mentioned above. It seems like ratios higher than 1:1 have been studied in limited extent (4, 13, 24, 31, 32, 41). Maegele *et al.* however, compared ratios FFP:PRBC ratios < 1:1, 1:1 and > 1:1 among patients that received massive transfusions and proved that ratios higher than 1:1 increased 6-hour, 24 hour and 30-day survival compared to lower ratios (51).

The number of days treated

As mentioned earlier, there was no significant difference regarding how the two different ratios of FDP and PRBC affect the number of days treated. As mentioned in the results section, all results concerning the number of days treated are based on data for surviving patients only. The results related to the number of days treated are illustrated in table 13 (Number of days treated for surviving patients), figure 4 (Number of days treated for surviving patients) and figure 5 (ISS for surviving patients according to the number of days treated). Regarding ISS for the surviving patients, all ISS percentiles were higher for group B compared to group A, however there was no significant difference across the two groups ($p = 0.151$). As shown in figure 5, ISS also increases in relation to longer lengths of stays for the entire study population, which is a reasonable and logical tendency since higher ISS correlate to more severe injuries. The median value for the number of days treated for surviving patients was 11 for both group A and group B. In group A, only 16.7 % of the surviving patients were treated for 1-7 days, while 37.0 % of the surviving patients in group B were treated for 1-7 days. Group B also had relatively fewer patients treated for 8-14 days and ≥15 days than group A (see table 13). Seen to these descriptive statistics in this study population, higher ratios of FDP and PRBC seemed to correlate with fewer days of treatment. This trend is contradictory since all ISS percentiles were higher for group B than for group A. However, there was no significant difference between the two ratio groups regarding the number of days treated and ISS. In the previously mentioned study by Maegele *et al.* ratios of FFP:PRBC higher than 1:1 increased the length of stay and the number of ventilator days (51). Similar findings were made in a study by Sambasivan *et al.* where FFP:PRBC ratios higher than 1:2 correlated with fewer ICU-free days and ventilator-free days (52).

Transfusion related complications

The results concerning transfusion related complications are illustrated in table 14 (Transfusion related complications that occurred 24 hours). Regarding the *transfusion related complications*, the number of patients positive with AKI, TRALI, ARDS and MODS ≥ 24 hours after admission were too few to perform any statistical tests. Multiple patients developed AKIN before arrival or during the first 24 hours after admission. Since the patients were allocated to a specific ratio group first 24 hours after arrival, it would only be relevant to conduct statistical tests on the transfusion related complications that occurred ≥24 hours after admission. An important fact to consider is that, especially for AKI and MODS, there are multiple other risk factors than transfusions for these syndromes (48) (53). AKI and MODS were the complications with highest frequency in this study, however it is not unlikely that these cases could have been generated by other aetiologies than transfusions. Murad *et al.* showed that for patients receiving massive transfusions, ratios of FFP:PRBC greater than 1:3 correlate to lower frequency of multiorgan failure, though the quality of the findings was low (54). The study by Maegele *et al.* instead discovered that the frequency of organ failure was higher for trauma patients transfused with FDP:PRBC ratios of 1:1 compared to higher and lower ratios (51).

No cases of TRALI and one case of suspected ARDS were recorded. In one study, the frequency of adverse reactions due to plasma transfusion was set to one reaction per 300 to 1,700 administrations (55). A study investigating risk factors for TRALI, showed that plasma and platelets were the blood products that were most likely to cause TRALI (56). Regarding ARDS, high ratios of FFP to PRBC has been suggested to correlate with higher risk of developing ARDS (57). However, another study suggests that high ratios of FFP:PRBC is not correlated to either TRALI or ARDS, even for patients who did not receive massive transfusions (58).

Methodological considerations

As mentioned in the introduction, studies on transfusion ratios can be associated with methodological difficulties. Because of ethical and practical reasons, prospective trials are challenging to conduct, thereby advocating retrospective studies. This study was a retrospective chart review based on information retrieved from medical records and a database. In medical records, information important for the patient care might be recorded properly whereas information important for study purpose might not be recorded adequately or not at all, since this is not the primary purpose for the medical records. For some parameters there was sometimes missing or conflicting data in the medical records. In addition, scanned documents could sometimes be hard to interpret. This occasionally led to difficulties in estimating the exact amount or number of units of fluids, blood products and medicine that had been administered. This could lead to difficulties or possibly even incorrectness in estimating which ratio of FDP and PRBC patients had received. Lack of data, especially from referral letters or ambulance forms, could possibly result in that a patient who actually had been transfused with FDP and PRBC was not included in the study since no information about transfusions could be found. This possibility of under coverage would mean that the study population is not completely representative. Occasionally, the date but not the exact time of injury was known. In these cases, a basic assessment based on other parameters was made to evaluate if the patient most likely was admitted to IALCH within 24 hours after injury or not. Regarding diagnoses, the diagnoses were mentioned in reports and discharge summaries, though no ICD codes could be retrieved. This could possible lead to under coverage of complications. Despite these issues, there was generally adequate and correct data to be retrieved for many of the patients. Still, overall the quality of the collected data is not as high as preferable.

Except for data related matters, methodological and analytical factors must be concerned. The aim of the study was to investigate how different ratios of transfused FDP and PRBC affect different outcomes. However, there are multiple other factors than the ratio of FDP:PRBC that affect the outcomes, for example the type of trauma, the severity of the injury or injuries, time from trauma until treatment, management of the trauma, physiological capacity and reserves, unexpected complications etc. Futility is a term which alludes to that the patient's condition and prognosis are so poor that the patient will expire regardless option of treatment. Futility can be a difficult factor to manage when studying mortality since too high frequency of futility might conceal the effect that the preferred independent variable (transfusion ratios in this study) has on mortality. Exclusion criteria were designed to prevent inclusion of patients with futility. However, it is hard to formulate exclusion criteria that completely prevent all futility, especially without risking excluding patients without futility. For example, two patients with ISS 75 were included in group A and both these patients expired at the day of arrival. Another complicated factor to consider is that after the surviving patients have been treated at the TICU at IALCH, they are either transferred to a primary or secondary hospital or to their home. After the transfer it is not possible to track the number of days treated, mortality or transfusion related complications. For practical and economic reasons, patients with poor prognosis and high probability of near expiration or patients with palliative treatment can be transferred to their local hospital for terminal treatment. In these cases, possible positive outcomes cannot be recorded. One of the included patients had bad prognosis and high probability to expire and was sent back to base hospital. Since this study was retrospective, the patients were not randomised to a specific ratio. Therefore, there is a probability that hidden confounders could contribute to which amount and ratios of FDP and PRBC that the patients receive. In advance, a confounder considered possible, was that severely injured patients with major haemorrhage and coagulopathy would receive massive transfusions and therefore receive equal units of FDP

and PRBC. Consequently, these patients would end up in group A and likely have worse outcomes than the other groups because of poorer initial condition and prognosis. However, this scenario was not realized in this study. A possible confounder though, is that FDP occasionally is administered instead of cryoprecipitate. Which of these products that were used clinically could possibly affect which ratio group a patient finally was allocated to. Lack of blood products could likely have the same effect.

The duration demanded for collecting data was greater than expected, resulting in a smaller study population than planned. As described earlier there are sometimes signs of trends or differences that are not statistically significant. If the number of participants would have been greater significant differences might would have been detected if there were any.

Strengths in this study are that many variables were collected which might increase the probability of detecting confounders. Another strength is that only two persons collected data for a short period of time, thereby reducing the risk for methodical errors.

Suggestion on further studies

Since there are few studies investigating how different ratios of FDP and PRBC affect mortality, the number of days treated and transfusion related complications, there is great potential for research within this field. In future studies comparing ratios of FDP and PRBC there are multiple factors that can be considered and improved. One of the most important factors might be to investigate a significantly greater study population in order to achieve greater power. Accurate power calculations should be made so that sufficient number of participants can be included. Considerably longer time for data collection could also be preferable in order to obtain greater numbers. Instead of a retrospective study design a prospective study design would be eligible. The advantages for a prospective study design are that recording would be more reliable and adapted for study purpose and that confounders and factors that might affect the outcomes are easier to track. During the initial phase of the trauma where the number of transfused FDP and PRBC affect which ratio group the patient is allocated to, no cryoprecipitate should be used since it has similar effects on coagulation as FDP has. Patients might also be tracked for a longer time period and over different health care institutions regarding the outcomes, alternatively only short-term outcomes could be investigated. The number of patients in the different ratio groups would preferably also be equal in numbers to increase the power.

Conclusions

No significant differences between the groups were found. Therefore, no general conclusions regarding FDP:PRBC ratios for trauma patients could be drawn. Additional studies with greater numbers of patients will be required to further evaluate the impact of different ratios of FDP and PRBC transfused to trauma patients.

Populärvetenskaplig sammanfattning

Rubrik: Frystorkad plasma och ogynnsamma utfall

Underrubrik: En journalstudie som undersöker förekomsten av ogynnsamma utfall hos traumapatienter i förhållandet till proportionerna av frystorkad plasma och röda blodkroppar som patienterna behandlats med

Sammanfattning: I denna studie undersöktes behandlingseffekten av olika förhållanden av röda blodkroppar och frystorkad plasma som givits till traumapatienter. Röda blodkroppar och plasma kan utvinnas från blodet från blodgivare. Plasma kan beskrivas som den del av blodet som innehåller koagulationsfaktorer, vilka är ytterst viktiga för att blodets normala förmåga att koagulera (levra sig). För att kunna förvara och sedan använda plasman, kan plasman tillredas och behandlas på olika sätt. Traditionellt används färskfrusen plasma, men det finns också en annan form av plasma i pulverform som heter frystorkad plasma (på engelska freeze-dried plasma: FDP). De stora fördelarna med FDP är att den kan förvaras i omgivningstemperatur, har lång hållbarhet, är lätt att transportera och endast behöver blandas med sterilt vatten innan den ska ges till en patient. Användningen av FDP inom sjukvården har varit begränsad men dess många fördelar har ökat intresset för användning inom sjukhusvård och ambulanssjukvård. Traumapatienter kan ibland behöva behandlas med både FDP och röda blodkroppar för att ersätta förlorad blodvolym och behandla försämrad koagulationsförmåga, blödning och brist på röda blodkroppar. När traumapatienter är allvarligt skadade och stora mängder blodprodukter behövs brukar man eftersträva att ge patienten lika många enheter FDP som röda blodkroppar. Det är dock omtvistat vilket förhållande av FDP och röda blodkroppar som är mest optimalt. Syftet med denna studie var att undersöka hur olika förhållanden av FDP och röda blodkroppar påverkar olika förutbestämda faktorer, nämligen: antalet vårddagar, dödlighet och förekomsten av komplikationer från blodprodukterna. Studien genomfördes på en traumavårdsenhet på Inkosi Albert Luthuli Central Hospital i Durban (IALCH) i Durban, Sydafrika, där man sedan

flera år tillbaka använt FDP. Data samlades in från en lokal databas och medicinska journaler på traumavårdsenheten på IALCH. Patienterna delades in i två olika grupper beroende på vilket förhållande av FDP och röda blodkroppar de behandlats med. Patienterna i grupp A fick färre enheter FDP än röda blodkroppar eller lika många enheter FDP som röda blodkroppar, medan patienterna i grupp B fick fler enheter FDP än röda blodkroppar. Totalt inkluderades 73 patienter i studien. De statistiska tester som användes för att undersöka frågeställningarna visade inga signifikanta skillnader mellan grupperna, alltså går det utifrån denna studie inte att dra några slutsatser kring vilket förhållande av FDP och röda blodkroppar som är mest optimalt för traumapatienter. Ytterligare studier med större patientantal behöver genomföras för att ytterligare utvärdera effekten av olika förhållanden av FDP och röda blodkroppar som traumapatienter behandlas med.

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