Utilisation of emergency blood in a cohort of emergency centres in Cape Town, South Africa

by

David Morris

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Supervisors:

Dr SR Bruijns
Division of Emergency Medicine
University of Cape Town

Dr M Stander
Division of Emergency Medicine
University of Cape Town

Dr DJ van Hoving
Division of Emergency Medicine
University of Stellenbosch

Declaration

By submitting this dissertation electronically, I, declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature: …….. Date: December 2017

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List of Abbreviations

AIDS - Acquired Immunodeficiency Syndrome

FAST - Focussed Assessment with Sonography for Trauma

FDA - United States Food and Drug Administration

HIV - Human Immunodeficiency Virus

HREC -Health Research Ethics Committee

SANBS - South African National Blood Services

WPBTS - Western Province Blood Transfusion Services

WHO - World Health Organisation

ZAR - South African Rand

Part A: Literature review

Aim and objectives of this literature review

The aim of this literature review was to describe the various aspects surrounding the transfusion of uncrossmatched Group O blood in the hospital emergency centre. To achieve this aim the following objectives have been set:

- To describe the role of blood and blood products in the resuscitation of patients with haemorrhagic shock
- To describe the current utilisation of uncrossmatched Group O blood in emergency centres
- To describe the safety of, and risks associated with, transfusing uncrossmatched Group O blood
- To describe the availability of blood and blood products in a low or middle income setting and strategies to limit unnecessary use

This background information will be important to contextualise the findings of our study and to understand the factors which influence the decision to use and maintain availability of this resource.

Literature search strategy

The Stellenbosch University Medicine and Health Sciences Library website was used to perform searches and to obtain the original articles reviewed in this study. PubMed and Google Scholar were used to perform searches using the terms “emergency blood”, “uncrossmatched blood”, “blood transfusion” and “emergency department”, “emergency centre/room”. The terms “risks”, “indications” and “trauma” were added to the Boolean search terms to focus on specific areas of research. A “snowball” strategy was then used, whereby prominent articles cited in the papers obtained from the index search were also accessed and included in the review.

Inclusion criteria:

- Publication date: January 2000 - July 2016
- Language: English, including studies translated and published

Exclusion criteria:

- Studies outside of the stipulated timeframe
- Language other than English

- Studies focussed on very specific patient groups, eg Sickle Cell Disease or Malaria, were also excluded.

Quality criteria

Titles and abstracts were initially screened for relevance to the review and those deemed to have low relevance or poor external validity were excluded. High-quality evidence, including systematic reviews, was sought to address the aim and objectives. Papers were appraised against a checklist from the Oxford Centre for Evidence-Based Medicine. (Addendum C) A representation in tabular form of appraised papers is not required for the MMed and therefore was omitted. Very little data were available that directly addressed some parts of the aim and objectives – particularly with regards to the current practice of emergency blood transfusion in low and middle income settings – and thus criteria were applied less stringently here.

Terminology

"Emergency blood" is the term used to describe Group O blood stored for use in emergency situations without a crossmatch being performed. This is also referred to as "uncrossmatched blood" in the literature and the two terms have been used interchangeably in this article.

"Emergency centre" refers to a model in which all emergent conditions, including trauma, are seen and stabilised in one hospital unit before disposition to an admitting hospital team or discharge.

Review of the literature

The role of blood and blood products in the resuscitation of patients with haemorrhagic shock

The use of blood and blood products in the acute resuscitation of critically injured or haemorrhaging patients is an essential part of modern haemostatic resuscitation. The goals of haemostatic resuscitation are to restore circulating volume and tissue perfusion while preventing coagulopathy, acidosis and hypothermia. (1-3) Blood is the ideal fluid with which to restore circulating volume after blood loss, and the transfusion of red blood cells to the haemorrhagically shocked patient has been shown to improve perfusion and increase oxygen delivery to the tissues. (4) Growing awareness and concerns about the potentially harmful effects of intravenous fluids when used to treat haemorrhagic shock have led to a greater emphasis on the use of blood rather than crystalloid or other colloid to replace blood loss. The use of more than 1,5 litres of crystalloid in the emergency centre care of trauma patients has been identified as an independent risk factor for mortality. (5) The consequences of injudicious intravenous fluid use include dilutional coagulopathy, exaggerated inflammatory response, an increase in the incidence of acute lung injury and hypothermia; all of which are known to complicate the management of acutely ill patients. (5,6)

The pathophysiology of haemorrhage is complex and currently a focus of much research. The role of the endothelial glycocalyx in maintaining vascular integrity and the prevention of third space fluid

losses is increasingly being recognised, as is the deleterious effect of large crystalloid volumes on this glycocalyx. (7) As the glycocalyx is damaged by crystalloids, fluid moves into the tissues, causing oedema and injury rather than intravascular repletion. The disruption of the glycocalyx also causes local hypercoagulability and consumption of clotting factors with a resultant systemic coagulopathy. In addition to the coagulopathy prevalent as a result of resuscitation efforts, there is evidence that trauma itself results in coagulopathy which may be worse in a certain subset of patients. Haemostatic resuscitation looks to pre-emptively address this coagulopathy by limiting crystalloid volumes and by transfusing blood and blood products with a high ratio of plasma and platelets to packed red blood cells. (7) Raising the haematocrit by transfusion of red blood cells also assists in achieving haemostasis, possibly due to the release of platelet activating factor from the red blood cells, but also due to the increase in viscosity with haematocrit. (5)

Red blood cells used for transfusion are but one component of whole blood. The transfusion of large quantities of red blood cells alone will alter the constituency and clotting profile of the recipient's blood and they thus need to be combined with other blood products in a massive transfusion. The commonly quoted empiric ratio for the transfusion of blood products is one unit of platelets to one unit of fresh frozen plasma to one unit of red blood cells (1:1:1). However, this was not shown to be superior to a 1:1:2 ratio at 24 hours or 30 days when mortality was considered, despite improved haemostasis within 24 hours. (8,9,10) From the available evidence it appears that a ratio of fresh frozen plasma to red blood cells of 1:3 or less denotes an inflection point where patient mortality significantly decreases. (11) The ideal ratio of blood products in transfusion is likely to vary between individuals and disease conditions and should be guided by clinical as well as laboratory parameters, such as the viscoelastical haemostatic assays: thromboelastography and rotational thromboelastometry. (10-12) The viscoelastical assay allows the clinician to individualise blood product requirements by specifically identifying reduced platelet function, low fibrinogen or hyperfibrinolysis as a cause for poor clot strength. (12)

The emergency centre is often the place where blood transfusion is commenced, and a significant proportion of those requiring emergent transfusion with uncrossmatched blood go on to require massive transfusions. Indeed, the need for uncrossmatched blood in the emergency centre has been suggested as a predictor for those likely to require massive transfusion. (13) This highlights the need for the availability of blood in the emergency centre and the role of emergency physicians as stewards of this resource.

Current utilisation of uncrossmatched Group O blood in emergency centres

Very few studies have been done internationally to describe the patterns of utilisation of emergency blood in the emergency centre and the indications for which it is transfused, making it difficult to establish the current standard of care. In a trauma focussed study, Como, et al. of the R. Adams Cowley Shock Trauma Centre in Maryland, the largest integrated trauma system in the United States,

described their utilisation of blood transfusion for the year 2000. (14) They were able to link Blood Bank and Trauma Registry data to look for associations between injury severity score, transfused blood products and patient outcomes. They showed that 8% of their acute trauma patients received red blood cells. About one third of those receiving red blood cells were given at least one unit of uncrossmatched blood while waiting for crossmatched blood. The most uncrossmatched blood given to one patient was fourteen units. Mortality in those treated with uncrossmatched blood approached 45%, indicating the acuity of this subset of patients. They reported three cases where more than 100 units of red blood cells were transfused, with one of these patients surviving. Important associations from this study were an increase in the amount of blood required with an increase in the injury severity score and an increase in mortality with increasing volumes of blood. While the association between amount of blood and mortality was stronger than the association between injury severity score and mortality, the degree of confounding was not clearly defined. They also noted that in those receiving more than 10 units of blood there was a significant increase in mortality and suggest that this volume should be an indicator of a specific subset of patients at risk. The average number of red blood cells required by those receiving more than 10 units was 25 units. In the group receiving more than 10 units, 71% were male, 79% suffered blunt trauma and the mean injury severity score was 32. The type of patients dealt with were mainly polytrauma, limiting their ability to differentiate the indications for which blood was needed, but they did notice an association with abdominal and pelvic trauma and the need for larger transfusions. (14)

Despite the widespread acceptance and use of uncrossmatched blood in emergency centres, diligent search was not rewarded with other research describing this use and the accepted indications thereof. There has been more research interest on the indications for massive transfusion. As massive transfusion is often commenced with uncrossmatched blood the groups share some characteristics. An Australian study describing the indications for massive transfusion in their trauma centre showed that the majority of patients were involved in motor vehicle collisions (72%), whilst the other common indications were pedestrian traffic accidents (10%) and patients with penetrating trauma, in the form of stab and gunshot wounds (6%). Factors associated with the need for massive transfusion included initial systolic hypotension, initial low platelet count, metabolic acidosis and a haemoperitoneum on Focussed Assessment with Sonography for Trauma (FAST). (15)

The indications for massive transfusion in a tertiary South African hospital were studied in 2010 by Visser, et al. (16) Trauma accounted for 33% of the cases, with polytrauma, 13% the largest group, followed by motor vehicle accidents, 10% and penetrating trauma, 7%. The other major indications included obstetric conditions, 20% of the total (including postpartum haemorrhage, 13%), general surgical conditions, 20%, (including upper gastrointestinal bleeding 7% and perioperative bleeding 13%) and cardiothoracic surgical conditions, 7%. The mechanism of polytrauma was not defined and it would seem that there would be some overlap between polytrauma and motor vehicle accidents. These indications recur in the massive transfusion literature; in a general medical centre in Pittsburgh, McDaniel, et al. studied the indications for which immediate release red blood cells were ordered in

large quantities. They found that trauma was the indication in 61% of cases. Of the non-traumatic indications 33% had gastrointestinal bleeding, 9% “medical bleeding for other reasons”, 28% post-surgical or procedural complications and 28% vascular emergencies. (17) These numbers were similar to a Los Angeles medical centre studying massive transfusions at their facility, which found that trauma was the indication for 62% of their massive transfusions. Of the non-traumatic indications, 56% were accounted for by gastro-intestinal bleeding, 23% obstetric haemorrhage including postpartum bleeding and 11% unexpected bleeding following elective or emergency surgery. (11)

The safety of, and risks associated with, transfusing uncrossmatched, Group O blood

While the benefits of blood transfusion in certain patients are clear, the rate of complications associated with blood transfusion in general is likely higher than is commonly recognised. Specific transfusion reactions may be readily noticeable, but various other effects of blood transfusion, including those on the immune system, are more difficult to detect. In a large systematic review of blood transfusion in critically ill intensive care unit, trauma and surgical patients, Marik, et al. showed an association between blood transfusion and increased morbidity, including infectious complications, (pooled odds ratio 1.8, 95% confidence interval 1.5–2.2) acute respiratory distress syndrome (pooled odds ratio 2.5, 95% confidence interval 1.6–3.3), and mortality (pooled odds ratio 1.7, 95% confidence interval 1.4-1.9). While the mechanisms of harm were not elucidated by this study, the authors suggest that immunomodulation as a result of red blood cell transfusion plays a large role. Confounding factors were not clearly defined and further research is needed to determine to what degree the blood transfusion itself or the finding of anaemia in critically ill patients lead to the above complications, but these findings place significant responsibility on the clinician making the decision to transfuse blood to evaluate the necessity of this therapy in each case and weigh the benefits against the risks. (18)

The South African National Blood Services (SANBS) reported a total of 963 cases of transfusion related complications for over a million units transfused in 2014, equivalent to a rate of 83,5 events per 100,000 issues. (19) These data are for all transfusions; uncrossmatched transfusions were not evaluated separately. The most commonly reported transfusion reactions in the 2014 SANBS haemovigilance report are: febrile non-haemolytic transfusion reactions, 36% (n=347), allergic reactions, 31,6% (n=304) (of which 5,5% (n=53) were anaphylactic), transfusion associated dyspnoea, 8,3% (n=80), hypotensive reactions 5,9% (n=57) followed by the rare but far more serious acute haemolytic transfusion reactions 1% (n=10) and transfusion related acute lung injury 0,2% (n=2). While the reported data are carefully assessed and specimens examined for evidence of transfusion reaction by the SANBS, they rely on a passive reporting system. A passive reporting system requires clinical staff from the hospitals to notify the SANBS of the occurrence of a possible transfusion reaction, whereas an active system would include an ongoing surveillance mechanism. Due to the critically ill nature of the recipients of emergency blood the incidence of transfusion complications

may very well be underreported. Even of the cases that are reported to the SANBS, there are often not samples available to confirm the occurrence of a transfusion reaction. (19)

16 cases of mortality were reported to the SANBS in 2014 where blood transfusion was suspected to be contributory to the adverse outcome (1,4 cases per 100 000 units). Following investigation, transfusion was excluded as a cause of death in 7 cases, transfusion was considered a possible cause in 7 cases and transfusion was considered to be contributory in 2 cases. (19) Internationally, the direct attribution of mortality to transfusion is also rare. The most frequently reported causes of transfusion-related mortality are transfusion related acute lung injury (1 case per 50,000 units transfused), transfusion associated sepsis (6,9 cases per million units transfused) and haemolytic transfusion reactions (1 case per 250,000 to a million units transfused).(20, 21, 22). As these are infrequent events, the reported incidence per unit transfused varies widely and is strongly influenced by the type of reporting; active versus passive. Indeed, a study by Hong, et al. suggests that the rate of detection of transfusion associated sepsis may be 10 to 40-fold higher should an active detection system be implemented. (23)

One particular reason for concern when transfusing uncrossmatched blood is alloimmunisation, an immune response following exposure to foreign cells or tissues. The transfused donor red blood cells are attacked by the recipient's antibodies to ABO or other antigens. This may then manifest as an acute haemolytic transfusion reaction (within 24 hours), delayed haemolytic transfusion reaction or as haemolytic disease of the newborn if a woman of childbearing age is transfused. (24, 25) In emergent uncrossmatched transfusions the rate of identified alloimunisation has been shown to be between 1,9% to 3%. (26, 27) The risk is lowest in patients below 30 years of age, and rises with age and female gender. Clinically significant antibodies were found in 5,1% of haematology and oncology unit patients. This increased rate is due partly to previous transfusions and partly to haematological disease itself. (27) These patients should thus be of particular concern to clinicians when considering the use of uncrossmatched blood. This is compounded by the fact that they may often present with severe anaemia as a part of their chronic illness or any exacerbation thereof. The severity of an acute haemolytic transfusion reaction is determined by the potency of the recipient antibody reaction and the volume of blood transfused. (27) In the past, serious or fatal haemolytic transfusion reactions were usually ascribed to ABO incompatibility, hence an error in the crossmatching or allocation of blood had occurred. As only type O blood is transfused uncrossmatched this risk should be low in emergency blood transfusions, but an increasing number of haemolytic transfusion reactions are being reported due to non-ABO antibodies.(25) Between 2005-2008 non-ABO antibodies were implicated in 60.7% of all fatal haemolytic transfusion reactions reported to the United States Food and Drug Administration (FDA). Responsible antibodies include Jk^b, Jk^a, Kell, Fy^a, Fy^b and E antibodies. (25) Transfusing Group O blood will not prevent these transfusion reactions.

The major respiratory complication, transfusion related acute lung injury, has been reported from the transfusion of all types of blood products, including red blood cells, but the most common association

is with the transfusion of fresh frozen plasma. While the pathogenesis is not yet clear, there is an association with white blood cell antibodies in the plasma and the clinical acute respiratory distress syndrome-like picture of transfusion related acute lung injury. Studies have also shown an increase in the rate of transfusion related acute lung injury when fresh frozen plasma from women is used, and impaired pulmonary function in patients receiving fresh frozen plasma from multiparous women vs controls. (24)

The rate of transfusion associated sepsis and transfusion transmitted infection is difficult to detect and to define. The bacterial contamination rate of red blood cells is about 0.1%, likely due to the low storage temperature (four degrees Celsius) inhibiting bacterial growth. The majority of contaminants are skin flora, namely Staphylococcus Aureus and Staphylococcus Epidermidis, followed by Eschericia Coli, Bacillus Cereus and Yersinia Enterocolitica, which are able to replicate at lower temperatures. (20) On the other hand, platelets are stored at 22 degrees Celsius and thus allow for proliferation of a wide range of bacteria to significant levels. While cooling platelets may seem desirable from a microbiological perspective, cooled platelets have been shown to be rapidly cleared from the recipient's circulation. The rate of bacterial infection due to red blood cell transfusion is quoted as 1 per 500,000 units transfused, compared to 1 per 2,000 units of platelets. (20) Hence the majority of cases of transfusion associated sepsis have been related to platelet transfusion. In addition, platelets have a shorter allowed storage time, just five days while undergoing constant agitation, compared to 42 days for red blood cells. (20) Significant reductions have been made to the rate of transfusion associated sepsis by implementing screening cultures of platelets being stored and rejection of contaminated units, but this is not yet universally routinely performed. In 2014 the SANBS tested 11.1% of the apheresis platelet units collected by culture and detected a 1.4% contamination rate. (19) There is also an association with the use of pooled platelets and a higher rate of sepsis, due possibly to the greater donor exposure and greater number of venepunctures in collection.

The rate of viral transmission by blood transfusion is low, but remains a concern, particularly of the chronic viruses; Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C. The rate of HIV transmission was significantly reduced by the use of screening questionnaires to identify donors at risk and further minimised by the use of p24 antigen testing of donated blood. There was nevertheless one reported case of HIV transmission from blood transfusion in South Africa in 2014 (after 1.1 million units transfused). (19) The rate quoted in the USA is approximately 1 case per 1.9 million units. The reported rate of transmission of Hepatitis B is 1 per 180,000 units and Hepatitis C 1 per 1.6 million units. (20) Cytomegalovirus transmission is a concern particularly in immunocompromised recipients, including the recipients of stem cell transplants and patients with HIV/AIDS. Parvovirus B19 transmission is important again in certain groups: pregnant women, those with haemolytic anaemias and immunocompromised patients, in whom a chronic aplastic anaemia may develop. In healthy individuals there are generally no clinical manifestations of Parvovirus infection.

Transmission of Human T-Cell Lymphotropic Virus I and II by blood transfusion may lead to myelopathy and predispose to T-cell leukaemia. (20)

Availability of blood and blood products in a low or middle income setting and strategies to limit unnecessary use

Blood products and particularly the Group O blood used in uncrossmatched transfusions are a valuable and limited resource. While South Africa is fortunate to have a zonal donor based blood bank system, many other sub-Saharan countries do not have a regular supply of blood available, or rely on friends and relatives to donate should blood be required. A Tanzanian study as recently as 2010 showed that 90% of children with severe anaemia as a result of Malaria relied on family and friends to donate blood. Often, only rudimentary testing was done to screen for transfusion transmitted infections. (28) The 2010 World Health Organisation report of blood safety in Africa showed that only five of the 43 countries that responded to the survey were achieving the World Health Organisation target of ten donations per 1,000 population – with an average donation rate of 4.3 units per 1,000 population. Only 27 of the 43 countries reported screening for transfusion transmitted infections in a quality assured manner. Of these, the proportion of blood screened for HIV was 95.3%, Hepatitis B 88.9%, Hepatitis C 90.1% and syphilis 79.9%. The study highlighted the demand for safe blood in Africa due to the burden of malaria, sickle cell disease and complications of pregnancy and childbirth. (29)

In South Africa, the majority of the blood received by the blood bank is due to public health initiatives that encourage unpaid volunteers to donate blood. This allows a reserve supply to be maintained, which is typically enough to provide for three to eight days of service. Surplus blood is used to manufacture blood products which have a longer storage potential. At the time of writing the cost of a unit of packed red blood cells in the Western Cape is approximately ZAR 1,217.00. In addition to this a ZAR 330.00 surcharge per visit is added for the stocking of the emergency blood fridge. (30) Such a cost may be acceptable when the transfusion is clearly justified and beneficial, but this may not always be the case. The term ‘potentially avoidable transfusion’ is used retrospectively to note episodes of blood transfusion that may not have been warranted by the clinical condition of the patient. In a registry study of major trauma patients in Victoria, Australia, the authors identified that of the patients receiving blood transfusion in the acute phase of their care, 36.1% of these transfusions were potentially avoidable. (31) Common characteristics of the patients that were transfused unnecessarily included lower injury severity scores, a low frequency of a shock index above one (normal 0.5 to 0.7) and the absence of systolic hypotension. In addition, the absence of a clearly defined endpoint for transfusion was noted, so that when the patient’s condition had stabilised, but ordered blood was still at the bedside, these units were often transfused too. The authors remarked that the initiation of transfusion was generally at the discretion of the treating physician and that there were no guidelines dictating the use of emergency blood. (31) A similarly concerned group in the United Kingdom studied the amount of red blood cell discarded in their hospital. They found that the

emergency centre was responsible for the second largest amount of red cell discards, following Anaesthesia and Critical Care combined. The most common reason for red cell discards was that the blood was no longer within its storage requirements, including elevated temperatures and removal from hampers. They also noted a high rate of discard when patients were transferred from the emergency centre together with units of blood to a ward, where the blood was no longer deemed necessary but not promptly returned to the blood bank. Conditions associated with a high rate of red cell wastage included young, male trauma victims and elderly females with gastrointestinal haemorrhage. (32)

A number of recent papers demonstrate the safety and efficacy of a restrictive transfusion strategy in certain patient groups. This included a study of patients with upper gastrointestinal-intestinal bleeding that were haemodynamically stable, demonstrating improved outcomes when a lower haemoglobin value, 7g/dL, was implemented as a transfusion threshold. (33) Goodnough, et al. showed that by implementing a hospital-wide blood management strategy, essentially requiring motivation for initiating blood transfusion in a patient with a haemoglobin level greater than 7g/dL, they were able to significantly reduce the number of transfusions, while concurrently improving patient outcomes. Indeed, they cite blood transfusion as one of the five most overused therapeutic procedures in the United States. (34) The use of a restrictive strategy in trauma has also been suggested but not yet adequately researched.

Several strategies exist to reduce the amount of allogenic transfusions (blood collected from a donor, usually before it is required) during resuscitation. The most simple and elegant of these remains early definitive haemorrhage control, hence preserving the patient's own blood volume. The challenge is that this often requires an operating theatre and specialised skills and equipment, as in the case of exsanguinating limb haemorrhage or penetrating chest trauma, and the incident may occur in an area where this is not immediately available. Recent military experience has shown the value of haemostatic dressings and tourniquets in gaining rapid temporary control of haemorrhage in the field until definitive care can be reached. (3) These techniques may also be of value in a resource constrained or overburdened environment where a theatre is available but currently occupied and waiting times are prolonged. Another appealing strategy is autologous transfusion, whereby the patient's own blood can be salvaged and returned intravenously as whole blood. In the emergency centre this is most practical in the case of chest trauma with large volumes of blood being captured in a specifically designed chest drain. It has been shown that this blood can be safely returned to the patient, saving costs, time, and limiting the type of transfusion reactions that may occur. (35) The properties of blood sampled from a chest drain compared to venous blood from the same patient, however, show a reduction in haematocrit by about 30%, a reduction in platelet count by about 70% and reduced clotting properties, indicating a degree of degradation during the bleeding and capture process. (36) In the operating room similar strategies are occasionally employed in vascular and cardiothoracic surgery, when rapid haemorrhage may be salvaged in a sterile fashion and returned to the patient, typically via an intraoperative cell salvage device. (35)

Limitations of this literature review

While the practice of transfusing emergency blood in hospital emergency centres is common, the literature surrounding this practice is scant. This review attempts to provide the reader with an understanding of the factors involved in the transfusion of emergency blood, including the benefits, risks, constraints to availability and current practice, but much of the information had to be gleaned from research with a slightly different focus. Much of the data regarding benefits comes from studies describing massive transfusion specifically, not just the use of emergency blood as in our study. Similarly, the risks of blood transfusion are documented for transfusion in general, but not specifically for the type of emergency blood transfusion that we commonly practice. The indications for massive transfusion have been described, but not the indications for uncrossmatched blood as a time-critical intervention in quantities that are not massive. Hence, while the information gap in this area is emphasised, our ability to compare and contrast our study with previous similar research is severely limited.

Conclusions and recommendations

The transfusion of blood is an essential part of the resuscitation of patients with haemorrhage. Group O blood is often used uncrossmatched for this purpose until crossmatched blood can be obtained. There are clear benefits to the use of blood in resuscitation, including the restoration of circulating volume, improvement in oxygen carrying capacity and improvement of haemostasis; but there are also risks of which the clinician should be aware, including transfusion reactions and transfusion transmitted infections. Blood is a costly and limited resource and should be used judiciously. The utilisation of uncrossmatched blood in hospital emergency centres is not well described and it is difficult to establish a reference standard in this regard.

Our study aims to address this gap in part by describing the utilisation of emergency blood in a cohort of secondary level emergency centres and at a tertiary hospital in the Cape Town Metropole. The indications for which emergency blood is being transfused as well as the volumes thereof will be documented, and demographic details of the recipients will be collected. The study will also note the amount of emergency blood from the emergency centre reserve that is used outside of the emergency centre as another important factor in the stewardship and planning of this resource.

Beyond this, a number of important questions remain, with significant opportunities for further research. In our middle-income context, the decision to use emergency blood as opposed to crossmatched blood may well be influenced by the expected time to obtain crossmatched blood, particularly from a blood bank that is not on site. In addition, patients requiring emergency transfusions at a district level may require transfer to a larger centre for definitive care, often the location of the blood bank. It would thus be informative to know more about the clinical course of our patients receiving emergency blood e.g. are they frequently transferred? Do they generally go on to require massive transfusions as is suggested by the international literature, or is emergency blood

being used in lieu of crossmatched blood due to its ready availability in hospitals without blood banks? In addition, it would be valuable to know how we perform with regards to the ratio of fresh frozen plasma and platelets to red blood cells in our emergency transfusions. Are we approaching international standards in this regard? At present fresh frozen plasma and platelets are not available at centres without a blood bank, severely limiting this capacity, although they are available at the tertiary hospitals. As suggested by many of the authors cited in this review, the practice of emergency transfusion is not well described and there is significant local variation. Until we are able to measure our performance in this regard it remains difficult to implement strategies to improve our practice.

Our study may thus be seen as a first step in the description of the way that we utilise emergency blood. It is our hope that this foundation will create awareness and lead to further hypothesis generation and quality improvement processes; that others will join us on the path to excellence in this area of our clinical emergency care.

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Part B: Article in Journal Format

South African Medical Journal

Utilisation of emergency blood in a cohort of emergency centres in Cape Town, South Africa

Abstract

Background

The transfusion of blood and blood products forms an essential part of the resuscitation of patients with acute haemorrhage. Group O blood is stored for this purpose in many emergency facilities and transfused uncrossmatched at physician discretion. Minimal data are at present available to describe this practice, particularly the indications for which emergency blood is transfused and the volume thereof.

Objectives

This study aimed to describe the indications for which emergency blood was utilised in selected emergency centres in the Cape Town Metropole. Volumes were also noted. Practice at secondary level emergency centres was compared with the tertiary Groote Schuur Hospital.

Methods

A cross-sectional study was carried out at three secondary level emergency centres and a tertiary hospital. Data from all recipients of emergency blood from the emergency centre blood reserve were recorded in study registers over the three month study period. The indications for transfusion, volume of blood in units and location of transfusion were recorded. Indications were described as categorical variables and reflected as proportions.

Results

Over the three month study period a total of 329 units of emergency blood were transfused to a total of 210 patients. Haemorrhage as a result of trauma accounted for 39% (n=81) of the cases for which emergency blood was used. This was followed by surgical conditions at 22% (n=47), particularly upper gastrointestinal bleeding 11% (n=24) and perioperative bleeding 8% (n=16) . Medical conditions accounted for 15% (n=31) of the blood, with anaemia, 13% (n=27) the most prevalent, particularly at the secondary level hospitals. Gynaecological conditions required 15% (n=32) of the total, particularly ectopic pregnancy 8% (n=17) . The majority of emergency blood, 77% (n=253) was used in the emergency centres and trauma unit, followed by the operating theatres at 6% (n=21).

Conclusion

Trauma was the most frequent indication and accounted for the greatest volume of emergency blood transfused. Upper gastrointestinal bleeding, early pregnancy complications and anaemia were the next most common indications. Perioperative bleeding was the most common reason for emergency blood to be used outside of the emergency centre. Ongoing monitoring of this resource is recommended.

Utilisation of emergency blood in a cohort of emergency centres in Cape Town, South Africa

Introduction

The historical and philosophical association between blood and life is borne out in the critical role that blood and blood products play in modern haemostatic resuscitation. Early use of blood and the limitation of the use of crystalloid fluids have shown significant mortality benefit in the critically injured as well as those with haemorrhage not related to trauma. (1-5) The most common preventable cause of death in trauma patients remains haemorrhage and blood is often needed to replace a proportion of the blood that is lost. (6)

In the Cape Town Metropole, public patients undergo their initial resuscitation and investigation in emergency centres at a number of secondary and three tertiary level hospitals. Only the three tertiary hospitals have 24-hour staffed blood banks to provide direct access to blood and blood products. The remaining hospitals are provided with a modest supply of Group O blood to be transfused as uncrossmatched emergency blood until crossmatched blood can be obtained from the nearest blood bank, or the patient is transferred to a facility with a blood bank on site. To accommodate the lack of a 24-hour staffed blood bank, emergency blood is stored in dedicated fridges in strategic areas of these hospitals, typically the emergency centre, labour ward or theatre. These fridges are stocked by the Western Cape Blood Transfusion Services according to predetermined levels of anticipated use (written communication, 18 September 2014). Emergency blood is transfused at the discretion of the treating physician. There are at present no formal guidelines directing the use of this resource and, anecdotally, wide variations in local circumstances and patient presentations exist.

While doctors are required to complete request forms for the use of crossmatched blood from the blood bank, the same process is not followed for emergency blood, as the blood is immediately at hand and record keeping is therefore less robust. The result is that whilst blood taken from the fridge for emergencies can usually be traced to whom it was transfused , there are little data on the indications for which this costly and limited resource is being utilised. Without this data it is difficult to define a reference standard regarding its use in emergency situations. There is currently little accountability for inappropriate use, despite the unnecessary risk and cost resulting from uncrossmatched transfusions using emergency Group O blood. (7-11)

Understanding the way emergency blood is utilised may provide the first step towards implementing local guidelines that will encourage safe and effective use of emergency blood. Our study aimed to address this information gap by describing the utilisation of emergency blood in a cohort of emergency centres in the Cape Town Metropole. The main objective was to determine the indications for which emergency blood was transfused in the emergency centres of three secondary level hospitals and one tertiary hospital.

Methods

A cross-sectional study was conducted from 1 August 2016 to 31 October 2016. Ethics approval was obtained from the Stellenbosch University Health Research Ethics Committee and additional permission to collect data at the specific study sites was obtained from the Western Cape Provincial Health Research Committee. Data from the blood bank at Groote Schuur Hospital was supplied with the consent of the Western Province Blood Transfusion Service.

The setting included the three public secondary level hospitals in the Cape Town Metro West drainage area; New Somerset Hospital, Mitchell's Plain Hospital and Victoria Hospital and the tertiary Groote Schuur Hospital. These hospitals serve the western part of the city of Cape Town as well as some of the surrounding suburbs and informal settlements. The private hospitals in this area were not included for logistical reasons.

Subjects included from the secondary hospitals were patients that were administered emergency blood from the blood fridge in the emergency centre, whilst subjects included from the tertiary hospital were all patients that were administered emergency blood from the staffed blood bank at Groote Schuur Hospital. Groote Schuur Hospital does not have a single emergency centre model, but receives and stabilises patients in several separate areas, hence a respective emergency centre population could not clearly be defined. Of the secondary hospitals, Mitchells Plain Hospital has a blood fridge in the emergency centre, labour ward and theatre; New Somerset Hospital has a fridge in the emergency centre and labour ward and Victoria Hospital has a fridge in the emergency centre only. As the study was emergency centre focussed, data from the labour ward or theatre were not collected, unless patients in labour ward or theatre required blood from the emergency centre fridge. The converse, that blood from the labour ward or theatre be used for a patient in the emergency centre, is not practised at either of the relevant facilities. Data collection was set for a three month period detailed above and all data collected during that time were included.

Data were collected at the participating secondary level emergency centres by means of bespoke study registers which were created specifically for the study and were distributed by the study team, to be kept at the emergency blood fridges. Staff were familiarised with the correct use of the registers and regular follow-up telephone calls and site visits were used to encourage compliance in data collection. Variables collected included the indication for which blood was transfused, the location of the patient at the time the transfusion was initiated, the number of units transfused and the age and gender of the patient. Incomplete data were supplemented from patients' electronic hospital records. Conversely, at the tertiary hospital blood is obtained directly from the blood bank, making the same strategy impractical. The blood bank provided records of all emergency blood issued during the study period and included the same variables as for secondary hospitals, except for the indication which is not captured in their records. To obtain the indication for which the emergency blood was required, patients' electronic hospital records were reviewed.

Data were captured in Excel 2013 spreadsheets (Microsoft Office, Redmond, USA) and were analysed using Stata version 14 (StataCorp LLC, College Station, USA). Demographic details were calculated for the study population as a whole. Age was calculated as a mean with standard deviation and gender was directly compared. A transfusion episode was defined as a discrete clinical event or presentation for which a participant was transfused emergency blood. This may have included multiple units of emergency blood. In rare cases where a single participant had more than one separate transfusion episode during the study period, these were counted separately. ICD-10 codes were not used to describe indications as these were generally not available to the staff completing the study register at the time of transfusion. Indications were divided into the categories trauma, surgical, gynaecological, obstetric and medical, with each category containing further subcategories to better describe the sample. The number of transfusion episodes were calculated for each indication, and for the categories these were divided into. The number of units of emergency blood were also calculated for each indication, as were the mean number of units per transfusion episode for each indication. Given the small numbers a measure of spread was not calculated. To reflect differences between the various hospitals the frequency of transfusion for the major categories at each hospital were individually calculated and represented as a bar chart. Finally the total number of units per hospital location were calculated, to reflect where in the hospital the emergency transfusions are being initiated.

Results

A total of 329 units of emergency blood were transfused to 210 patients over the three month study period. Of these, 141 transfusion episodes occurred at the secondary hospitals: Mitchells Plain Hospital n=70 (33%), New Somerset Hospital n=53 (25%) and Victoria Hospital n= 18 (9%), and at the tertiary Groote Schuur Hospital n=69 (33%).

Age and gender data for each indication category group are reflected in table 1 below.

Table 1: Age and gender for each category of indications

	Mean age in years (SD)	Male n (%)	Female n (%)
Trauma	33 (13,8)	69 (85)	12 (15)
Surgical	56 (16,8)	29 (62)	18 (38)
Gynae	29 (6,7)	0	32 (100)
Obstetric	29 (7,3)	0	10 (100)
Medical	44 (21,8)	16 (52)	15 (48)
Unknown	53 (17,1)	3 (38)	5 (62)

The indications for which emergency blood was transfused as well as the volumes have been represented in table 2.

Table 2: Comparison of the indications for and volumes of emergency blood transfused

Indication categories	Secondary hospitals			Tertiary hospital		
	Transfusion episodes n (%)	Units n (%)	Units/ episode	Transfusion episodes n (%)	Units n (%)	Units/ episode
Total	**141**	**186**	**1,3**	**69**	**143**	**2,0**
Trauma	**36 (26)**	**58 (31)**	**1,6**	**45 (65)**	**96 (67)**	**2,1**
Gunshot abdomen	1	1	1,0	1	3	3,0
Gunshot chest	1	1	1,0	4	9	2,3
Gunshot head	1	1	1,0	1	2	2,0
Gunshot limb	1	2	2,0	0	0	-
Multiple gunshots	1	1	1,0	6	11	1,8
Multiple stabs	7	12	1,7	3	5	1,7
Stab abdomen	0	0	-	1	1	1,0
Stab chest	14	20	1,4	9	23	2,6
Stab heart	2	5	2,5	0	0	-
Stab neck	1	3	3,0	3	7	2,3
Stab limb	2	4	2,0	1	1	1,0
Blunt assault	3	4	1,3	2	4	2,0
Road traffic polytrauma	2	4	2,0	14	30	2,1
Surgical	**38 (27)**	**49 (26)**	**1,3**	**9 (13)**	**15 (10)**	**1,7**
Upper gastrointestinal bleed	20	25	1,3	4	7	1,8
Peri-operative bleeding	13	16	1,2	3	5	1,7
Acute abdomen	3	4	1,3	1	2	2,0
Malignancy	1	1	1,0	1	1	1,0
Bowel obstruction	1	3	3,0	0	0	-
Gynaecological	**29 (21)**	**39 (21)**	**1,3**	**3 (4)**	**4 (3)**	**1,3**
Ectopic pregnancy	17	26	1,5	0	0	-

Miscarriage	6	6	1,0	0	0	-
Gynaecological not specified	5	5	1,0	3	4	1,3
Abnormal uterine bleeding	1	2	2,0	0	0	-
Medical	**30 (21)**	**32 (17)**	**1,1**	**1 (1)**	**1 (1)**	**1,0**
Anaemia	27	29	1,1	0	0	-
Haemoptysis	2	2	1,0	1	1	1,0
Medical not specified	1	1	1,0	0	0	-
Obstetric	**4**	**4**	**1,0**	**6 (9)**	**15 (10)**	**2,5**
Postpartum haemorrhage	4	4	1,0	0	0	-
Obstetric not specified	0	0	-	6	15	2,5
Unknown	4 (3)	4 (2)	-	5 (7)	12 (8)	-

At Mitchells Plain Hospital 89 units of blood were used: all blood dispensed from the emergency centre blood fridge was used in the emergency centre. At New Somerset Hospital 74 units of blood were used: 47 (64%) were used in the emergency centre, 15 (20%) in theatre, 5 (7%) in the surgical ward, 3 (4%) in the labour ward and one unit in the medical, paediatric, gynaecology and ICU wards each. At Victoria Hospital 23 units of blood was used: 17 (74%) were used in the emergency centre, 5 (22%) in theatre and 1 (4%) in the surgical ward. At Groote Schuur hospital 143 units of emergency issue blood were issued from the blood bank: 100 (70%) were used in the trauma centre, 15 (11%) in the labour wards, 10 (7%) in the surgical wards and 18 (12%) in a number of unspecified general wards.

Figure 1: A comparison of the indications for transfusion at the individual study sites

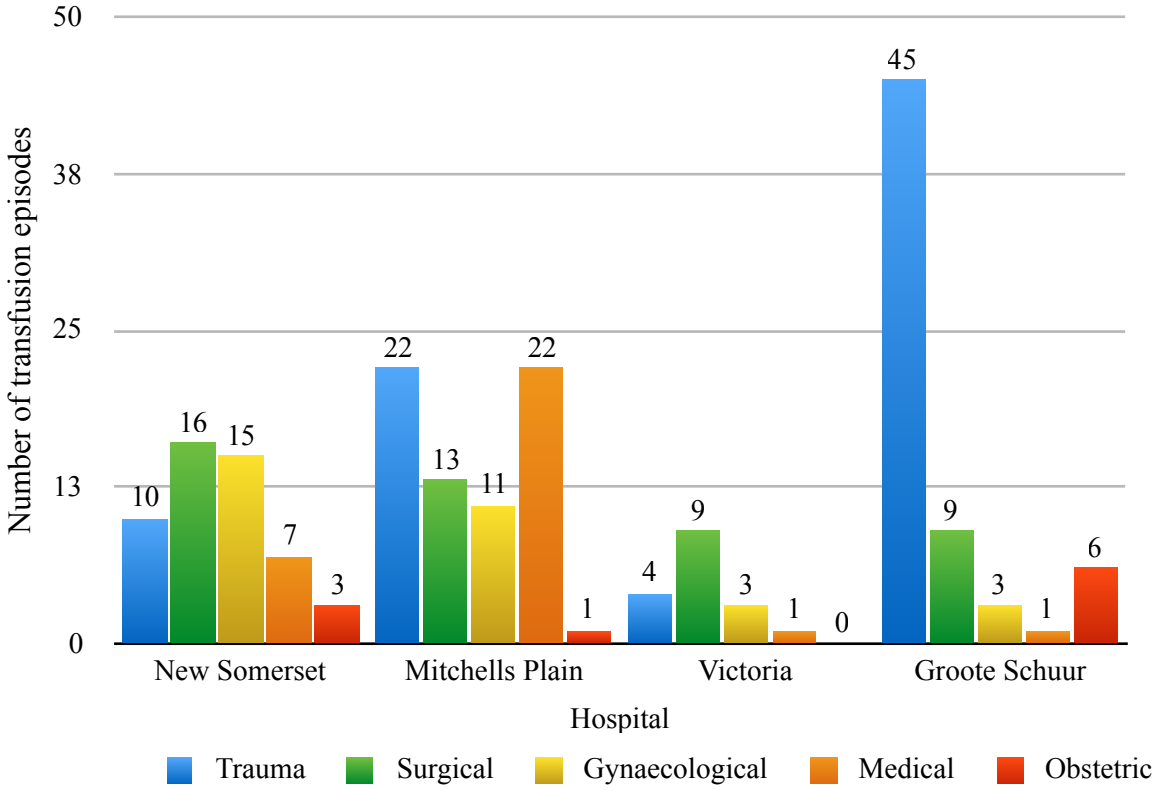

Figure 1 visually compares the major indication categories for transfusion between the individual study sites.

Discussion

In keeping with the existing literature, trauma was the major indication for the use of emergency blood both in the secondary level emergency centres and in the tertiary hospital. (13,14) Trauma also accounted for the largest volumes of blood used. Victims of trauma were likely to require a higher volume of emergency blood in their acute resuscitation (mean 1,9 units) than those receiving blood for other reasons (1,3 units). Trauma patients managed at the tertiary hospital tended to receive larger volumes of emergency blood (mean 2,1 units) than those at the secondary level emergency centres (mean 1,6 units) despite the presence of a blood bank on site to crossmatch blood. A number of factors may play a role in this observation. The prehospital triage of severely injured patients to the tertiary hospital is intended to match patient requirements to the available resources, including blood and blood products. The availability of larger volumes of emergency blood at the tertiary hospital and the familiarity of doctors working at a trauma centre with the use of large volumes of blood may lead to the administration of larger volumes of blood by the doctors at the tertiary hospital. The availability of advanced imaging to detect occult bleeding at the tertiary hospital may also predispose these patients to a larger volume of blood transfused. These factors remain speculation and further research is

needed to better define the factors leading to the use of larger volumes of emergency blood. Another possible consequence of the prehospital triage policy in practice is the higher proportion of polytrauma and gunshot wound victims seen requiring transfusion at the tertiary hospital compared to the secondary level hospitals, which saw a larger proportion of stab wounds. The burden of penetrating trauma; 61 of the 81 trauma cases (84%), reflects the prevalence of interpersonal violence, particularly gang-related violence, in the area.

The use of emergency blood for patients with anaemia is probably the most contentious finding of this study. While we did not attempt to define appropriate and inappropriate use, this is an indication that many would deem inappropriate for most of the wide variety of underlying conditions. Concerns about the use of emergency blood in this population include the expected need for repeat transfusions and the increased prevalence of alloimmunisation, raising the risk of transfusion reactions. (10,11,12) The major objection, however, is that the condition has often been present for a long period of time and should be managed in a planned fashion that limits the need for transfusion in general and emergency transfusion in particular. The tertiary hospital used no emergency blood for this indication, while there were 27 such episodes at the secondary level emergency centres, with one emergency centre in particular recording this indication frequently. It was beyond the scope of this study to record additional data such as the haemoglobin value and vital signs of these patients, but these data would help to ascertain whether emergency blood was indeed indicated or whether it would have been more appropriate to wait for crossmatched blood. The transport times, both real and perceived, of samples to and blood from the blood bank may also play a role, with the emergency centre using the most emergency blood for anaemia located furthest from the blood bank. Combined with the desire for prompt patient care and disposition from a busy emergency centre, a long blood transport time may influence doctors to utilise blood from the emergency blood fridge, although it remains difficult to justify. Further investigation is warranted into the use of emergency blood for patients with anaemia and perhaps the implementation of a guideline or gatekeeper strategy is necessary to limit the potentially avoidable transfusion of emergency blood.

Limitations of this study included the small sample size and short duration of the study period. While this limited the confidence of the infrequent indications, certain indications tended to occur commonly and at all study sites lending credibility despite the small sample.
The study was largely dependent on clinical staff to complete the study registers and record the indications for which emergency blood was transfused as these data are not routinely collected. While they were familiarised with the study and encouraged to confirm indications with the responsible doctor, this remained a potential source of misinformation. The small size of the study did not allow for dedicated research staff for the purpose of data collection. The variety of methods required to recover missing data would make the study difficult to replicate until such time as the study data sample becomes a part of routine data collection by the blood bank or the individual emergency centres.

The tertiary hospital included in this study does not offer a paediatric service, leading to significant underrepresentation of the paediatric population. There is a dedicated tertiary paediatric hospital within the study area to which the majority of paediatric trauma patients are transported directly. Children with less severe injuries and those presenting directly are treated at the secondary level emergency centres, which were included in the study. This limits the generalisability of the results with regards to the need for emergency blood in paediatric emergency care.

The strength of this study is that it traces the outlines of an area of practice that was hitherto uncharted. The results lay a foundation on which further research can build and to which similar studies can compare. The information can be used in drawing up local clinical guidelines for the use of emergency blood and in planning a massive transfusion protocol. The Western Province Blood Transfusion Service's knowledge of the clinician's use of their products may be expanded.

Conclusions

Trauma was the major indication for the transfusion of emergency blood in this study. Other frequent indications included upper gastrointestinal bleeding, ectopic pregnancy and anaemia. The volumes of emergency blood transfused per episode were highest in trauma patients, and higher at the tertiary hospital compared to the secondary level facilities. The majority of emergency transfusions were commenced in the emergency centres, with a small amount of the emergency blood stock being used in other areas of the hospitals, particularly theatre. Further research is needed to evaluate the clinical outcomes of the recipients of emergency blood as well as to describe the use of associated blood products in emergency transfusions. Appropriate use of this limited resource needs to be defined for each facility, and ongoing monitoring of the indications for which emergency blood is transfused at an individual hospital level is encouraged.

Acknowledgements

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Part C: Addenda

Addendum A: SAMJ research article submission guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Addendum B: Data capture instrument

The following chart represents a page from the study register that was distributed to the participating emergency centres showing the data set that was collected. The standard hospital sticker placed in the first column contains the hospital folder number, gender, date of birth and address of the patient.

Date	Patient sticker	Blood Unit sticker/s	Indication for transfusion eg "stab chest", "Upper GI Bleed"	Location of transfusion eg "EC" or "blood taken to surgical ward"

Addendum C: Oxford Centre for Evidence-based Medicine systematic review checklist

What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The ***Title***, ***Abstract*** *or final paragraph of the* ***Introduction*** should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
F - Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The ***Methods*** section should describe the search strategy, including the terms used, in some detail. The ***Results*** section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
A - Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The ***Methods*** section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
A - Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up)	The ***Methods*** section should describe the assessment of quality and the criteria used. The ***Results*** section should provide information on the quality of the individual studies.

This paper: Yes ? No ? Unclear ? Comment:	
T - Were the results similar from study to study?	
What is best?	Where do I find the information?
Ideally, the results of the different studies should be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored.	The ***Results*** section should state whether the results are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present.
This paper: Yes ? No ? Unclear ? Comment:	

Addendum D: Research Protocol

Indications for the use of Emergency Blood in selected Emergency Centres in the Cape Town Metropole

Principal Investigator: Dr David Morris (14101793)
Division of Emergency Medicine
University of Stellenbosch

Co-investigators: Dr Stevan Bruijns
Division of Emergency Medicine
University of Cape Town

Dr Melanie Stander
Division of Emergency Medicine
University of Cape Town

Supervisor: Dr DJ van Hoving
Division of Emergency Medicine
University of Stellenbosch

Table of Contents

1. Background

It is well established that the early use of blood to replace acute blood loss is associated with improved outcomes when compared to crystalloids or other colloids. (1) Emergency blood (including packed red cells, platelets and plasma) currently represents an essential part of the treatment of patients with major haemorrhage. This stems from a growing body of literature surrounding massive transfusion protocols. (2,3) International data indicate that the majority of emergency blood transfusions in hospitals are commenced in the Emergency Centre, but there is a paucity of local data regarding blood product use in the emergency setting. (4) The high incidence of blunt and penetrating trauma in the Cape Town Metropole and the role of Emergency Centres in the resuscitation and stabilisation of patients with major haemorrhage would suggest that this holds true in this setting as well. (5) However, blood is a scarce resource, particularly emergency or type-O blood, and its use should be carefully considered in order to provide maximum benefit.

2. Motivation

Of the public hospitals in the Cape Town Metropole only the three tertiary hospitals (Tygerberg, Groote Schuur and Red Cross War Memorial Children's Hospital) have round the clock, staffed blood banks within the hospital. The remaining hospitals have a limited supply of emergency blood stored in dedicated fridges, usually in accessible areas such as the resuscitation area of the Emergency Centre and theatre. Emergency blood fridges at these hospitals are stocked by the Western Province Blood Transfusion Service (WPBTS) in order to maintain a constant supply at a predetermined threshold as guided by the anticipated emergency need at any of the facilities.

Given local blood volume restriction (i.e. the limited supply in the emergency blood fridge), the available supply may deplete before resuscitation has been completed, resulting in suboptimal care until the supply can be replenished. Inappropriate use has the same effect but in addition depletes provincial stores of type-O blood where cross-matched blood would have been more appropriate. It also increases the risk of transfusion reactions and antibody formation. (6-8) Use of emergency fridge blood in areas other than the Emergency Centre, such as the obstetric ward, the operating theatre or in the general wards, places an additional pressure on available emergency blood resources.

There is currently no available local data on the indications for, or area in the hospital where emergency blood stored in Emergency Centres in the Cape Town Metropole is being used. While registers are required by the WPBTS of the patients to whom emergency blood is given, the indications are not routinely documented, nor are the locations of these patients. Describing the indications and reviewing user practices within the various settings around the Cape Town Metropole

will provide an understanding of the way that this resource is being used. This information may potentially inform both local Emergency Centre and hospital management and the WPBTS on emergency blood management within the metropole.

3. Research Question

For what indications and in which hospital areas are emergency blood from the Emergency Centre blood fridge used in a selection of Emergency Centres in the Cape Town Metropole?

4. Aim and objectives

The aim of the study is to describe the indications for and areas where emergency blood from the emergency blood fridge is used in three secondary / district level hospitals and the blood bank at one tertiary hospital within the Cape Town Metropole.

The objectives are:

i. To describe the indications for and volume of emergency blood used from the emergency blood fridge at three secondary/ district level hospitals: Mitchell's Plain, Victoria and New Somerset hospitals

ii. To describe the hospital areas where emergency blood from the emergency blood fridge are used at three secondary/ district level hospitals: Mitchell's Plain, Victoria and New Somerset hospitals

iii. To describe the indications for and volume of emergency blood used from the blood bank at Groote Schuur hospital adult medical emergency centre and trauma unit

iv. To compare the use (indications, volume and area of use) of emergency blood between the three secondary/ district level settings and tertiary hospital

5. Study Methodology

5.1. Study design

Retrospective review

5.2. Study setting and population

The study will be conducted at four Metro West Hospitals: Mitchell's Plain Hospital, New Somerset Hospital, Victoria Hospital and Groote Schuur Hospital. The former three hospitals are secondary/ district level hospitals that operate an emergency blood fridge with a finite volume of blood available. Groote Schuur hospital comprises the adult medical emergency centre (C15) and the trauma unit (C14) and represents a tertiary level facility with a 24-hour blood bank on site.

It is anticipated that emergency blood use at the three secondary/ district level hospitals will include mainly Emergency Centre patients. However, we will report on the use of emergency blood taken from the Emergency Centre blood fridge but used elsewhere in these hospitals as the use of emergency blood elsewhere in the hospital would affect use of emergency blood in the Emergency Centre. For Groote Schuur hospital the focus would be the indications for use of emergency blood products only in the adult medical emergency centre (C15) and the trauma unit (C14) - a whole hospital focus will not be taken in this instance. Use of emergency blood at Groote Schuur hospital should differ from the other study sites as blood is more readily available in all its forms. It should be noted that it is not meant to use Groote Schuur hospital as a control site for the other three sites as the population it serves differs significantly. It should theoretically however, provide information about a facility where blood use might be better regulated given the on-site blood bank as opposed to the other sites where it is not.

The sample as described above focusses specifically on how the Emergency Centre is affected by use of emergency blood and the investigators feel that review of these four sites should provide a reasonable overview of emergency blood use. Significant findings from this study can be followed up by review of blood product use at other Cape Town hospitals.

A three month sample will be collected from all study sites. Sample size estimation using Stata 13 (©1996–2016, StataCorp LP) reveals that this timeframe (with approximately 500 units transfused) would reflect the proportions of the major indications within an approximate 10% range.

5.3. Research procedures and data collection methods

All emergency blood used will be recorded consecutively over the three month period following study approval. Emergency blood taken from the emergency blood fridges is already being recorded as required by the WPBTS. The WPBTS require facilities to keep a folio book to record details from the patients that received emergency blood. These vary between institutions and are not uniformly standardised. Where a blood bank provides the emergency blood (e.g. Groote Schuur hospital), the WPBTS keeps the formal record. While the WPBTS requests that the indication for the transfusion be recorded (at facilities keeping records on behalf of the WPBTS), anecdotal evidence suggests that this is not properly done in all cases. For this reason, at the start of the study period, investigators will survey the existing folio books in place at the three self-recording facilities. Where these contain

sections for indication for emergency transfusion and location of patient, the investigators will encourage the doctors and nursing staff to continue to record these data. Where the folio books do not contain sections for indication or location of patient, the investigators have been given permission by the WPBTS to replace it with folio books with the required areas in place. The study team will continue to provide these for the duration of the study. Ongoing liaison with nursing managers and heads of the clinical units will be made throughout the study period to encourage compliance.

The folio books' contents will be transcribed onto an electronic spreadsheet on a monthly cycle. This will be done on site to reduce any potential effect on service delivery which will also allow the study team to address non-compliance with completing required fields. The data will include the patient folder number, age at the time of transfusion, gender, date and time of transfusion, indication for transfusion and the volume and type of emergency blood transfused. Patient names, contact details or addresses will not be included. Hospital numbers will be used to obtain patient records (paper or electronic) in order to obtain more information regarding indication and location of use. Hospital numbers will be replaced by an individual study number as soon as all the data have been collected in order to establish an anonymised sample. Indications for transfusion will be recorded by speciality (trauma, surgery, medicine, obstetrics, gynaecology, etc.) and then further subdivided based on prominent patterns that arise during the study period, e.g. trauma may be subdivided into blunt and penetrating, or chest and abdominal trauma.

5.4. Data safety and monitoring

Data from the folio books will be transcribed by the principal investigator into an Excel (Microsoft Excel, Microsoft Corporation, Redmond, Washington, USA) spreadsheet on a password protected work computer situated at the UCT division of Emergency Medicine's office complex at the Old Main Building, Groote Schuur Hospital. The Excel document itself will also be password protected. Data from electronic registers will be extracted by the WPBTS and emailed to the investigators using standard encryption associated with the institutional email (Stellenbosch and the WPBTS). The information will then be stored on the same work computer that contains the transcribed paper registries. The data will be backed up and stored in an internationally recognized, password protected database in the 'cloud'.

The folio books will remain at the relevant hospitals as part of general record keeping.

5.5. Data Analysis

Descriptive statistics will be presented for all variables. Categorical variables will be reported as proportions with 95% confidence intervals. The broad indications (trauma, surgery, medicine, obstetrics, gynaecology, etc.) will be further subdivided according to indications that become prevalent. Continuous variables will be summarised using means with standard deviations. A Chi test will be used to compare the proportions between the hospitals with and without blood banks. Figures

will be used to illustrate the important findings from the study. The data will reflect the indications for which the blood is being transfused, the amount of blood being transfused outside of the emergency centre and the age and sex of the recipients. Data will be presented for each hospital as well as for all the study populations combined.

A consultant at the Biostatistics Unit within the Centre for Evidence Based Health Care (CEHBC), Stellenbosch University assisted with the design and will assist with the analysis of this study through support from the Faculty of Medicine and Health Science's dean's fund. The latest version of Stata© software will be used to perform the statistical analysis

6. Ethical Considerations

6.1. Risks and benefits

As this is purely a descriptive study it poses minimal risk to the study population and will not impact on patient care. The data that is being captured should already have been captured for WPBTS records. Personal information from patients will not be included and the reason for transfusion will be broadly categorised and not specific.

The benefit of the study will be a greater awareness of the local patterns of use of a scarce resource, which may aid in optimising utilisation of a scarce resource as well as further research.

6.2. Informed consent process

The study will have no immediate impact on patient care and patients will generally not be aware that the study is in progress. The data collected is a part of general record keeping already in place and required by the WPBTS. Patients will not be consented to participate in the study and a waiver of consent is requested on the basis of the following: Firstly; data sampling will be retrospective. Given the poor record keeping at public hospitals (addresses and phone numbers) it would not be feasible to try and trace patients for consent. In fact an attempt at consent will either require a much better resourced study- which is not feasible- or a much smaller study- that will have less power to provide valuable information. Secondly, there is a clear data protection plan in place that will safe keep data even beyond anonymization on several levels. The investigators have no individual interest in any of the patients and as clinicians understand the sanctity of patient information. Use of the folder number is merely a practical way to link data sources in the absence of existing anonymised databases that contains this information. It is our view that the benefits of understanding the way blood products are used in the emergency setting can have a significant impact on resource allocation, cost reduction and quality of care and that this benefit outweighs the minimal risk of data loss given the existing data management plan. The prospect of further hypothesis formation in the light of the results may likely lead to further studies involving blood product usage that can improve the listed benefits further. We

appreciate that a consent waiver is not standard given the data collection plan, but given the risk/ benefit context provided above we strongly feel that is required to address the study question robustly.

Individual institutions will be approached for their cooperation and consent through the National Health Research Database. Permission has already been obtained from the WPBTS pending HREC approval (Appendix 1).

6.3. Privacy and confidentiality

Patient names are not required in the data set and will at no point be included. The folder numbers will initially be used for veracity of records and to allow more complete data collection, but will be replaced with a study number at an early stage, prior to analysis, allowing anonymity of the study population.

7. Resources Utilisation

Key to the success of the study will be the cooperation of the participating centres and the data keeping requested of them. Although this is not a new task - the record keeping should already be performed, we will be encouraging compliance and meeting at times with Clinical and Nursing managers. These meetings will require their time, but will be kept brief. The impact of the data collection to service delivery within the unit will not be significant.

Cross-referencing with the clinical record where indications are unclear will be performed on-site at the facilities from where the data originated. Clerical support may be required to achieve this.

7

8. Budget

The budget for this study is ±R3600 and will be self-funded.

Budget

Transport[1]	1010km @ R3.29/km	R3323
Communications[2] (Telephone)	150 minutes @ R1.20/minute	R180
Stationery[3]	9 folio books @ R10/book	R90
Total		**R3593**

[1]Transport will be required to visit study sites to distribute appropriate stationery, to meet with clinical personnel and to collect data. We foresee five trips per hospital to be adequate. Return distances from Faculty of Health Sciences, Stellenbosch to:

- Mitchell's Plain Hospital = 40km
- Groote Schuur Hospital = 48km
- New Somerset Hospital = 50km
- Victoria Hospital = 64km

[2]Telephones, including private cell phones, will be used to communicate between the investigative team

as well as to communicate with study sites during the research period.

[3]Appropriate folio registers will be supplied as detailed to the study sites where the current registers are less than satisfactory.

9. Timeframe

- HREC approval: May 2016
- Institutional approval: July 2016
- Data Collection: August to October 2016
- Data management and analysis: November to December 2016
- Write-up: January to March 2017

10. Limitations

It is beyond the scope of this study to describe which indications are appropriate and which are not. We would expect to see that the majority of the emergency blood would be used in cases of acute, unstable haemorrhage. Where it is noted that emergency blood is being used in less acute cases, e.g. medical anaemia the study will help to bring this to the attention of the relevant clinical management.

The registers are most often completed by the nursing staff, hence the indications for transfusion will be recorded by them. We expect that this will be adequate as we aim to record broad categories of indications. We will encourage the nursing staff to check the indications with the treating doctor where they are unsure.

Groote Schuur hospital is not considered an ideal control setting given the vastly different patient population. It should however come closest and at least offer a comparison with blood use practices where emergency blood is more managed. It is for this reason that the study investigators want to compare the other sites with Groote Schuur hospital. The main focus of the study would be describing the volumes of emergency blood used, the indications and location of use.

References

(1) Duke, M.D, Guidry, C. Restrictive fluid resuscitation in combination with damage control resuscitation: Time for adaptation. *Journal of Trauma and Acute Care Surgery*. 2012;73(3): 674-678.

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(3) Derek Norfolk. 7.3 Transfusion management of major haemorrhage. In: Derek Norfolk (eds.) Handbook of Transfusion Medicine. 5th ed. UK: The Stationery Office; 2013. p82-87

(4) NHS Blood and Transplant. Survey of Massive Blood Loss in the North East of England 2013. Available from: file:///C:/Users/NvHoving/Downloads/rtc-ne_2014_12_A_massive_blood_loss_v2.pdf (accessed 11/4/2015).

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(8) National Guideline Clearinghouse. Blood transfusion: indications, administration and adverse reactions. Available from: http://www.guideline.gov/content.aspx?id=34955 (accessed 4/11/2015).

Addendum E: Approval from the Stellenbosch University Health Research Ethics Committee

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
Jou kennisvennoot • your knowledge partner

Approval Notice
New Application

18-May-2016
Morris, David D

Ethics Reference #: S16/04/065
Title: **Indications for the use of Emergency Blood in selected Emergency Centres in the Cape Town Metropole**

Dear Dr David Morris,

The **New Application** received on **13-Apr-2016**, was reviewed by members of **Health Research Ethics Committee 1** via Expedited review procedures on **18-May-2016** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **18-May-2016 -17-May-2017**

Please remember to use your **protocol number** (**S16/04/065**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics

approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389657.

Included Documents:
7b vHoving_CV.pdf
5 Synopsis_EM_blood.pdf
8b Investigator Declaration vHoving.pdf
8a Investigator Declaration Morris.pdf
7c Bruijns CV.pdf
7a Morris CV.pdf
8d Investigator Declaration Stander.pdf
2 Checklist_EM_blood.pdf
6 Waiver_EM_blood.pdf
4 Proposal_EM_blood.pdf
1 Application_EM_blood.pdf
Expedited_review_EM_blood.pdf
7d Stander CV.pdf
8c Investigator Declaration Bruijns.pdf

Sincerely,

Franklin Weber
HREC Coordinator
Health Research Ethics Committee 1

Addendum F: Approval from the Western Province Blood Transfusion Services

WP Blood Transfusion Service
Do something remarkable

www.wpblood.org.za / info@wpbts.org.za
Head Office
Old Mill Road, Pinelands, 7405 • PO Box 79, Howard Place, 7450
T: 021 507 6300 / F: 021 531 0322

02 April 201[illegible]

TO WHOM IT MAY CONCERN:

The Western Province Blood Transfusion Service (WPBTS) was approached by Dr. David Morris to provide information which would assist him in a study titled "Assessing indications for the use of Emergency Blood at Emergency Centers in the Cape Town Metropole".

The Service will be willing to supply the information required, provided that the following criteria are met:

- Ethics Committee approval by the relevant Institution is granted.
- Standard confidentiality protocols are followed regarding access to (and dissemination of) patient personal data.

Kind Regards
Karen-C Dramat

Karen-C Dramat
Blood Bank Technical Manager
Tel: 021 507 6389
Cell: 082 774 3452
Fax to e-mail: 0866453097

Paarl
263 Main Road, Paarl, 7646
PO Box 422, Paarl, 7620
T: 021 871 1030 / F: 021 872 5945

Worcester
26 Napier Street, Worcester, 6850
PO Box 194, Worcester, 6849
T: 023 342 2450 / F: 023 342 7556

George
Medical Centre, Courtenay Street
PO Box 65, George, 6530
T: 044 874 2074 / F: 044 874 6097

Fractionation
101 Connaught Rd, Beaconvale, Parow, 7500
PO Box 79, Howard Place, 7450
T: 021 933 9400 / F: 021 931 5551

WP Blood Transfusion Service NPC
Pr. No: 7800045 / Reg. No: 1943/016692/08

Directors: GRM Bellairs, AR Bird, GR Bosman, MR Burton, NB du Toit, F Essop, BdL Figaji, I Kaprey, N Parker, R Ramsbottom, PK Slack (Chairman), E Steyn

PBR19 (05 Oct 12)