Recent developments in military transfusion practice and their impact on civilian healthcare

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SCIENTIFIC ENVIRONMENT

The source material thesis is derived from the author's military and civilian professional and academic practice from 2002 until the current date. The author has been employed by NHS Blood and Transplant with contracted clinical session for the University Hospital, Birmingham and the Ministry of Defence.

The academic environment has been provided through an ongoing honorary contract as a Senior Clinical Lecturer in Transfusion Medicine within the University of Birmingham, UK. The author currently holds a contract as a Senior Lecturer within the Academic Department of Military Anaesthesia and Critical Care, Royal Centre of Defence Medicine.

The author has worked as an active member of the Trauma Hemostasis & Oxygenation Research network in Norway since 2013 and she was awarded a fellowship from the Medical Women's Federation in 2016 to study within the Haukeland University Hospital.

Since then she has acted as an adviser for Emergency Blood Preparedness for Bergen and a lecturer for the Norwegian Red Cross.

ACKNOWLEDGEMENTS

The recent advances in military transfusion medicine have been described as a military medical revolution.[1] [2] Innovation is about the translation of theory into practice and the work presented here is primarily focussed on my contribution as a practitioner. Successful innovation requires team work and collaborative effort between organisations and academic disciplines. The author acknowledges the commitment and expertise of the wider Defence Medical Services, especially the military biomedical scientists.

Throughout the last decade of 2006-2016, the Birmingham military-civilian blood supply partnership led by these scientists has provided a global, safe and secure supply of blood to British military personnel, whilst fully complying with changing EU and UK standards. New clinical and technical capabilities were developed in response to the emerging clinical challenges. The *'Operational Apheresis'* and '*Blood to the Battlefield'* partnerships were recognised by several Military and Civilian Health Partnership Awards for both Innovation in 'Service Development' and 'Deployed Healthcare'.

Key partners in this development programme have been the US Armed Services Blood Programme, NHS Blood and Transplant, THOR, the NATO Blood Panel, the University Hospital Birmingham and the Blizard Institute. I am indepted to NHS Blood and Transplant for supporting me both as a military reservist and researcher. Special mention must be made of my sponsor Prof Tor Hervig and his colleagues in Bergen for enabling me to formalise this work as a thesis. Lastly, I thank my colleague, Dr Emma Watkins and my family, especially my husband Prof Jim Storr, for their unfailing support.

It has been a privilege to contribute to a new body of knowledge which I hope leaves a legacy to wider healthcare. My philosophy is captured in a quote from my TED talk in 2014.[3] '*In the last decade there has been a revolution in*

military medicine. We have changed the paradigm of how care is delivered, from pre-hospital care, to hospital, through to rehabilitation. There has been a revolution in the continuity of care, based on collaboration and cooperation instead of competition. We have joined the dots to get the sort of survival that we could never dream of.'

ABSTRACT

Introduction. Massive haemorrhage is the leading cause of preventable death following trauma. The mortality rate is high unless actively managed from Point of Injury (POI). However, during the last decade advances in military medicine, including transfusion support, appear to have delivered extraordinary survival advantages. A new transfusion policy was introduced in 2007 in response to the emerging analysis of combat experience underpinned by a revised understanding of the pathophysiology of trauma. Transfusion support was redesigned as part of Damage Control Resuscitation (DCR) to mitigate Trauma Induced Coagulopathy. The Massive Transfusion Capability was an ambitious programme designed to provide transfusion support throughout the continuum of care. The success has led to transfusion support being considered in military and civilian environments where there is a risk of haemorrhage but there is minimal medical infrastructure. Developments such as: a more portable cold chain; whole blood and lyophilised products offered Remote Damage Control Resuscitation (RDCR) whilst addressing the logistic tail. The delivery of the military capability has required considerable innovation during an era in which transfusion practice became subject to an increase in legislative and regulatory measures. The overall objective of this study is to evaluate the recent developments in military transfusion practice and to assess the impact on civilian practice.

Methods. The study describes the developments in military transfusion support in a linear sequence from 2006 to 2016. The adoption of military principles and practice is then explored in the context of civilian practice and national emergency transfusion preparedness for Mass Casualty Events (MCE). The source material thesis is derived from the author's military and civilian, professional and academic practice. The thesis submission is structured around four aims; two military thematic areas which are the recent changes in UK military blood transfusion practice and the development of pre-

hospital transfusion. These are followed by two civilian themes; the introduction of Massive Transfusion Protocols (MTPs) and transfusion planning for Mass Casualty Events (MCEs). The military data has been extracted from the UK Joint Theatre Trauma Registry complimented by quality management systems. The civilian data is derived from the relevant Trauma Registries, Patient Administration Systems and Laboratory Information Management Systems. Descriptive statistics were used to summarize the number of components by year, speciality and patient demographics. Statistical analysis was performed using a variety of software tools.

Results. The paradigm of military transfusion has changed in the last decade. The developments have been credited with contributing to survival of the critically injured. Survival is the product of the entire system of care, which – in this setting of combat, incorporates the early external haemorrhage control, hybrid resuscitation; rapid and physician-led recovery from the battlefield, damage control surgery, transfusion support and expert critical care. It is thus not possible to ascertain the individual contribution of transfusion however it has been an important element.

Transfusion support is increasingly being considered in at risk environments with minimal infrastructure and logistic support. The collection of Whole blood from a pre-tested Emergency Donor panel is a viable transfusion management option. Knowledge sharing from the Bergen based Blood Far Forward program has enabled the further development of UK military practice. In addition, the concept of the safe universal whole blood donor has informed the wider transfusion community leading to the acceptance of group O Low titre as a new standard.

Massive Transfusion Protocols (MTP) have been successfully introduced into civilian practice for both trauma and other causes of massive haemorrhage. Massive Transfusion (MT) is a phenomenon of surgery not trauma and the

organisational principles can be applied to all causes of haemorrhage. MT is resource intensive and has implications for both hospital and blood service organisation. However, the civilian studies have not demonstrated a survival advantage and the definitions of MT require standardisation to allow comparison of practice and the design of further studies.

The pattern of blood use in civilian Mass Casualty Events differs from that seen in the recent military experience in Afghanistan and Iraq. Far fewer injured require blood and few require Massive Transfusion and haemostatic component support. However, military style planning has added value to the preparation for MCEs and the response to Major Incidents. Elements of military planning have included the optimisation of pre-hospital care, haemorrhage control, transfusion triage, MTPs and emergency donor management. Transfusion Emergency Preparedness should become an integrated part of healthcare emergency planning.

Conclusions. Transfusion has emerged as an essential and successful element of modern combat care. The success must be placed in the context of the whole healthcare system, especially pre-hospital care. The nature of military and civilian trauma differs however, many of the recent lessons identified have been intelligently applied to civilian hospital healthcare. Military practice has also informed both pre-hospital emergency care, blood component development and transfusion planning for MCEs. In turn, combat care has benefitted from civilian transfusion governance and regulatory expertise. The continued military-civilian collaboration and innovation in transfusion practice has the potential to benefit not only the military, but also the wider healthcare community.

LIST OF PUBLICATIONS

1. Jansen, J.O., Morrison, J.J., Midwinter, M.J. & **Doughty, H**. (2014). Changes in blood transfusion practices in the UK role 3 medical treatment facility in Afghanistan, 2008-2011. *Transfusion Medicine,* 24 (3), 154-161.

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3. **Doughty, H**., MacGuire, A. Fitchett G & Parker, P.J. (2017). The feasibility of Group O LOw titre panels for small combat teams. *Journal of the Royal Army Medical Corps,* published online first 06 September 2017. doi:10.1136/jramc-2017-000830.

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LIST OF ABBREVIATIONS

This section provides details of the principal abbreviations used within the thesis

Abbreviation	Represents
ABC	Airway, Breathing and Circulation. A structure for resuscitation
ACoTS	Acute Coagulopathy of Trauma/Shock
AGoMM	Advisory Group on Military Medicine
AJP	Allied Joint Doctrine
AME	Austere Medical Environment
APTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
ATD	Adult Therapeutic Dose
ATLS	Advanced Trauma Life Support
ATP	Acute Transfusion Package
ATR	Acute Transfusion Reaction
BMS	Biomedical Scientist
BSH	British Society for Haematology
BSMS	Blood Stocks Management Scheme
BSQR	Blood Safety Quality Regulations
BST	Blood Supply Team
CCAST	Critical Care Air Support Team
CDL	Component Development Laboratory
CE	Conformité Européene (literal)
CGOs	Clinical Guidelines for Operations
COMEDS	Committee of the Chiefs of Military Medical Services in NATO
CPA	Clinical Pathology Accreditation
CPD	Citrate Phosphate Dextrose anticoagulant solution
CT Scan	Computerised Tomography Scanner

DAT	Direct Antiglobulin Test
DCR	Damage Control Resuscitation
DCS	Damage Control Surgery
DIC	Disseminated Intravascular Coagulation
DLoD	Defence Lines of Development
DMS	Defence Medical Services
DMSTC	Defence Medical Services Transfusion Committee
ED	Emergency Department
EDP	Emergency Donor Panel
FBC	Full Blood Count
FFP	Fresh Frozen Plasma
FWB	Fresh Whole Blood
GCP	Good Clinical Practice
GHB	Golden Hour Box®
GHOST-T	Golden Hour Offset Surgical Trauma-Team
GMP	Good Manufacturing Practice
HBc	Hepatitis B Core
HBsAg	Hepatitis B surface antigen
HEMS	Helicopter Emergency Medical Service
HEV	Hepatitis E
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
HPA	Health Protection Agency
HT	High Titre
ICRC	International Committee of the Red Cross
ICU	Intensive Care Unit
IED	Improvised Explosive Device
IOCS	Intra-operative Cell Salvage
ISBT	International Society of Blood Transfusion
ISS	Injury Severity Score

ITU	Intensive Treatment Unit
JADTEU	Joint Air Delivery Test and Evaluation Unit
JPAC	The Joint Professional Advisory Committee
JTTR	Joint Theatre Trauma Registry
LIMS	Laboratory Information Management System
MCE	Mass Casualty Event
MEDEVAC	Medical Evacuation
MERT	Medical Emergency Response Team
MHRA	Medicines and Healthcare products Regulatory Agency
MoD	Ministry of Defence
MT	Massive Transfusion
MTC	Massive Transfusion Capability
MTF	Medical Treatment Facility
MTP	Massive Transfusion Protocol
NATO	North Atlantic Treaty Organisation
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NISS	New Injury Severity Score
PAS	Platelet Additive Solution
PBM	Patient Blood Management
PHEC	Pre-Hospital Emergency Care
PI	Pathogen Inactivation
PJHQ	Permanent Joint Headquarters
PLT	Platelet
PoCT	Point of Care Testing
POM	Prescription Only Medicine
RCC	Red Cell Concentrate
RDCR	Remote Damage Control Resuscitation

RIP	Relief in Place
ROTEM	Rotational Thromboelastometry
rFVIIa	Recombinant Factor Seven
SAG-M	Saline-adenine-glucose-mannitol
SGPL	Surgeon General's Policy Letter
SHOT	Serious Hazards of Transfusion
SIRS	Systemic Inflammatory Response Syndrome
TARN	Trauma Audit and Research Network
TCCC	Tactical Combat Casualty Care
TEG	Thromboelastography
THOR	Trauma, Hemostasis and Oxygenation Research network
TIC	Trauma Induced Coagulopathy
TP	Thawed Plasma
TRALI	Transfusion-Related Acute Lung Injury
TXA	Tranexamic Acid
UKBTS	UK Blood Transfusion Services
UOR	Urgent Operational Requirement
vCJD	Variant Creutzfeldt-Jakob disease
VHA	Visco-Elastic Haemostatic Assay

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1: INTRODUCTION

1.1 Catastrophic haemorrhage

Setting the scene *On 22 March 2017 at 14.40, an attacker drove a car along a pavement on Westminster Bridge in London, stabbed an unarmed policeman and was shot dead by police in the grounds of the UK Parliament. Five people died. Initial police reports suggested that at least 50 people were injured, with 31 requiring hospital treatment.*

Immediately after the attack, an ex- soldier tried to stop the bleeding and delivered CPR to the critically injured policeman. Within minutes there was an armed response unit present with control of the situation. Outside the Palace of Westminster, the emergency services had gone to work, setting up makeshift treatment areas for the wounded. An air ambulance carrying 'Blood on Board' landed in Parliament Square.

Patients were triaged with the most seriously injured taken to Major Trauma Centres. One example was Imperial College Healthcare NHS Trust where eight casualties were received. Casualties were assessed by senior clinicians with rapid transfer to surgery. Massive Haemorrhage Protocols were delivered as part of Damage Control Resuscitation

NHS Blood and Transplant, the English Blood Transfusion Service was stood up at 15.15 hr. Orders were placed for group O red cells, group A plasma and platelets. Emergency deliveries were made to 3 hospitals and validation of newly collected platelets was brought forward. By 16.00 157 units of platelets were validated and released into the system. All customer orders were met.

This vignette describes an incident in which the medical response includes: pre-hospital haemorrhage control and resuscitation by a trained first aider; the early

arrival of a helicopter borne medical team with blood on board; pre-hospital triage with the most severely injured transported to specialised trauma centres; early treatment with Massive Transfusion Protocols (MTP) and operational response by the blood service. In 2003, this co-ordinated response could not have taken place within either military or civilian practice.

The lessons identified from the US and UK military casualties in Iraq, from 2003, appear to have led to a 'revolution' in modern military and civilian trauma care which includes a revised role for blood transfusion.[4] This thesis explores that journey of how military transfusion has developed during the last decade and the impact on civilian practice.

Haemorrhage control

Massive haemorrhage is the leading cause of preventable death following trauma.[5;6] The mortality rate is high unless actively managed from the point of wounding or injury. During the last decade (2006-2016) the advances in military medicine, including preventative measures, appear to have delivered extraordinary survival advantages.[7;8] These findings are welcome but not surprising. History has taught us that conflict is a powerful stimulus to innovation, especially in trauma medicine. DeBakey proposed that 'rapid progress in trauma care occurs when the results of translational research are promptly integrated into clinical practice.[9] Experience with a high volume of severely injured casualties expedites the process'. Historically, these conditions converge during times of conflict.[10]

The early experience from recent operations in Iraq from 2003 onwards had identified that haemorrhage was the cause of death of many 'survivable casualties'.[11] Urgent action was required. The UK response was crystallised in an internal report issued by the Director General of the Army Medical Services (UK) in August 2004. The report was entitled 'Increasing surviving on

the battlefield'. It called for new programs focused on advances in pre-hospital care to provide 'tools' to the frontline soldier. The management of life-threatening haemorrhage was prioritised over and above the traditional ABC of resuscitation, i.e. Airways, Breathing, and Circulation. The new paradigm became <C>ABC where the C represented catastrophic haemorrhage. A 'ladder of haemorrhage control' was developed starting with a pressure dressing and elevation and then progressing with new haemostatic dressings,[12] tourniquets,[13] injectable haemostatic agents and surgery. See Figure 1.

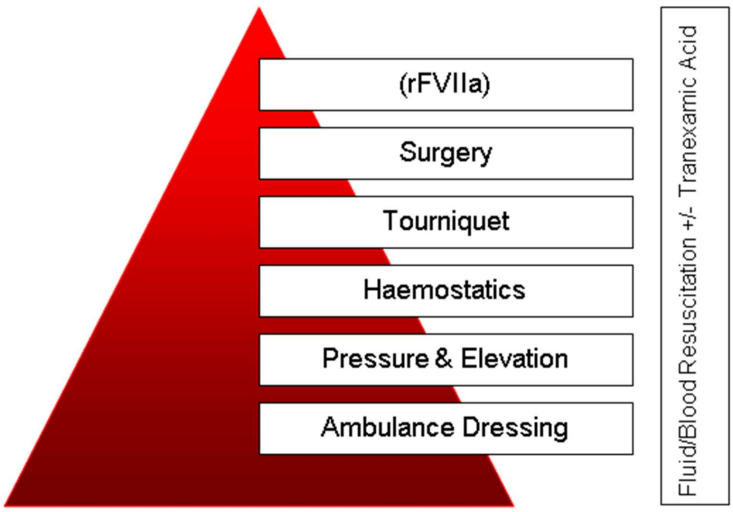

Figure 1. Ladder of haemorrhage control (Adapted from Mallison, 2011)[14]

Damage control surgery

The definitive management of physical haemorrhage in combat is Damage Control Surgery (DCS). The term 'Damage Control' was first adapted by Rotondo and Schwab in 1993.[15] The concept was taken from the United States Navy who initially used the term as "*the capacity of a ship to absorb*

damage and maintain mission integrity". Articles on the damage control sequence were available from the mid-1990s[16]. In summary, DCS limits the immediate surgical interventions in severely injured trauma patients to those that address life-threatening injuries such as haemorrhage. Further surgery is deferred until metabolic and physiological derangements have been addressed. These derangements included the '*lethal triad'* of hypothermia, acidosis and coagulopathy which had long been recognised as a significant cause of death in patients with traumatic injuries. In 1982, a study described a "bloody vicious cycle" in which haemorrhage together with tissue injury cause this predictable triad of complicating factors.[17] Resuscitation had focused on the rapid reversal of acidosis and prevention of hypothermia. However, Hess *et al.* contended in their 2006 review, that the direct treatment of coagulopathy was relatively neglected.[10] The coagulopathy following trauma was then seen largely as a byproduct of resuscitation, haemodilution, hypothermia and delays by blood banking logistics. Other contributions included consumption caused by disseminated intravascular coagulation (DIC) and platelet dysfunction caused by colloids used for resuscitation.[18] A greater understanding was required of the epidemiology and underlying pathophysiology of trauma induced coagulopathy (TIC) if the problem was to be successfully addressed.

Trauma induced coagulopathy

During the early 2000s, the historic view of the lethal triad was being replaced by epidemiologic and molecular evidence for a distinct syndrome of trauma-associated coagulopathy or physiological bleeding. The seminal work by Brohi *et al.* 2003[19] in London, described the phenomenon that one third of civilian trauma patients had abnormal clotting on admission to hospital. The coagulopathy appeared to be an independent marker of morbidity and mortality. The findings from London were subsequently confirmed by studies from the USA[20] and Germany[21]. The cause of the early coagulopathy was

thought to be due to an intrinsic response to tissue damage. Evolving work from Brohi[22] introduced the concept of an Acute Coagulopathy of Trauma-Shock (ACoTS) in which hyperfibrinolysis, activation of protein C and up-regulation of thrombomodulin pathways all contributed significantly to this early coagulopathy. This process, as well as endothelial activation and subsequent coagulation changes, was thought to be mediated by hypoperfusion and tissue hypoxia. The term TIC has increasingly replaced the term ACoTS. [23] Figure 2 depicts the various inter-related contributions to this evolving concept and the implications for potential management. The concepts underpinned the subsequent development of 'an integrated and coherent pre-hospital shock resuscitation plan that addressed the intravascular treatment of coagulopathy'.[24]

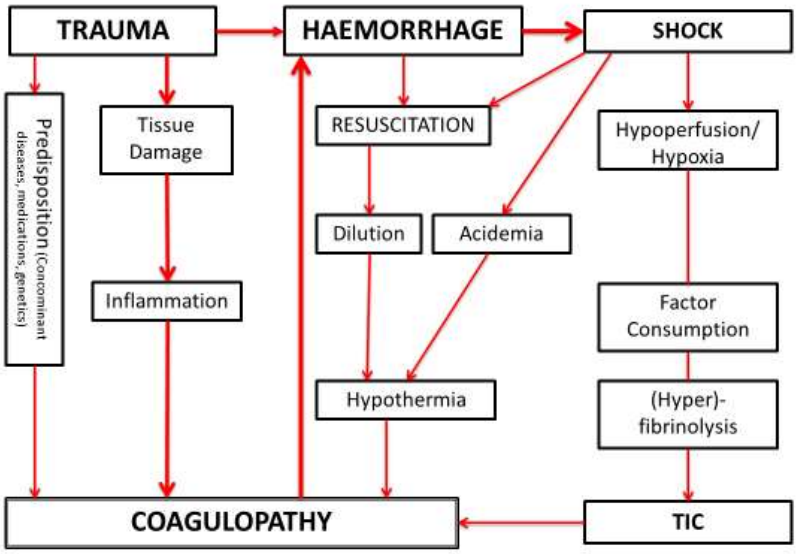

Figure 2. Diagram showing some of mechanisms leading to coagulopathy in the injured. TIC = Trauma Induced Coagulopathy.
Adapted from Brohi et al. 2009 [23]

Shock resuscitation

The goals of shock resuscitation had been to restore blood pressure and urine output to reverse the metabolic consequences of hypoperfusion. Pre-hospital trauma life support and advanced trauma life support early resuscitation practice was based on using crystalloid and colloid solutions. However, aggressive crystalloid based resuscitation may worsen the presenting acidosis and coagulopathy as well as increase acute respiratory distress syndrome (ARDS), abdominal compartment syndrome, systemic inflammatory response syndrome (SIRS) and multiple organ failure.[24] The revised aim was to minimise the use of crystalloid and to accept hypotensive resuscitation for the first hour.[25] Holcomb and others argued that where feasible, blood components should be used early in the resuscitation phases instead of crystalloids.[26] Plasma provides intravascular volume, buffering capacity and clotting factors. However, there is evidence that plasma based resuscitation does not correct conventional laboratory coagulation tests.[27;28] It may be that the protective effect of plasma is due to its ability to restore the endothelial glycocalyx and syndecan-1, which plays an important role in maintaining vascular stability.[29 30] Whatever the mechanism, recent animal studies endorse the biologically plausible approach of haemostatic resuscitation.[31]

The emerging concept of Haemostatic Resuscitation using blood components was directly at odds with the prevailing civilian transfusion practice.[32] The reason for this was twofold, firstly that blood is often in short supply and second, blood as a biological material is associated with adverse effects, including infection. The historic and recent scandals of infected blood products were well known to both physicians and politicians. Recent evidence had demonstrated that red cells could be safely withheld in the haemodynamically stable patient.[33] Civilian guidelines for transfusion within the UK and most other countries had moved towards a more conservative and cautious approach focussed on minimising, rather than appropriate, blood use. The

appropriate use of blood was formalised within the UK as 'Better Blood Transfusion',[34] which was the forerunner of the subsequent Patient Blood Management (PBM) movement.[35]

Changing newly established practice back to transfusion led resuscitation would require evidence and endorsement from blood services. Creating the evidence base for change would be a challenge. Massive transfusion was uncommon (1-2%) in civilian trauma practice making it difficult to develop and test new management concepts.[36] However, recent military practice offered a unique opportunity to inform a change in practice with quality, prospectively collected data. For the first time in UK and US warfare, data for all admitted trauma casualties were entered into a joint theatre trauma registry (JTTR).[37] Using a retrospective review of the US JTTR data, Holcomb demonstrated that 5-7% of US combat casualties required massive transfusion, i.e.10 or more units of red cells. In addition, the early evidence, subsequently published from Borgman *et al.*, suggested that early transfusion with plasma and platelets saved lives.[24] Borgman's retrospective analysis of 246 patients showed that the overall mortality rate was 19% when a high ratio (1:1.4) of plasma to red cells was used in contrast to a mortality rate of 65% when the plasma to RCC ratio was low at 1:8. As a result, Holcomb and others proposed a radically different approach to resuscitation for the critically injured based on a pre-emptive plasma rich MTP.[24]

Global massive transfusion practice

Massive transfusion was traditionally defined as the transfusion of ten or more units of red cells in less than 24 hr.[38] The definition is historic and is intended to represent the replacement of an average adult blood volume. The author suggests that it existed in part, due to practical clinical and laboratory accounting practice. The use of fluids in resuscitation practice had traditionally been sequential. Most massively transfused patients were initially

treated with crystalloid and colloids followed by red cells. The use of plasma and haemostatic components were prescribed once coagulopathy had been confirmed.[32;39] In 2005, Malone *et al*. reviewed massive transfusion practice around the globe.[38] Most of the protocols were from within the US. Mention is made of protocols obtained from Canada, France,[40;41] Finland and the UK.[39] It is probable that this list was based on researchers and practitioners known to the researchers and was not comprehensive. Despite this limitation, the conclusions were valuable.

Malone *et al.* proposed a pragmatic MTP based on a simple 1:1:1 ratio of red blood cells (RBC): plasma: platelets.[38] The practicalities for such protocols were defined by the different local platelets preparation. For instance, the apheresis pack in the US provided the equivalent of a pool of 6-11 buffy coat derived platelets, whereas other countries such as the UK were using pools of 4-5 buffy coats. The details of the transfusion protocol were important. For instance, if platelets were not given until after the RBC and plasma, they recognised that the 1:1:1 balanced ratio may not be achieved until about 20 units of RBC had been given. There was a risk of dilutional coagulopathy due to the use of RBC, as demonstrated by Seppo Hiippala.[42] These early works refer to the dilution of coagulation factors and fibrinogen following total blood volume replacements. However, more recent mathematical work by Hirshberg and colleagues had shown that initial resuscitation with as little as five or more units of RBC led to dilutional coagulopathy.[43] Smaller 'Acute Transfusion Packages' (ATP) would be required.

A commentary paper by Holcomb in 2007 [24] described an MTP based on 6 units of plasma, 6 units of packed RBCs, 6 packs of platelets and 10 units of cryoprecipitate, each stored in individual coolers. The protocol was similar to the Copenhagen concept in which the transfusion protocols were combined with ongoing monitoring during surgery and the post-operative phase.[44] A paradigm shift was required in which plasma, platelets and cryoprecipitate

would be used proactively. In addition, military practitioners were successfully using fresh whole blood (FWB)[45] as an adjunct to component therapy. It is noted that this was a controversial practice but FWB provided fresh red cells and platelets and delivered good results. The underpinning theory was that protocols that reduced coagulopathy through restoration of an intact coagulation system should reduce overall blood use[46] and improve survival.[47]

UK Massive transfusion policy

The UK policy for the management of massive haemorrhage on operations was developed during 2006 and first issued as a UK military Surgeon General's Operational Policy Letter (SGPL) in July 2007. Further editions were released to incorporate pharmaceutical adjuncts such as tranexamic acid.[48;49] The policy maker's challenge was to agree on a simple, safe and standardised protocol based on opinion and emerging practice rather than high-grade evidence. The policy provided a brief rationale for the proactive use of blood and a new MTP. The policy recognised the limitation of the prevailing definition of massive transfusion, such as 10 units of RBC in 24 hr.[38] Therefore, it incorporated more practical criteria for the initiation of transfusion support based on rates of blood loss, mechanism of wounding, and physiology to identify the casualty at risk. The key elements of the military policy, including the definitions and principles, are shown in Box 1. Close monitoring was required to optimise transfusion support and to minimise the potential complications.

Practicalities. The MTP was designed to be initiated by clinical staff who were concerned that the patient has had, *or may be at risk,* from the effects of massive or rapid haemorrhage. Ordinarily, this was the medically qualified trauma team leader. However, any hospital based triage officer or pre-hospital teams could trigger the request. Speed, security and systems were essential. Roles were assigned, as per updated Advanced Trauma Life

Support (ATLS) algorithms to staff members with the appropriate expertise, e.g. anaesthesiology for securing airway, emergency medicine for intravenous access. A new development was the redeployment of laboratory staff to the Emergency Department (ED)[50] to receive baseline blood samples and to hand over the 'Shock pack'. The Shock Pack was 4 units each of Group O RhD negative red cells and thawed Group AB Fresh Frozen Plasma (FFP). Later, this practice was modified to deliver mini-Shock Packs of 2+2, especially for small patients and pre-hospital work. Blood components were initially released as 'universal' blood, i.e. group O RhD negative RBC and group AB FFP. The red cells were issued as less than 14 days old to minimise the risk of the red cell storage lesion. [51] This had a considerable implication for managing the supply chain. [52] [53]

Box 1. Key elements of military massive transfusion policy

Definitions: Massive transfusion was defined as:

1. The replacement of an equivalent amount of blood to an entire circulating blood volume of the patient with 24 h; or
2. Administration of more than 10 units of red cell concentrate within 24 h (whichever comes first).

Criteria: In the acute military operational setting, additional criteria include:

1. The transfusion of over 4 units of red cells in 1 h; or
2. The replacement of 50% of the total blood volume in 3h; or
3. A rate of loss of >150mLmin−1.

Principles of the Defence Medical Services (DMS) Operational Massive Transfusion Protocol

The DMS operational MTP adopted an aggressive resuscitation approach in which the primary aim is to avoid a significant degree of coagulopathy. This approach required:

1. Active avoidance of hypothermia using fluid warmers and rapid infusion devices.
2. Maintain the haematocrit at 35%.
3. Use of FFP to RCC in a 1:1 ratio as soon as practicable.
4. Early use of cryoprecipitate to maintain the level of fibrinogen above 1.0 g L−1.
5. Early intervention with platelet support to maintain the platelet count above 100×10^9 L−1.
6. Frequent measurement of FBC and coagulation studies to confirm successful application of the MTP.
7. Frequent measurement of potassium and calcium levels to identify the development or presence of hyperkalaemia or hypocalcaemia so that appropriate therapy can be started.
8. Appropriate intervention with rFVIIa in accordance with current military guidelines.
9. Regular assessments of the base deficit to monitor, along with hypothermia and coagulopathy, the lethal triad associated with massive trauma.

An overview of the staged approach to the delivery of the UK MTP is shown in Figure 3. The UK protocol did not include platelets (PLT) or a source of fibrinogen in the initial pack, in contrast to the emerging military[24] and civilian protocols.[24 54-56] This was due in part to a perceived need to carefully manage scarce resources as there was limited access to these components. This staged approach was consistent with the Canadian National Advisory Committee on Blood and Blood Products – Massive Transfusion Consensus Conference 2011.[57] The evidence at the time for the use of a 1:1:1 RBC: FFP: PLT protocol was limited to retrospective and historical case-control series with no prospective randomised trials addressing ratio-based blood support. The influential consensus argued that the published data exhibited potential survivorship bias and the poor generalisability of single site studies.

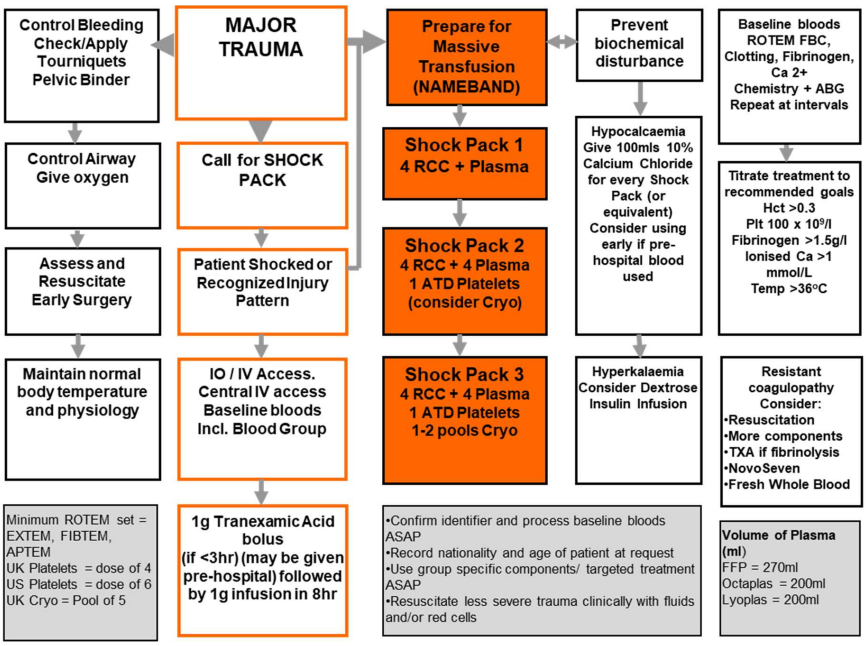

Figure 3. An overview of the Massive Transfusion Protocol.

Adapted from JSP 999.[49]

The counter argument for a phased use of haemostatic components was the developing evidence base for the role of fibrinogen in major haemorrhage. Fibrinogen levels fall following traumatic haemorrhage. The CRYOSTAT study showed that the mean blood fibrinogen level in all trauma patients at admission was 1.55 g/L.[58] Further resuscitation may dilute this.[42] A prospective observational study of 517 patients had reported that admission fibrinogen levels are an independent predictor of mortality in trauma patients. There was a good rationale for fibrinogen replacement using either cryoprecipitate or fibrinogen.[59] Recent guidelines[60-62] recommend that if fibrinogen remains low (<1.5 g/l) despite the use of plasma, then cryoprecipitate or fibrinogen concentrate should be administered. In summary, the UK approach started with a foundation ratio of red cells and plasma followed by individualised or 'goal directed therapy' guided by coagulation monitoring. However, during the study period of this thesis there was an increasing trend for the inclusion of platelets and cryoprecipitate during the early phase of resuscitation.

Coagulation monitoring

Goal directed therapy required diagnostic support to guide the use of blood components, especially the use of platelets and cryoprecipitate. In 2006, the UK Field Hospital laboratory could only provide the conventional coagulation tests and did not have access to the whole blood Viscoelastic Haemostatic Assays (VHA) used in civilian practice.[56] The available conventional coagulation tests were the Activated Partial Thromboplastin Time (APTT), the Prothrombin Time (PT) and the fibrinogen assay. However, these tests were designed to diagnose factor deficiencies and have limitations when used for guiding treatment in acquired coagulopathies such as TIC.[63] In contrast, VHAs determine the functional coagulation status of whole blood. The relative contribution of fibrinogen and platelets to clot strength can be tested through the use of specific inhibitors. The viscoelastic properties of unspun

whole blood samples are recorded under low shear conditions and can be displayed as a visual profile of clot formation and breakdown over time. VHAs may be performed as a point of care test to provide clinically relevant information at 5-10 minutes. The tests have traditionally been used in major surgery leading to massive transfusion (MT) but are currently not approved in the UK for routine use in trauma.[64] Further guidance is required for trauma. The currently recruiting iTACTIC trial is a randomised controlled trial designed to compare VHA guided resuscitation versus optimised conventional coagulation tests.

Pharmaceutical adjuncts

Factor Seven. The new UK military massive haemorrhage policy in 2007 introduced the use of activated recombinant Factor Seven (rFVIIa). rFVIIa is a manufactured version of Factor VIIa and is licensed to control bleeding in patients with haemophilia and those with clotting factor inhibitors. The drug was also available off-licence for the use of acquired coagulopathy. A multicentre randomised controlled trial (RCT) had examined the efficacy of rFVIIa,[65] and found that treatment with rFVIIa in blunt trauma produced a significant reduction in the massive transfusion requirement of patients surviving for more than 48 hours. The first recorded UK military use of the drug was described in 2005.[66] UK military guidance for use was provided in 2007[67] and the drug was incorporated into policy. Recombinant FVIIa was to be considered only after first line therapy had failed. When used, it was to be given alongside haemostatic substrate and normalisation of physiology including core temperature. Later, a Cochrane review concluded that the use of rFVIIa as a haemostatic drug remained unproven.[68] In addition, Levi *et al.*[69] reviewed the safety of rFVIIa and found an increased rate of arterial thromboembolism, which increased with patient age. In practice, the drug was rarely used in military hospital practice after the development of the

military Massive Transfusion Capability and the evolution of Damage Control Resuscitation.

Tranexamic acid. Tranexamic acid (TXA) had long been shown to reduce blood loss in surgery without the risk of thrombotic complications.[70] Renewed interest and experience in civilian practice had led to early informal adoption of TXA within battlefield resuscitation.[71] However, it was the CRASH-2 trial,[72] a huge global randomised controlled trial, that led to the wider adoption of TXA. The findings of the trial showed that TXA safely reduced the risk of death in bleeding trauma patients and that the all-cause mortality was reduced. However, the risk of death from bleeding was reduced by a modest 0.8%. Further sub-analysis of the CRASH data suggests that it was the early use of TXA, within 3hr, which delivers benefit. [73] Despite some reservations about the CRASH study there was emerging evidence for the use of TXA in combat related haemorrhage. The MATTERs study published in 2012 demonstrated the synergistic effects of TXA and fibrinogen in military practice.[74] TXA was added to the MTP within the Clinical Guidelines for Operations (CGOs)[49] and a supportive commentary was provided by the North Atlantic Treaty Organization (NATO) Blood Advisory Team.[75]

Damage control resuscitation

The concept of Damage control resuscitation (DCR) was formally introduced into the UK Defence Medical Services in 2007 to draw the range of advances in pre-hospital and hospital-based trauma care together into a coherent doctrine. [25] DCR was developed with a similar goal to that of DCS, i.e. to prioritise those interventions that address life-threatening bleeding and restore normal physiology. The authors note that the concept can also be used as a tool to assist military planning as in the tactical lay down of medical assets. The recognised framework for medical planning is the NATO 10-1-2 treatment timelines.[76] In summary, enhanced first aid should be delivered within 10 min

of wounding with access to DCR within 1 hour. Damage control surgery should be provided no later than 2 hours from wounding.

The UK definition of DCR was '*a systematic approach to major trauma combining the catastrophic bleeding, airway breathing and circulation (<C>ABC) paradigm with a series of clinical techniques from point of wounding to definitive treatment to minimise blood loss, maximise tissue oxygenation and optimise outcome'*.[25] It should be noted that this definition differed from the US military definition in which DCR starts from arrival in the ED and continues through to the Intensive Treatment Unit (ITU).[24] The US definition continues to exclude pre-hospital interventions. It is perhaps this definition which subsequently led to the perceived need for a 'Remote' or pre-hospital DCR. The haemostatic elements of the mature UK doctrine of DCR included:

- Haemorrhage control techniques from the point of wounding
- Battlefield Advanced Trauma Life Systems interventions
- Advanced in-flight intervention by a primary retrieval team which later included the administration of blood and plasma
- Consultant-based trauma team at the field hospital
- An aggressive approach to coagulopathy, hypothermia and acidosis using early blood component support referred to as haemostatic resuscitation
- Diagnostic imaging support
- Damage control surgery

Changing Injury Patterns. In 2006, the mechanism of injury was largely ballistic. By 2010 this had changed to blast trauma with a more proximal injury pattern. The signature injury became bilateral high transfemoral amputations and associated pelvic and perineal injury. This small cohort of critically injured patients required extraordinary surgery and massive resuscitative effort. [77] Whereas the concepts of DCR and DCS were initially

described as separate activities in a linear sequence of resuscitation, surgery and critical care, the elements were increasingly combined. Midwinter and Woolley elegantly described the emergence of integrated DCR/DCS shown in figure 4.[78] The speed of translation from theory to practice was extraordinary - Battlefield Medicine was 'Transforming in Contact' and would require considerable support from the transfusion community.

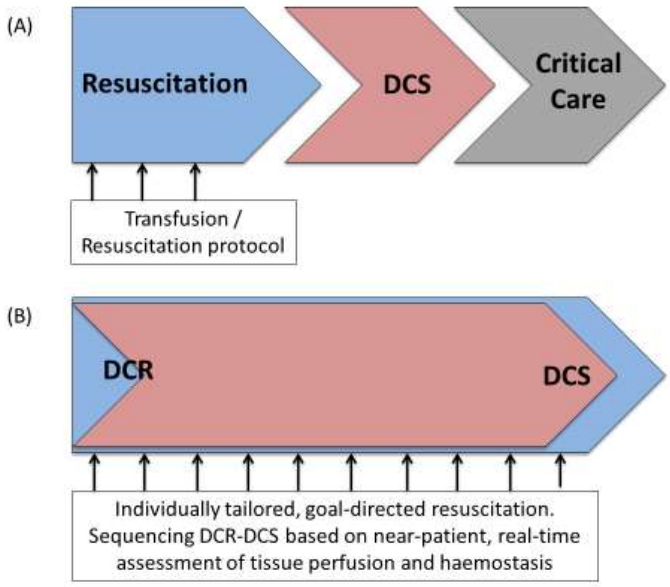

Figure 4. The evolution of damage control resuscitation adapted from Midwinter and Woolley 2011 [78]

1.2 Developing the British military Massive Transfusion Capability

The Massive Transfusion Capability

Introduction. The Massive Transfusion Capability (MTC) was the wider defence programme developed in response to both the new haemorrhage policy and the

requirement for a greater transfusion capacity and capability. Capability is defined as *the combination of equipment, trained personnel and support that gives the armed forces the capacity to achieve the tasks they are given*.[79] The purpose of the MTC was to deliver transfusion support, as an integrated part of resuscitation, delivered as far forward as possible. The programme was co-ordinated within the Defence Medical Services (DMS)

Organisation of military healthcare. The organisation of military medical support is important for understanding the delivery of haemorrhage control and transfusion-based resuscitation. The organisational framework provides the context for the introduction of the MTC and the subsequent developments in pre-hospital transfusion. The care of the patient outside of the UK is termed the operational care pathway. Care is organised in echelons or roles with increasing medical capability. Current NATO doctrine recognises 4 roles from the basic first medical treatment facility (MTF) to the sophisticated home base hospitals.[76] The details for each Role are provided in Appendix 1. The focus for this section is the Role 3 field hospital whereas the next section is focused on Roles 1 and 2.

Transfusion logistics. The supply of blood for the armed forces within this framework may be a function within logistic or medical commands. It is a considerable logistic challenge to deliver short shelf-life products with demanding storage criteria within a military 'Line of Communication'. Therefore, blood supply and distribution has historically been the role of specialised units. In the UK, both models of command have been used, however, during the period of study, transfusion was a defence logistics responsibility. Organisational restructuring had led to the creation of the Medical Supplies Integrated Project Team (Med S IPT) on 1 April 2005. The Blood Supply Team (BST), a sub-unit comprising of 3 biomedical scientists (BMS), was established in Birmingham. The team was charged with the co-

ordination of global military blood supply compliant with the new European Directive.[80]

Regulatory framework. The assumptions underpinning the capability recognised the new transfusion regulatory framework and the need for appropriate clinical use of blood (Doughty and Walker, internal briefing papers). The European Directive 2002/98/EC[81] set standards of quality and safety for the collection, testing, processing, storage and distribution of blood. Directive 2004/33/EC[82] provided further technical guidance and required member states to bring into force the necessary laws, regulations and administrative provisions by 8 February 2005. The UK Blood Safety and Quality Regulations 2005 (BSQR)[83] were laid before Parliament on 18th January. The regulations designated the Medicines and Healthcare Regulatory Authority (MHRA) as the competent authority. Designated Blood Establishments were authorised to collect, test, manufacture and distribute blood. BST was to hold limited Blood Establishment status for blood distribution and storage. However, blood collection and military donor testing was contracted out to the civilian English blood service, NHS Blood and Transplant (NHSBT). Blood components from Birmingham were shipped using the military assets and logistics chain. The principle framework for blood component specifications are the Guidelines for the UK Blood Transfusion Services.[84] Blood components were sourced from other countries, agencies and field programmes as required. An overview of the transfusion process from the donor to the hospital is shown in Appendix 2.

Delivery of the MTC programme.

Defence Lines of Development. The MTC was an extraordinarily ambitious programme which covered many aspects of the logistics, laboratory and clinical capability. An overview is outlined in Appendix 3. The main MTC was delivered from 2010 within the framework of Defence Lines of Development

(DLOD).[85] The British Ministry of Defence's (MoD) DLOD is an example of a best-practice paradigms or frameworks where the interlinking functions and activities of the enterprise may be defined. A capability is typically managed and assessed using several dimensions or integrative elements.[86] In addition, the UK Defence Medical Services (DMS) cites *Interoperability* and *Clinical* as overarching themes that must be considered when any DLOD is being addressed. Such frameworks can take time to deliver as each dimension is developed by subject matter experts before integration. An overview of the key developments in military transfusion is shown in Appendix 3.

Urgent Operational Requirements. Several transfusion developments had started before the MTC as separate Urgent Operational Requirements (UORs). Urgent Operational Requirement (UOR) is a system used by the British MoD to obtain urgent equipment for operations. UORs arise from the identification of previously un-provisioned and emerging capability gaps where there is increased urgency to bring the capability into service.[87] The timeline for the key individual elements that were delivered rapidly as UORs were: operational platelet apheresis (2008), new transport and storage boxes based on phase change material (2008), a Laboratory Information Management System (2009) and the introduction of Rotational Thromboelastometry (ROTEM) (2009). The MTC programme continued through to October 2013. Some of the other elements in this program, especially the laboratory modernisation items were delivered as part of a later project.

Concept of Employment. The 'Concept of Employment' for the Massive Transfusion capability was described as 4 sub-capabilities that together delivered the Massive Transfusion Capability. These are listed below and considered in turn:

a) Blood product transport and storage
b) Blood product delivery, including blood warmers and rapid infusers.
c) Blood testing: Laboratory and Near Patient Testing,

d) Blood product generation including platelet apheresis and microbiology testing

Table 1 An overview of the recent developments in military transfusion practice

Year	Month	Development	Notes	Ref
2007		Massive Haemorrhage Policy	Including the Massive Transfusion Protocol. Updated in 2009.	[48]
2007	May	Regular supply of platelets from the UK	Validation of phase change material technology	
2008	April	Operational platelet apheresis	Generation of platelets in plasma	[53]
2008	June	Blood for helicopter based Medical Emergency Response Team	Use of Golden Hour Box	[88]
2009	May	Expansion of Emergency Donor Panel	Resilience measure for Pandemic Flu	
2009	June	LIMS (Laboratory Information Management System)	Blood component issue and accounting	[53]
2009	Jan	ROTEM (Rotational Thromboelastometry	Point of Care Test for haemostasis	[89;90]
2009	Jan	Evaluation of point of care testing for Blood Borne Viruses	Commissioned civilian evaluation	
2009	Jul	Role 2 Transfusion policy	Designed initially for the Navy	
2010		Paediatric transfusion guidelines	Clinical Guidance for Operations and training	[91]
2011	Jan	Lyoplas-N	Lyophilised plasma	[92]
2011	Nov	Defence Medical Services Transfusion Committee	Reports to DMS Clinical Committee	
2011	Nov	Belmont Rapid Infuser	Rapid Infuser System	

Blood product transport and storage

Cold chain management. Blood components are a valuable temperature-sensitive licensed resource that requires carefully controlled and monitored transport and storage.[83] A summary of the storage requirements and shelf-life is shown in Table 2. All storage equipment is calibrated, maintained and temperature mapped in accordance with Blood Safety and Quality Regulations 2005[83] and the Guidelines for the Blood Transfusion Services in the United Kingdom.[84]

Table 2 Blood component storage requirements (UK 2016)[93]

Component	Storage temperature (°C)	Shelf-life (days)	Post reconstitution or post-thaw shelf-life
Whole Blood (in CPD-A)	4°C ± 2	28 days	NA
Red cells	4°C ± 2	35 days (can be extended to 42)	NA
FFP	-20°C -25°C	6 months 3yr	1-day 4°C ± 2 5 days if dry thawed
LyoPlas	2-25 °C	15 months	6 hours at 2-25 °C
Cryoprecipitate	-20°C -25°C	6 months 3yr	24 hr at room temperature. Do not refrigerate.
Platelets	22°C ± 2 (with agitation)	5 days	7 days with bacterial testing or pathogen inactivation

Phase change material. One of the most significant advances in cold chain capability was the introduction of a new generation of passive transport containers which could maintain temperature without power.[53] These were sealed containers consisting of a fabric outer case and a vacuum insulated chamber with an inner, removable thermal isolation compartment. The product

used was the Golden Hour Box® (GHB) (Minnesota sciences and Credo) which offered products with a range of both sizes and temperature range. The two litre model selected for the Medical Emergency Response Team (MERT) maintained storage temperatures of 2-8°C for up to 72 hours in external temperatures of 45°C. The storage temperature was continuously monitored using the TempIT® tag, temperature indicator together with single-use time-temperature indicators WarmMark® and ColdMark®. The platelet version of the box was introduced to maintain a similar temperature control chain but optimised at 22°C (+/- 2).

Op Vampire. The new capability revolutionised the transport and storage of blood components and enabled blood to be projected as part of the airborne capabilities and later for ground based troops.[94] However, the need to recondition the thermal isolation compartment in freezers tied the forward units to the field hospital.[88] The GHBs were used for the pre-hospital delivery of blood and plasma for the UK enhanced Medical Emergency Response Team (MERT) co-located with the Field Hospital. The MERT is a multi-disciplinary advanced medical retrieval team working in the back of a Chinook helicopter. Pre-hospital transfusion was considered for patients without a palpable radial pulse or who had a non-invasive systolic blood pressure of less than 80mmHg. The aim was to restore these parameters, rather than to resuscitate to normotension, unless a traumatic brain injury was suspected, or time to definitive care was anticipated to exceed one hour. If more than one unit of RBC was required, plasma was co-administered, to achieve a ratio of 1:1. A loading dose of 1g of tranexamic acid (TXA) was given to all transfused patients. A fuller description of the organisation and capability is provided in paper 2 of this thesis. The call for MERT blood was affectionately termed *Op VAMPIRE*. The call led to the rapid issue of blood from the laboratory directly to the MERT team and also alerted hospital staff that critically ill patients would be arriving soon.

Blood Product Delivery

Blood warmers and rapid infusers. Critically ill patients were being delivered alive to the hospital. Many were hypovolaemic and hypothermic despite the extraordinary efforts of the pre-hospital team. Traditional pressure infusion devices exert pressure through the inflation of a bag in which a blood product bag has been placed. They have the advantages of being lightweight, easily stowed and manual rather than electronic. However, they do not warm blood products or deliver specified volumes, or deliver at the speeds required to resuscitate the severely hypovolemic patient, whereas, modern rapid infusers can support the rapid replacement of blood products and simultaneously warm blood products from a low initial temperature (4°C) to 37.5°C. In addition, any such system should be able to maintain a high flow rate without either inadvertently introducing cold fluid or air embolism. The Belmont FMS 2000® Rapid Infuser System was selected with use of the 3.0 litre reservoir or 'Bucket'. The use of this reservoir enabled red cells and thawed FFP to be pre-mixed in a 1:1 ratio. The resulting mixture was fondly referred to as 'Bastion Pink'. The Belmont could deliver controlled flow rates of up to 750mls/min of fluid at 37ºC and was brought into service in November 2011.

Other initiatives. Other initiatives included a feasibility study of Intra-operative cell salvage (IOBS). In November 2011, a small study demonstrated the feasibility of IOBS in a military field hospital within the combat environment.[95] However, the red cell savings were modest at the cost of logistic burden. A paediatric massive haemorrhage protocol was published in 2010.[91] The paediatric workload in the military environment during recent conflicts was estimated at 4% during Op TELIC (Iraq) and 8% for Op HERRICK (Afghanistan).[91] The figure for admissions to US Combat Support Hospitals (CASH) was 10%.[96] The military Massive Transfusion Policy was adult-based and needed to be translated for paediatric practice.

Blood testing: Laboratory and Near Patient Testing

Close monitoring was essential to guide transfusion therapy and minimise the potential complications of rapid and massive transfusion. Pathology monitoring may be via the laboratory or using Point of Care Testing (PoCT). PoCT supports rapid clinical decision-making but requires a quality framework and good record keeping.

Electrolyte disturbance. The two most significant biochemical disturbances complicating massive transfusion are hyperkalaemia and hypocalcaemia. Hyperkalaemia during massive transfusion is not uncommon and may prove fatal.[97] Postulated mechanisms include shock, older stored RBC, mechanical cell lysis due to high flow pressure bag type infusers, cell damage from blast, dehydration and massive fluid shifts from rapid whole-body reperfusion. Donated blood is collected in a citrate containing anticoagulant which chelates both ionised calcium[98] and magnesium.[53] Rapid transfusion of citrate may overcome the liver's ability to metabolise citrate with resulting citrate toxicity. Hypocalcaemia may cause death[99] due to a decrease in cardiac contractility and a predisposition to arrhythmia.[100] Calcium is also critical for coagulation, and platelet activity.[101]

Coagulation. 'Goal directed therapy' to guide component use followed the initial pre-designated Shock packs. The challenge was whether to use standard laboratory diagnostic testing or to re-explore visco-elastic methodology. One of the drivers for introduction of VHA technology was that appropriate blood component use should reduce the demand.[47] ROTEM® was deployed to Afghanistan as a field trial in 2009 to determine its usefulness and reliability.[90] The investigators concluded that the machine was robust enough to be used in a field environment, and was useful in detecting coagulopathy and improved outcomes.[102] The field trials demonstrated that the early A5 and A10 values could predict hypocoagulation, with sensitivities and specificities of

0.98/0.69 (A5) and 0.97/0.78 (A10).[89] Goal directed therapy was subsequently incorporated into the Military Operational Surgical Training (MOST) course which provided DCR team training.

Blood product generation

The final sub-capability of the MTC was blood product generation including microbiology testing for the Emergency Donor Panel (EDP).

Emergency Donor Panel. The EDP is a group of pre-screened volunteer donors who may be called upon at short notice to give FWB or platelets by cell separator (apheresis). The process is overseen by the military Blood Supply Team.[103] Donors are normally screened in the UK before deployment and managed by the deployed BMS. The donors are re-screened and tested by PoCT at the time of each donation. The donation will be used before the results are confirmed in a reference laboratory. Therefore, there is a theoretical risk of transfusion transmitted infection. The most significant risks to donors in civilian practice are delayed vaso-vagal reactions and neurovascular injury. [104] The benefits of the EDP must be weighed against those risks.[53] Traditionally UK donor panels were only group O, designed for the provision of whole blood. However, where there is a BMS present, policy permits the use of all blood groups, which has the advantage of expanding the panel and supporting platelet apheresis.

Operational platelet apheresis. The increasing numbers of casualties and the severity of injury in 2006 and 2007 highlighted the need for a platelet supply. Early collaborative work between BST and NHSBT had enabled a supply of fresh platelets from May 2007. In addition, there was access to supplies from the US at Kandahar. However, both relied on the air bridge from Kandahar Air Field to Bastion. Resilience necessitated the scoping of a local supply. The main options considered were a frozen program based on the Dutch model[105]

or a platelet apheresis program based on the US model.[106;107] At the time, there were no reported clinical studies from the Dutch for their frozen platelet programs. Therefore, platelet apheresis was selected as the best option for resilience despite the potential complexity. Apheresis was introduced by the 3-man team including the author in both Iraq and Afghanistan, with a full operating capacity declared in April 2008.[53] The selected platform was the Haemonetics MCS® which was being successfully used by the deployed United States (US) program.[107]

Platelet donors. The characteristics of the platelet donor would need to be slightly different from those of the whole blood donor. The main determinant of the ABO blood group selection would be the plasma rather than the red cell group. However, there was a risk of residual red cell stroma and therefore the RhD, or "D" group would need to be taken into consideration. Theoretically, the universal donor was blood group A RhD negative. However the percentage of the donor panel that was 15%.[108] The EDP was expanded to recruit group A donors of both RhD types. Donors were invited to give repeat single donations at monthly intervals. The single dose was selected to reduce the time required for donation. However, in May 2009 following the threat of a pandemic influenza in the UK, further resilience was required. It was met by the expansion of the EDP and the introduction of double platelet doses.

Blood safety. Blood safety starts with careful donor selection especially when they are from a closed community. Infections such as gastro-intestinal and upper respiratory tract disease are common especially after group movement of personnel. Pre-screened donors should be well at the time of donation, have an acceptable medical and life-style history and be vaccinated against hepatitis B.[109] In 2009, a study was commissioned from the UK's Health Protection Agency (HPA) to evaluate a commercially available method for *donor testing* in the military environment. The challenge was to find CE marked tests with suitable sensitivity to detect infectious disease with a very

low prevalence in donor blood samples. However, high sensitivity may be associated with low specificity and give rise to false positives. Any positives, true or false positive, require very careful counselling and management when the donor is deployed. DMS introduced PoCT tests for syphilis, hepatitis B and HIV1/2. Access to a suitable CE marked Hepatitis C kit has been more challenging. Platelets stored at 22ºC are at risk of bacterial growth from skin commensals. Options for assuring the microbiological safety of collected components include pathogen inactivation and bacterial testing. Bacterial testing had successfully been used by the US. The BacT/ALERT system (BioMerieux, Durham, N.C.) was subsequently introduced into the UK MTF at Bastion.

Transfusion safety

Transfusion safety served as a unifying clinical dimension of the MTC programme. The biggest risk in transfusion is the transfusion of ABO incompatible blood, rather than infection. Transfusion of the wrong blood to the wrong patient can result from errors made anywhere in the transfusion process, from blood collection through to the administration of blood.[110] Errors can arise within both the clinical and laboratory areas. However, despite the large number of components used in these recent conflicts, there were remarkably few events, and no patient deaths due to transfusion. Errors can be prevented by training. Individual training and assessment was based upon the national competence programme.[111] Team training was consolidated through pre-deployment group training and validation.[112]

Throughout the period of study there was only one reported incident of incorrect blood transfused. As a consequence, further patient safety measures was initiated in 2012 to further reduce the risk of error. These included the establishment of a Defence Medical Services Transfusion Committee (DMSTC); formalisation of training requirements including access

to a national e-learning package,[113] a transfusion aide-memoire[49] and local clinical standard operating procedures (SOPs). Transfusion serious adverse event (SAE) reporting was computerised as part of the new defence electronic event reporting system in 2012. Most events reported were minor and near misses, related to process rather than transfusion reactions or clinical events. A new CGO was introduced in 2013[49] to reflect recently issued national guidance for the recognition and management of Acute Transfusion Reactions (ATR).[114] The number of transfusion events *per annum* fell from an estimated 1 per 1900 components transfused in 2012, to 1 per 3625 in 2013.[115]

The impact of the Massive Transfusion Capability

Clinical impact. The capability was designed to safely and swiftly deliver Massive Transfusion to the critically injured. The first formal analysis of these clinical cases and the resources required took place during 2009. [116] During the 12-month period, 59 personnel received massive transfusion. The median use of blood components was 45 (IQR 28.5-62) units. Of note, seven cases received more than 100 units. Five of these personnel including the one that received 237-units, survived to be discharged from hospital. The severity of the trauma was considerable with a median injury severity score (ISS) of 30 (IQR 22.5-36) and a new ISS (NISS) of 44 (IQR 34-58.5). Despite these injuries and the requirement for critical care, the overall survival was 86%. The Allcock paper compared the outcomes with Borgman *et al.*, 2007[117], McLaughlin *et al.*, 2008[118] and Perkins *et al.*, 2007[119] and demonstrated better survival despite higher injury severity scores. The authors concluded that massive transfusion had become an integral part of combat care and that ultra-massive transfusion could be successfully delivered in an austere environment.

Logistics support. The delivery of the MTC placed extraordinary demands on transfusion services and medical logisticians. Once the delivery systems were

mature, blood was packed, transported and delivered 3,500 miles within 24 hours of request. Operational statistics were collated monthly. The total number of blood components transfused during the recent operations in Afghanistan is shown in Figure 5a. together with the number of boxes shipped by the military Blood Supply Team in the period of 2006 to 2014 (Figure 5b). The workload for the deployed laboratory services was considerable as they not only had to prepare blood for issue but also achieve a 100% traceability rate. The introduction of a deployed Laboratory Information Management System (LIMS) in 2009 together with the use of bar code readers, transformed the speed and accuracy of issue and accounting for large amounts of blood components. By 2011, the red cell used in Camp Bastion equated to that of a UK district general hospital but with the complexity of running a dual inventory with segregated US and UK components.

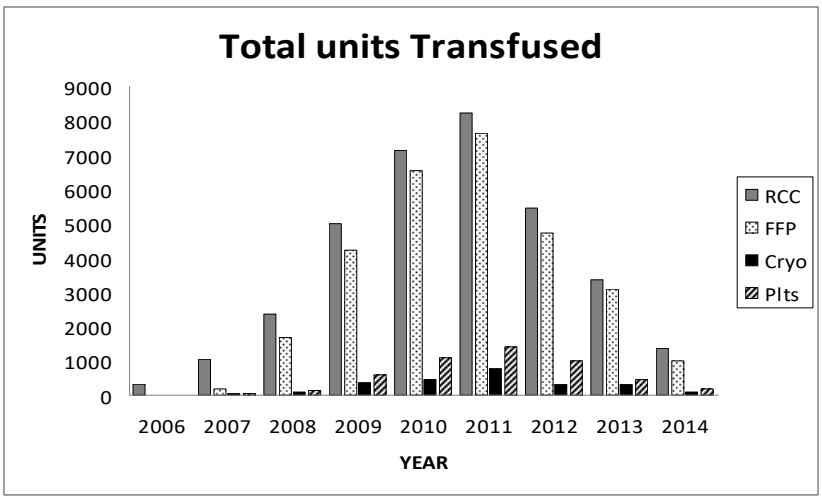

Figure 5a. Total number of components transfused during 2006-2014 RCC: Red cell concentrates, FFP: Fresh Frozen Plasma, Cryo: Cryoprecipitate, Plts: Platelets

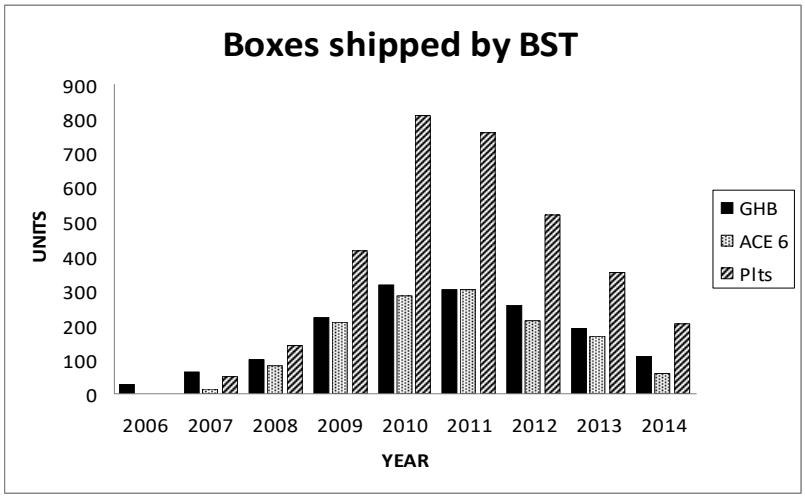

Figure 5b. Number of boxes shipped by the Blood Supply Team during 2006-2014. The three temperature controlled transport systems are represented by: GHB for Red cells, ACE 6 for frozen, Plts for Platelet boxes

1.3 Taking transfusion forward

Doughty and other UK authors had proposed that military transfusion support should be taken further forward where appropriate and feasible.[120] The success of the MTC at Role 3 and during en-route care had led to the question of whether the principles could be applied to forward damage control MTFs and the wider pre-hospital community. The rationale is that the risk of death or permanent impairment is significantly reduced if injured or wounded personnel are treated as soon as possible after injury or wounding. However, there remains a tension between two main approaches to early medical care; 'a Scoop and run' versus 'Stay and play' i.e. rapid evacuation to MTFs or the projection of capability with the risk of delay and losing high priced assets. An overview of the medical capabilities based on modular expansion together with the requirements for mobility is shown in figure 6. The flow of casualties usually follows the continuum of care. However, MTFs may be bypassed due

to patients' needs and/or the workload of MTFs. An example of this would be use of the helicopter response team with direct transfer from First Response to a Field Hospital.

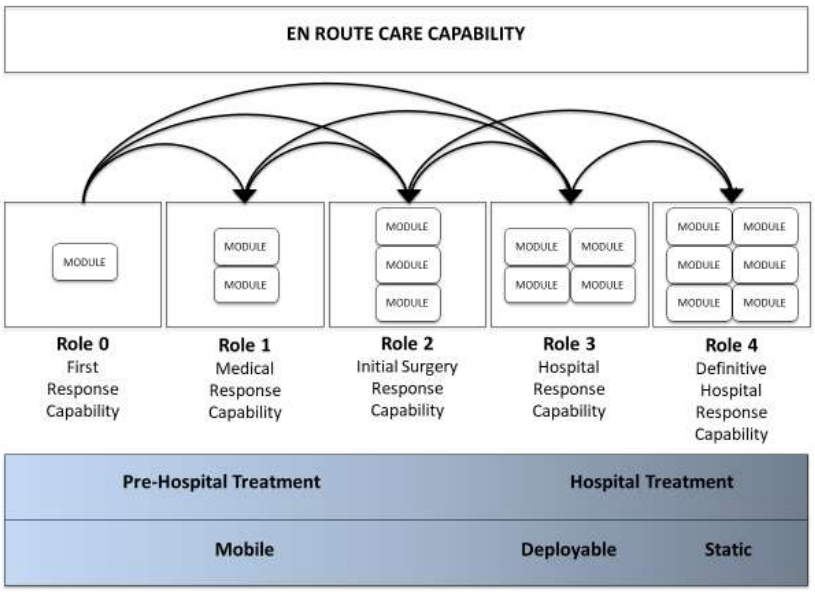

Figure 6. The organisation of military healthcare. Figure adapted from AJP 4.1, 2015.[76]

Development of Role 2 transfusion

The considerations for forward deployment of transfusion both on land and at sea include environmental control, weight, size, power, and re-supply. Some degree of environmental control is required for laboratory equipment and consumables, during both storage and transit. Equipment should be protected against a wide range of ambient temperatures, humidity and high levels of dust. Consideration must be given to a reliable power supply for automation and cold chain. Examples of Role 2 units include Role 2 Light Manoeuvre

(LM) and the maritime equivalent, Role 2 Afloat. The generic clinical requirements for forward transfusion support at Role 2 included: the early use of TXA; RBC holdings based on the casualty estimate and resupply; plasma; a source of fibrinogen; calcium and rFVIIa together with appropriate PoCT. Greater freedom from the logistic burden could be provided by freeze-dried or lyophilised products together with whole blood.[120] In addition, consideration would be needed for resupply where appropriate.

Anti-piracy operations in the mid-2000s had led to a request to revisit transfusion support at Role 2 Afloat. The shelf-life of red cells is 35 days and is therefore nearly always likely to be shorter than the planned time at sea. As a consequence, the resupply of red cells at sea necessitated regular trips ashore, removing the ship from mission. The options were the use of an EDP, as used by the Norwegian during anti-piracy operations[121] or exploration of re-supply. The feasibility of air-dropping a transfusion capability pack was examined by a UK group during 2012 and 2013. The pack included red cells, lyophilised plasma and essential equipment. The challenge was not so much the mechanics of air-drop and sea-recovery, but demonstrating the integrity of the red cell membrane during post-drop storage for up to 35 days. A literature search had identified work by the Canadians who had demonstrated that red cells remained intact soon after an airdrop and a forced march. [122] However, the red cells had not been studied during the remaining shelf-life. A study was required to confirm the suitability for clinical use following storage for at least 28 days. A project was successfully conducted in partnership between Joint Air delivery and Training Evaluation Unit (JADTEU), the Blood Supply Team, the NHSBT and the thesis author to deliver an approved air drop capability for the maritime capability in 2014.[123]

Freedom from frozen

Plasma and cryoprecipitate are conventionally presented as frozen components. However, alternatives for plasma include liquid (never frozen) plasma and dried plasma. A lyophilised fibrinogen concentrate is widely used in Europe. Lyophilised products promise a useful alternative to frozen components due to the ability to store them at ambient temperature for 1-2 years.[124] Whereas they do not need thawing, they do require reconstitution before use. A further disadvantage is that they are manufactured and presented in medicinal glass which limits their use in the pre-hospital environment.[92] A question is whether to use whole plasma or combinations of plasma fractions such as fibrinogen concentrate.

Lyophilised plasma. Lyophilised plasma provides a balanced mix of clotting factors and fibrinogen in a volume of approximately 200ml when reconstituted.[125;126] Commercial products vary in their clotting factors, solubility, donor exposures, pathogen inactivation and licencing maturity. However, in 2009, only LyoPlas-Nw, subsequently referred to as Lyoplas, made by the German Red Cross (DRK), was available for procurement. LyoPlas is a single donor whole plasma product, which has been fielded in both civilian and military German units. It is classed as an un-licenced drug in the UK. Lyoplas was introduced into UK service in January 2011 and the use was later documented in 2012.[92] The Israeli Defence Force (IDF) implemented the use of Lyoplas soon after in 2013 but have used a much greater volume than the UK. The context of use is the pre-hospital setting with delivery by advanced life support providers, both physicians and paramedics.[127] The concept of operations is a plasma first policy where plasma is used as the initial resuscitation fluid in the critically injured. The valuable review of their 3-year experience in 2017[128] concluded that the use of lyophilised plasma by trained soldiers was feasible. However, they reported that there was only a 57% adherence with treatment protocols, despite the

training program. In addition, they noted that the disadvantages of slow reconstitution in the pre-hospital environment and slow infusion progression in five out of the 109 cases.

Further developments The French military have a much longer history of lyophilised plasma production.[129] In addition, they have provided valuable contribution to the literature on the clinical use of French Lyophilised Plasma (FLYP) for military use [130] However, their product was developed for domestic military use and was not available for export until 2016. French lyophilised plasma is an attractive product in that it is a pathogen inactivated, lyophilised product based on a mini-pool of plasma to provide a universal plasma.[129] The US does not currently have lyophilised plasma but have worked closely with the French to develop a lyophilised plasma program. The development of a freeze dried or lyophilised plasma is now considered a developmental priority within NATO countries both for military and civilian emergency practice.[131] [132] Lyophilised blood products in lightweight containers promise advantages in civilian pre-hospital practice and as a wider resilience measure in emergency planning.[132]

Fibrinogen concentrate. Fibrinogen concentrate is an alternative source of fibrinogen to cryoprecipitate, but it is not currently licenced for use in acquired coagulopathies in the UK. It is a plasma fraction which has been subject to pathogen inactivation and is used extensively within Europe. Fibrinogen concentrate has the advantages of a pharmaceutical product and is usually given as an initial dose of 3 to 4 g. There is excellent evidence for both the effectiveness and safety of fibrinogen concentrate.[70-72] The Oxford group claims that current evidence does not support the superiority of fibrinogen over cryoprecipitate.[133] It is assumed that fibrinogen supplementation of either source may be used together with an anti-fibrinolytic drug such as tranexamic acid.[74] Fibrinogen concentrate was introduced into military service for Role 1 and 2 units in 2016.

Factor concentrates. Whilst there was increasing confidence in the rationale for the use of fibrinogen replacement, there was continued caution about the use of Prothrombin Complex Concentrates. This was consistent with the prevailing civilian opinion at the time.[134]

Moving Forward

Experience in Afghanistan and Iraq had enabled the DMS to refine field hospital transfusion support to enduring medium scale military operations. However, there was an increasing awareness that medical forces must be continually prepared for the entry phase of a military campaign. Such activities may require medical personnel to resuscitate and sustain patients for far longer than the doctrinal timeline of 2 hours. In addition, selected medical personnel would continue to be required to support isolated troops as well as deployed conventional forces. The variety of scenarios drove a clear requirement for MTF to be able to deploy at all scales of effort and concurrency. The delivery of transfusion support outside of the hospital presented challenges, chiefly relating to the logistic constraints. Modified transfusion support was successfully applied to Role 2 units however they did not translate easily to Role 1 MTFs.

The Role 1 MTF focuses on the provision of primary health care, specialised first aid, triage, resuscitation and stabilisation. The UK model is the use of a general practitioner with enhanced military medical skills. These practitioners must be able to sustain casualties for an extended period in isolated teams that frequently operate outside the NATO medical doctrine of 1 hour to a DCS capability. The requirement to deliver prolonged field care led to the exploration of using RBC and lyophilised plasma within small mobile teams working both in vehicles and on foot. Wild *et al.*, 2013[135] had described the equipment which enabled a Role 1 team to carry a vehicle-based blood capability on long-range mobility patrols. Gohkale *et al.*, 2016[92] described the

first use by the UK forces of LyoPlas carried and delivered by patrol medics. For most units, the evacuation times were short, however, increasingly Pre-Hospital Emergency care (PHEC) needed to evolve to meet the need for prolonged evacuation times.

The limitations of modified transfusion packages are well illustrated by the experiences of a UK Role 1 team published in 2016. [94] The context was a medical team supporting a helicopter assault force (HAF) based in southern Afghanistan. A Role 2 style transfusion package of tranexamic acid, red cells and Lyoplas was transported as a man-portable capability. During the two-year audit, Aye Maung *et al.*, [94] demonstrated that the Role 1 team, dislocated from a hospital laboratory, could maintain the cold chain required for forward blood products for prolonged periods. Considerable detail of the technical elements was included in this paper, including the use of the GHB. The GHB system worked well within the austere environment; however, it was not designed as a man portable system. The weight of the fully loaded box was 4.5kg when loaded and even when carried within a modified back pack was both heavy and uncomfortable. The authors concluded that a conventional transfusion capability at this point in the medical evacuation chain imposed a significant logistic, training and governance burden. Only 2 casualties required transfusion during the period of audit, which suggests that carrying blood at Role 1 places a relatively large logistical burden for a low clinical output. Alternatives to this approach included a plasma only policy as used by the IDF[127] or the development of a whole blood programme designed for the pre-hospital community.[136]

Fresh whole blood

Whole blood may be the best resuscitation fluid for massive haemorrhage.[137] FWB not only addresses concerns about the red cell storage lesion, but also provides a supply of both fresh plasma and a small dose of platelets. Whereas

the use of multiple components results in higher volumes of infused anticoagulant during resuscitation, FWB provides a physiological replacement therapy with less anticoagulant.[26] There is some evidence that the partial use of FWB, i.e. used together with components, is associated with survival advantage.[138] Few mature civilian blood services provide FWB[139] for either their military or civilian users. The Bergen group in Norway is a notable exception and has led the way in the supply of whole blood (WB) to both military and civilian use. Table 3 shows a comparison of reconstituted whole blood using a 1:1:1 mix of components, with a unit of whole blood, based on a paper from the group.[140] However, this is simplistic summary and a more detailed appreciation of the interactions of the different components is required to determine the optimal storage conditions and duration for future whole blood preparations. In addition, WB is initially collected into a citrate-based anticoagulant at a volume ratio of 1:7 anticoagulant to WB. In this sense, WB is already a diluted blood product from the outset.

Table 3. A comparison of reconstituted whole blood using a 1:1:1 mix of components with a unit of whole blood. Adapted from Murdock et al.[140]

	"Reconstituted" whole blood (1:1:1)"	**Whole blood**
Total volume	660 mL	570mL
Haematocrit	29%	33%-43%
Platelet count	88 k	130,000-350,000
Coagulation factor activity	65%	86%

*Assumptions: PRBC haematocrit 55%, PLTs 5.5 x 10^{10}, FFP 80% coagulation factors.

FWB collection and use developed in the latter part of World War I (1914 – 1918).[120;141] WB was the only blood product available for transfusion in the military and civilian settings through to the late-1960s. However, by this time, the availability of plastic blood bag collection and storage systems enabled blood component development. The US military retained the capability and have considerable recent experience in the use of whole blood in combat conditions. Nessen *et al.* have shown that the widespread collection of FWB from emergency donors can be done safely[142] and that the risks are rare.[143] Whereas, the collection of whole blood was increasingly deployed during the period of study as a resilience measure within the UK field hospitals, it has a greater potential to support Forward Transfusion.[120] The major concern with the use of FWB from emergency donors is safety including the risks of infectious disease and ABO incompatibility. The risks can be mitigated through the use of pre-tested donors within an Emergency Donor Panel (EDP) together with a robust training in a whole blood programme designed for the pre-hospital community.

The Trauma, Hemostasis and Oxygenation Research (THOR) Network

The emerging expert collaborative for forward transfusion was the Bergen based Trauma, Hemostasis and Oxygenation Research (THOR) Network. The THOR Network is an international multidisciplinary network of civilian and military providers ranging from first responders and medics to critical care physicians, and from basic scientists to clinical trialists. THOR has promoted the concept of Remote Damage Control Resuscitation (RDCR) together with research priorities [26] RDCR is an evolving concept and the term is not yet accepted in UK military doctrine. The concept is further confused by the additional terms used by the THOR community such as *remote and austere.* The term *forward* is understood to mean the pre-hospital setting or phase of resuscitation. The use of transfusion in this environment has been well established with the increasing use of blood during air evacuation such as

MERT.[88] The terms *far-forward* and *austere* can be defined as the environments where professional health care providers do not normally operate and where the basic equipment and capabilities necessary for resuscitation are often not available. These are the conditions in which Special Forces might be operating. The US Rangers have also used the term *Tactical DCR*.[144] Whichever term is used, transfusion is traditionally not used in this environment. It might be feasible but at the risk of a logistic burden.[94] Despite the apparent constraints in this environment, it is proposed that the concept is worth exploring because remote DCR may have application for many remote civilian or widely dispersed communities, as well as for disaster medicine.[131] Developments require an academic underpinning coupled to translation into practice. THOR has embraced the Bergen based Blood Far Forward research program from Norway as an exemplar of operationally focussed research.

Blood Far Forward

The Blood Far Forward (BFF) research program was established to improve battlefield survival by developing a safe method for pre-hospital whole blood transfusions.[145] The program was initiated by the Norwegian Naval Special Operation Command in 2010. Collaborators and participants today include: The department of Immunology and Transfusion Medicine at Haukeland University Hospital, The Norwegian Armed Forces Medical Services, Norwegian Special Operation Command, Norwegian Army Special Operation Commando and the US Army Institute of Surgical Research. The aim of the program is to improve battlefield survival by developing a safe method for pre-hospital whole blood transfusion. The three primary research strands of the program are

1. Donor performance and safety
2. Blood efficacy and safety

3. Training and educational requirements

Module 1. Donor Performance and safety

Donor care and performance are key considerations for command. Donor care emphasises not just careful donor selection but also measures taken to reduce the risk of adverse effects related to donation. All care must be taken to minimise the risk of a second patient especially in small team work. There have been few studies on extreme performance and donation; therefore, the studies from the BFF program are very valuable. In one study, 25 Special Forces soldiers underwent Bruce Protocol treadmill stress testing, push-ups, pull-ups, a 50-round rapid pistol shoot and a 20kg uphill load carriage exercise as a baseline. The soldiers then repeated all tests two to six minutes after the withdrawal of 450ml of blood. No significant decrease in shooting or physical performance was seen.[146]

Such studies demonstrate that blood donation can be tolerated by elite soldiers[147] . Recent detailed studies have demonstrated that donation in fit civilians has a minimal effect on VO2 max and no adverse impact on cognition (Eliassen personal communication). The findings are consistent with the recent large scale INTERVAL study designed to explore the safety of donation intervals.[148] Both inform the safety of donation for EDPs used in both military and civilian practice. Donor safety is also delivered through well designed equipment packs. A pack designed for RDCR blood donation has been developed by the BFF program.[136] The Role 1 pack included all the materiel required for donation including PoCT. The pack weighs 780g including a unit of freeze dried plasma and a small lactate analyser. A US version is described in Fisher's paper on 'Tactical' DCR[144]. The US pack now has a NATO Stock Number which simplifies procurement.

Module 2. Blood Efficacy and Safety

The advantages of whole blood have been actively promoted by members of THOR[137;149] and considered by others.[150] [151] The efficacy and characteristics of both warm fresh and cold stored[121] whole blood have been described. The blood donor model in the BFF program is based both on the field blood bank and "buddy transfusion" where blood is collected and used immediately in the tactical situation. Donor selection is key to blood safety in the context of RDCR. Two papers are presented in this thesis which related to this research strand. One is related to the selection of donor by blood group serology and the other is the selection of the untested donor.

Haemolysin studies. The biggest risk in transfusion is the transfusion of ABO incompatible blood.[152] Whole blood is plasma rich and may pose a risk due to the naturally occurring haemolysins, anti-A and anti-B.[153] The use of group O blood from donors with low titers of anti-A/B blood group antibodies has been proposed as the safe universal whole blood for the emergency situation.[154] The UK has undertaken antibody screening for both whole blood and platelet donors since 2002. The primary purpose was the selection of safe group O platelet donors however, it provided a useful basis for the study of whole blood donors. The author concluded that a UK study was required to determine the feasibility of restricting whole blood donors to Group O Low titre in small groups. The work would be undertaken within a high readiness unit providing close support as a Role 2 (Light Manoeuvre).

The unknown donor. The provision of transfusion support to isolated military or civilian projects may require the use of an EDP for immediate Warm Fresh Whole Blood (WFWB). The number of screened personnel may not be large enough and isolated practitioners may be asked to collect blood from uncharacterised donors. Cordova *et al.*, 2014 graphically describe such an event where 5 units of fresh whole blood were transfused following a 12-hour

battle, during which building fires threatened the isolated aid station.[155] In 2017, a shark attack on Ascension Island led to emergency collection of blood from islanders and contractor staff highlighting the need for civilian access to emergency donation.[156] Training sessions conducted by the BFF teams had highlighted that practitioners need guidance for the selection of donors.

Module 3. Training and Education

The BFF programme espoused by the Norwegian Naval Special Operations Commandos[136;145] has supported high fidelity training for an international community. The principles have been exported to the US and the UK but are not routinely delivered outside of the Special Forces community.

Warm blood for GHOST-Ts. Benavides *et al.* 2017[157] described the development of an emergency didactic educational program based on the BFF program for a US forward surgical team sub-unit known as a Golden Hour Offset Surgical Trauma Team (GHOST-T). They demonstrated that confidence improved in all members of the team but especially the clinical staff. The Benavides paper is interesting in that it describes medical support to the withdrawal phase of war fighting which is rarely published. Withdrawing forces from the Iraqi operational theatre challenged the delivery of high quality combat casualty care.[158] Withdrawal from Afghanistan presented similar challenges, with relevant lessons for the military's return to "contingency operations" in contrast to the enduring activities in Iraq and Afghanistan. Contingency operations are military activities whose characteristics include the rapid deployment of forces, typically without the benefit of established medical facilities. The emergency collection of blood is becoming a key medical resilience measure for any isolated community.

Implications for UK military practice. As transfusion moves geographically and technically forward the requirement for staff training will change. Blood

collection is not a core clinical skill. Training is currently provided only to selected personnel who are considered to need it for their mission. The Benavides paper by US and UK authors concluded that training in all aspects of RDCR, including the use of whole blood, is essential for teams providing medical and surgical support to Special Operations personnel and other operations in austere environments. In the UK, this training has been restricted to doctors and nurses. However, experience from the US,[144] forward surgical teams[157] and the Norwegian Blood Far Forward programme[159] have demonstrated that a much wider range of staff can be successfully trained. Perhaps now is the time to consider the introduction of non-medical authorisation in the UK military and to extend the collection and administration of blood to a wider range of medical providers. This would a require a revised governance framework but afford battle space commanders much greater Freedom of Action.[120]

Pre-hospital transfusion governance

The increased complexity of transfusion services and the potential risks associated with pre-hospital transfusion had highlighted the requirements for governance. The format for the Defence Medical Services Transfusion Committee (DMSTC) mirrored the civilian structures[160] with a multi-disciplinary committee answerable to the DMS Medical Director through the DMS Clinical Committee. However, the Terms of Reference for the committee were unique in the UK in that its remit covered all aspects of clinical transfusion practice, including pre-hospital and donor care. The DMSTC benefits from having both military and civilian members and actively supports participation in the national Serious Hazards of Transfusion hemovigilance scheme (SHOT). SHOT is the United Kingdom's independent, professionally-led hemovigilances scheme. SHOT has collated anonymised information on adverse events and reactions in blood transfusion in the United Kingdom since 1996.[161] The 2016 report continues to show that human error remains the biggest risk for ABO

incompatible transfusions. The Key SHOT message was that all staff participating in transfusion must have the knowledge and training to undertake their role.[152] The 2016 report included a chapter on donor haemovigilance for the first time. The report quantified the rate of Serious Adverse Events of Donation (SAED) as 0.21 per 10,000 in the UK. 42 SAED were reported, most were in repeat donors with equal rates between men and women. Ten donors had problems related to needle insertion lasting for more than a year. Thirteen donors required hospital admission. Most of these were due to vaso-vagal events including 10 with delayed faints. The findings have implications for the development of military and civilian emergency donor programmes and haemovigiliance.[156]

1.4 Implications for civilian practice

Overview. Massive trauma including ballistic trauma is a global healthcare problem.[162] The lessons identified during conflict offer the opportunity to optimise the survival for all traumatised patients. An emerging concept was that the outcome in survivable major trauma was determined very early on by physiological factors, and by the initial responses of the trauma teams. The doctrine of Damage Control Resuscitation carefully balanced haemostatic and hypotensive resuscitation.[163] The emerging opinion was that massive blood loss should be managed with blood replacement.[25] Should, and could, the philosophy of haemostatic resuscitation be applied to civilian trauma? Moor *et al.*, in their 2009 review suggested – *Yes* – but caution should be applied to the civilian use of individual military protocols.[163] They argued that the context, injury type and patients were different. Above all, the military medical system was different. The military MTP was nested within the paradigm of institutionalised Damage Control Resuscitation. It was institutionalised in that the system was optimised for trauma management of the individual from the point of wounding through to rehabilitation.

Transfusion support for the London bombings. The large scale use of the emerging concepts were first tested in the UK when, on 7th July 2005 the London transport network was subjected to a series of terrorist attacks. The bombings led to 700 injured and 56 fatalities. Glasgow *et al.* reviewed the blood for the event.[164] Approximately, 360 casualties were received in Emergency Departments and 110 were admitted to five hospitals during the morning. The estimated distribution of casualties by treatment priority was P1: P2: P3 ratio of 5:10:85%. By midnight, 23 patients, i.e. 3% of the total injured, had required transfusion. The initial mean use of red cells was 14 units in the first 24hr with a ratio of RBC: FFP of 3:2 in the most severely injured. The mean total use of RBC during the hospital stay was 17 (2-91) units. The requirement for blood continued over several weeks with small peaks of demand at days 5 and 7. The ongoing demand for blood due to repeat surgery was a relatively new concept that was reported for the first time following the London bombings.[165;166] A number of lessons were identified from this event which are pertinent to this thesis. These include: the organisation of transfusion support in mass casualty events (MCE), the benefit of structured guidelines for massive transfusion, the importance of good data collection and governance, and finally the importance of an integrated trauma system.

Massive Transfusion Guidelines. UK civilian massive transfusion guidelines were re-issued in 2006,[32] which coincided with the beginning of this study. The guidelines were based on sound traditional transfusion practice based on the review of laboratory results before the use of haemostatic components. The perceived limitations of this for military practice were the delays in both the return of laboratory results and blood component delivery. The pre-emptive use of plasma espoused by civilian 'enthusiasts' was acknowledged in 2007 within the European guidelines for the management of bleeding following major trauma.[167] The earliest UK guidelines to adopt the plasma rich protocols were the guidelines produced by the Association of Anaesthetists in

2010.[63] However, the haemostatic resuscitation philosophy was not adopted into mainstream UK haematology practice until 2015.[61] The reticence was based on the perceived lack of quality evidence both for trauma and for the extrapolation of trauma transfusion practice to all causes of massive haemorrhage. In addition, the haemostatic resuscitation strategy had been logistically challenging and had required considerable support from both the National Blood Service and laboratories.[53] Considerable planning would be required for the resources, training and organisation of civilian laboratory support.[168] In contrast, the military MTC had been well resourced. However, it was unlikely that similar developments would be forthcoming in civilian practice without further evidence and endorsement from the wider trauma and transfusion communities.

Civilian Trauma Services. The design and delivery of the military medical system was under the auspices of a single 'Defence Medical Service'.[2] In contrast, the delivery of civilian trauma service was, and remains, fragmented. Pre-hospital care, which had been shown to be essential in mitigating the impact of military injury, is delivered by organisations separate from the hospitals. In turn, civilian pre-hospital care is further divided with ground-based pre-hospital care delivered by Ambulance Trusts whereas UK air ambulances are normally charities. Any changes in civilian transfusion practice would be, in part, dependent on the demand for transfusion trauma services. The changes in civilian trauma practice would require reorganisation and the better use of data registries. The Trauma Audit and Research Network (TARN) had been established in late 1989. The TARN database was an important development, but its use was inconsistent; in 2007 only approximately 50% of trauma hospitals submitted data. The poor data submission and other failings of the trauma system were described in the UK National Confidential Enquiry into patient Outcome and Death (NCEPOD) 2007, Trauma: Who cares?[169] The NCEPOD study explored the organisation in trauma from the perspective of the patient journey. There were nine key

recommendations including the development of designated level 1 trauma centres within a robust assurance system. All agencies involved in trauma management, including pre-hospital care, should be integrated into the clinical governance programmes of a regional trauma service. A considerable change in the organisation of civilian trauma services would be required to leverage the lessons learnt from the developments in military transfusion.

Summary of introduction

Massive haemorrhage is the most immediate threat to the injured service person. The mortality rate after massive haemorrhage in trauma is high, unless actively managed from the point of wounding. Trauma also results in a complex disturbance of coagulation. Treatment requires early haemorrhage control and prevention of shock together with appropriate transfusion support. The introduction has provided an overview of recent development of UK military transfusion practice and indicates the potential for civilian healthcare. Four areas for exploration have been identified which will be developed into the aims of the thesis.

1. The Massive Transfusion Capability was developed to deliver both the laboratory and clinical elements of haemostatic resuscitation. The principles of the military hospital model were then applied to physician led pre-hospital care. The implementation and impact of both hospital and MERT practice require formal description to assist future military planning and developments.
2. The key considerations for RDCR are reducing the logistic burden and optimising training. International networking in Norway has contributed to knowledge exchange and practical solutions. Further developments are required, especially for emergency donor selection.
3. The lessons identified during conflict offer the opportunity to optimise the survival for all traumatised patients. Early adopters in England and

Norway have now had a decade of experience and offer an opportunity to study the impact of MTPs in civilian practice.

4. Finally, ballistic trauma is a global healthcare problem. Recent terrorist events have led to MCE with a renewed interest in emergency resilience, including transfusion. Studies are required to assess the implication of military transfusion practice for Transfusion Emergency Preparedness in both England and Norway.

2: AIMS OF THE STUDY

2.1 The overall objective of this study is to evaluate the recent developments in military transfusion practice and to assess the impact on civilian practice. The study describes the changes in transfusion support in a linear sequence during the period of 2006 – 2016. The early adoption of military principles is then explored in the context of civilian hospital practice and national emergency transfusion preparedness for Major Incidents leading to Mass Casualty Events.

2.2 The study aims to demonstrate the contribution to military and civilian trauma transfusion attributable to the author through the analysis of published work. Seven papers are presented here. A list of associated publications is included in Appendix 4. The thesis is that the recent developments in military transfusion practice are significant and that they have impacted on civilian healthcare. The thesis is explored through the following four aims:

1. **To describe the implementation and impact of recent UK military blood transfusion practice**
2. **To further develop donor selection for Remote Damage Control Resuscitation**
3. **To study the introduction and impact of Massive Transfusion Protocols in UK and Norwegian civilian centres**
4. **To assess the application of military transfusion practice on Mass Casualty Event Planning in both England and Norway**

3: METHODS

The methodology for the seven papers is grouped according to the aims, 1-4, followed by some general methodological considerations.

3.1 Developing Military blood transfusion practice

Overview. The setting and source data for the principal defence study; Paper 1 is similar for the associated descriptive paper, Paper 2. Paper 1 is a retrospective analysis of blood component used in a single combat support hospital. The study was approved by the Royal Centre for Defence Medicine (RCDM/Res/Audit/1036/12/0175). Paper 2 is a special report which covers the practical and clinical aspects of prehospital transfusion as practiced by the UK Armed Forces in Afghanistan and describes a cohort of patients who received treatment.

Setting. The retrieval of casualties in Helmand Province was almost invariably by helicopter, usually directly to the UK Medical Treatment Facility (MTF) at Camp Bastion. In-flight care was provided by paramedics or doctors. For casualties who are *in extremis*, transfusion with red blood cells (RBC) and plasma may be initiated *en-route* by the Medical Emergency Retrieval Team (MERT), but was more commonly administered at the hospital at Camp Bastion.

Source data. Data were extracted from the Joint Theatre Trauma Registry (JTTR), which records details of all casualties who receive treatment in deployed UK military MTFs. Since 2007, the JTTR has included all injured service casualties treated at Birmingham.

Data management and statistical analysis. Injury extent was quantified by three different injury severity scoring systems. The three were; the injury

severity score (ISS), stratified into mild (ISS 1-8), moderate (ISS 9-15) and severe (ISS≥16); new injury severity score (NISS); and by body region, using the abbreviated injury scales (AIS). Demographic characteristics were compared using Kruskall-Wallis tests for continuous data and Chi^2 tests for proportions. The number of units of individual blood components transfused were analysed by calendar year and injury severity strata and compared using Kruskall-Wallis tests. Transfused patients were also analysed by volume of red cells transfused before being dichotomised into massive and non-massive transfusion. The ratios of plasma to red cell concentrate and platelet to red cell concentrate are presented as three-month moving averages. Analyses were performed using Microsoft Excel (Microsoft, Redmond, Washington, USA).

3.2 Donor selection for Remote Damage Control Resuscitation

Overview. The context for papers 3 and 4 is the austere medical environment where evacuation to surgical support may be delayed. Individuals or small teams may be required to sustain prolonged field care with minimal medical assets. Transfusion support will require the use of Emergency Donors.

Paper 3 describes a retrospective review of routine volunteer blood donor samples performed at 6 monthly intervals during a 2-year period. The donor testing protocol was the UK standard for donation[84] which included transfusion microbiology, blood grouping (ABO, Rh and K) and screening for atypical antibodies. All results were processed through the NHS Blood and Transplant's (NHSBT) Laboratory Information Management System (LIMS) (*Pulse Blood Transfusion System*, *Savant Ltd, Cumbria, UK).* Plasma of all group O donors was screened for anti-A/B IgM using the Olympus PK7300® (Beckman Coulter) with a dilution of 1/85 against A_2B cells. Anti-A/B was defined as high titre (HT) positive if reactive at 1/128 (or equivalent dilution) by haemagglutination techniques and negative if reactive at 1:64 dilution.[170] Results were electronically transferred to the military Blood

Supply Team (BST). Data collation and analyses were performed using Microsoft Excel (Microsoft, Redmond, Washington, USA).

Paper 4. The initiative for this work follows the pre–conference exercise for the 2015 meeting of the Trauma, Hemostasis, Oxygenation and Research (THOR) Network, which took place in Norway. The work forms part of the 'Blood Far Forward' program - a whole blood-based research and training program for austere environments. Staff and participants identified that there was little guidance for the rapid assessment and triage of blood donors for the non-expert. The principal author attended the field teaching and exercise during which she consulted practitioners before reviewing the literature. The draft Field Emergency Donor Panel (EDP) Questionnaire and Triage Tool was then refined using a modified Delphi method with the writing group and then a wider group of experienced military and civilian practitioners.

Literature review. The following donor screening guidelines were reviewed. Military: US Special Operations Command, Tactical Trauma protocols (TTP) 2013[171] and the Journal of Special Operations Medicine Training supplement 2012.[172] Civilian: Standard Operating Procedures for the collection of whole blood, United Kingdom,[173] THOR guidance,[136] United Kingdom Blood Transfusion Services,[84] American Association of Blood Banks (AABB)[174] and the World Health Organisation (WHO).[175] A search was performed of PubMed and CINAHL using the search terms: *Emergency Donor Panels, collection of whole blood, austere medical environment, and Special Forces medicine.* The search covered articles published up until September 2015.

3.3 Introduction of Massive Transfusion Protocols in civilian centres

Overview. The setting and source data for Paper 5, the principal UK hospital-based study presented here is similar to paper 6 from Bergen. Both are

retrospective observational reviews of practice in a single institution, closely associated with military practice.

Birmingham study design

Paper 5 was a quality improvement initiative from the Queen Elizabeth University Hospital Birmingham, UK. The purpose of this before-and-after study was to determine the impact of modifying a Massive Transfusion Protocol (MTP) to include emergency red cells. The usage study was a retrospective study of sequential MTP activations over three years, before and after protocol revision. The study was approved as a clinical audit.

Setting. The Queen Elizabeth University Hospital Birmingham, UK is the receiving facility for UK military trauma patients and is equivalent to a US level 1 trauma centre. It serves a population of 1.2 million UK civilians. Following the UK wide reconfiguration of major trauma networks, the institution was designated a regional Major Trauma Centre in 2012. Blood is provided by a separate organisation, the centralised blood service, NHSBT.

Source data. All consecutive MTP activations throughout both periods were prospectively recorded by the transfusion laboratory manager using an audit template as part of ongoing quality management. Clinical outcome data were retrospectively collated from patients' electronic clinical record and the Trauma Audit and Research Network (TARN) database.[176]

Analysis. All analyses were performed with version 6 of the Graph-Pad Prism statistical software package, GraphPad Software, Inc. San Diego, California. Data were presented as mean with standard deviation or median and interquartile range as appropriate. The unpaired t-test with Welch's correction was used for parametric data comparison. The Mann–Whitney U test was utilised for non-parametric comparisons. Frequency comparison of categorical data was undertaken with either the Chi square test or the Fishers exact test.

Statistical significance was set at p value ≤0.05. The association between the trauma associated severe haemorrhage (TASH) and ABC score and the number of red blood cell (RBC) units used was tested with linear regression analysis and the R^2 statistic. The Area Under the Receiver Operating Characteristic (AUROC) analysis was undertaken to test the accuracy with which the need for >6 RBC could be predicted. This number of RBC units was chosen as it represents progression to MTP pack 2 in both our and others' protocol.

Bergen study design

Paper 6 was a study of the impact of a Massive Transfusion (MT) programme in a single Norwegian centre throughout the period 2002–2015. Haukeland University Hospital (HUS) introduced a MT programme during 2007 including education, an Acute Transfusion Package (ATP) and point-of-care measurements using thromboelastography *(TEG 5000, Haemonetics Corporation; Braintree, MA, USA)*.

Methodology. A retrospective review was conducted of all episodes of patients receiving a massive transfusion during the period of Jan 1st, 2002 and Dec 31st, 2015, i.e. 13 years. Massive transfusions were defined as 10 or more red cell concentrates (RCC) given during the first 24 hours after insult. [38] An initial search was made using the ProSang laboratory information system (LIMS) *(Databyrån AB, Stockholm, Sweden)*. Patient records were then reviewed manually for demographics, transfusion support, principal indication for transfusion, haemostatic drugs and mortality. The principal indication for transfusion was encoded using ICD-10.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0 *(IBM Corp., Armonk, NY, USA)*. Descriptive statistics were used to summarize the number of components by year, speciality, and patient demographics. The Student's t-test was used to

compare the mean number of RCC, plasma and platelet concentrates transfused per episode pre-2007 and post-2007. Differences in platelet inhibitor and anticoagulant use between cardiac and non-cardiac episodes were tested using Chi-squared tests. A p-value <0.05 was considered statistically significant. Excel 2010 *(Microsoft Corp., Redmond, WA)* was used to produce graphs.

3.4 Transfusion Emergency Preparedness

Overview. Paper 7 contrasted the planning approaches used for Transfusion Emergency Preparedness by NHSBT and Norway. The paper included a review of UK and Norwegian methodology. The UK methodology was a strategy based on component therapy. Planning was based on the response to Major Incidents such as the London bombings[164] together with the lessons identified from the preparation for the London Olympic Games.[177] The methodology for the Bergen planning was based on developments from the military whole blood programme in Bergen.[154]

London bombings. The transfusion response to the London bombings was analysed based on data from a variety of IT systems. Data was collated from the National Blood Service's LIMS (*Pulse Blood Transfusion System*). Pulse is a core software system that powers the blood donation lifecycle of NHSBT in England (formed by the merger of the National Blood Service & UK Transplant in 2005). The hospital data was derived from the respective hospital LIMS. All data was collected immediately following the event and included: all blood components requested, issued and transfused in relation to the bombings, blood stock levels at the time and the injury profiles of the casualties transfused.

Olympic planning. Glasgow *et al.* have described the blood service preparation methodology for the 2012 Olympics.[177] As part of the preparation,

a new civilian literature review was commissioned from the Blizard Institute, London to further inform blood demand per patient.[178] The potential demand was based on the average between past civilian demand,[178] demand from the London bombings[164] and recent military demand figures as in Paper 1.[179]

Blood demand per patient. Severely injured casualties or Priority One (P1) were estimated to require 10 units of RBC, i.e. a traditional massive transfusion. The ratio of red cells to haemostatic components was as outlined by a regionally agreed massive haemorrhage protocol.[180] The less severely injured patients/Priority Two (P2) casualties were assumed not to routinely require haemostatic component support and the walking wounded Priority Three (P3) casualties were deemed not to require any blood at all. A summary of the blood component requirement assigned for each triage category is shown in table 4.

Table 4. Blood component requirements assigned for P1-P3 casualties

Triage and treatment priority	Red cells (SAGM)[#]	Plasma (Fresh Frozen Plasma or Octaplas)	Platelets (Adult Therapeutic Dose = pool of 4)	Cryoprecipitate (Pool of 5)
Priority 1*	10	8	2	1-2
Priority 2	4	0	0	0
Priority 3	0	0	0	0

[#]Saline-adenine-glucose-mannitol

UK emergency planning. The planning approach developed for the UK was based on the number of casualties, potential red cell demand based on the priority and a demand factor of three.[181] A stock plan for red cells was modelled using the following equation together with the background seasonal and daily variations in demand. Similar modelling was done for platelets.

Red cell demand = Number of casualties x Demand per patient x Demand factor

The final blood component stock plan was based on a compromise between potential component demand, shelf-life and an appreciation of logistically achieving and maintaining the required stock level for the Games. In addition, the risk of stock build was considered against the risk of wastage. As a result, a decision was made to increase the blood-stock slightly but also to develop high readiness donor panels for both group O whole blood and group A platelet donors. Plans were widely communicated with key stakeholders and exercised using a table-top exercise.

Bergen emergency planning. The surge supply plans for Bergen was based on a novel approach proposed by HUS. HUS is in the process of implementing contingency plans that will involve the use of pre-screened military and civilian Group O low titre emergency donors. The donors will be recruited from three locations; a local naval base, from amongst the regional hospital employees and from city suburbs; they will be called to donate whole blood, to be fully tested and utilised as whole blood. Such as plan removes the necessity of detailed planning, component production and unnecessary stock build.

3.5 Methodological considerations and research governance

One of the main challenges to conducting research in a deployed setting is the obvious logistical difficulty of working many thousands of miles away from the UK and in a potentially hostile environment. In addition, there is a manpower limit imposed on numbers of personnel serving in a defined area of operations or theatre. Such difficulties can limit the potential to perform research, especially prospective randomised controlled trials (RCT). Most initial research and feasibility studies during this period of study were carried out by deployed clinicians who collected data when not fulfilling their primary tasks.[182] Examples supported by the author include CRYOSTAT[58] and evaluation of cell salvage.[95] However, many of the recent military studies are

retrospective studies using the Joint Theatre Trauma Registry (JTTR) housed by the RCDM.

The JTTR records details of all casualties who receive treatment in deployed UK military MTFs. Since 2007, the JTTR has included all injured service casualties treated at Birmingham.[183] The author has been closely involved in developing the data fields for both hospital and pre-hospital transfusion and has confidence that this data is complete. The use of the JTTR restricts the eligibility to patients studied who were British and coalition (non-Afghan) service personnel. Mortality for UK personnel was defined as in-hospital mortality which occurred within 30 days either in Afghanistan or in the UK. For other coalition patients, in-hospital mortality included only that which occurred at the treatment facility in Afghanistan. This approach is pragmatic but has been employed for other studies as it is very difficult to track the progress of casualties from other countries through their respective evacuation chains.

The issue of patient consent requires attention in circumstances such as severe trauma. Novel consultation methods have been devised by the NHSBT Clinical Trials Unit in a manner consistent with the Mental Capacity (England) Act (2005). The construct for patients with severe injury lacking capacity to consent, and without a Personal Consultee, is to use an independent clinician. Patients or their relatives are subsequently consulted at the first opportunity. Non-interventional studies do not require these procedures however all studies, including audit and service improvement, must be approved by the Royal Centre for Defence Medicine or the equivalent civilian sponsor.

All the studies presented in this thesis have been subject to the relevant research governance frameworks. In principal, where appropriate, trials are conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the Principles of Good Clinical Practice (GCP) and the UK

Data Protection Act and the NHS Research Governance Framework for Health and Social Care. Blood components are provided in compliance with European Commission Directive 2005/28/EC. Authority from the Medicines and Healthcare Products Regulatory Agency (MHRA) and approval by higher military committees such as AGoMM (Advisory Group on Military Medicine) were secured where drugs were used outside of current licence, such a Fibrinogen Concentrate, or as an un-licenced medicine such as LyoPlas-N.

4: SYNOPSIS OF RESULTS

4.1 Changes in UK blood transfusion practices in Afghanistan, 2008-2011

The aim of this paper was to document blood component usage in the UK medical treatment facility (MTF) at Camp Bastion, Afghanistan, over a period of four years; and to examine the relationship with changes in transfusion capability, injury pattern and survival. In the paper we analysed the period after the introduction of the new massive haemorrhage protocol in 2007 followed by pre-hospital transfusion in 2008. This was a retrospective study of all blood component use in service personnel admitted for trauma. The data variables were extracted from the UK Joint Theatre Trauma Registry (JTTR).

2618 patients were treated for trauma; 791 received blood components. The proportion of patients receiving blood components increased from 13% to 32% per annum. 417 (52.7% of all casualties transfused) received massive transfusion (≥10 units of red blood cells (RBC)), the proportion increasing from 40% to 62% during the period of study. Use of all blood components increased significantly in severely injured casualties, to a median (IQR) of 16 (9-25) units of RBC ($p=0.006$), 15 (8-24) of plasma ($p=0.002$), 2 (0-5) of platelets ($p<0.001$), and 1 (0-3) of cryoprecipitate ($p<0.001$). Cryoprecipitate ($p=0.009$) and platelet use ($p=0.005$) also increased in moderately injured casualties. Survival increased from 76% to 84%.

The number of blood components transfused to individual combat casualties increased during the 4-year period. Survival also increased despite no change in injury severity score or injury pattern. Combat casualties requiring massive transfusion had a significantly higher chance of survival (93.1%) than civilian patients receiving the same amount of RBC (59.7%). Survival is the product of the entire system of care, and transfusion was now available

throughout the evacuation chain. We proposed that the changes in military transfusion practice and capability contributed to increased combat trauma survival.

4.2 Initial UK experience of Pre-hospital Blood Transfusion in Combat Casualties

This report presents the UK Defence Medical Services' (DMS) initial experience of military pre-hospital transfusion. Experience derived from the field hospital resuscitation of severely injured patients had led to the development of damage control resuscitation (DCR). Pre-hospital transfusion was adopted by the UK armed forces as an extension of the resuscitation strategy.

Pre-hospital transfusion was considered for patients without a palpable radial pulse or who had a non-invasive systolic blood pressure of less than 80mmHg. The aim was to restore these parameters, rather than to resuscitate to normotension. Exceptions included; suspect traumatic brain injury (TBI) or if time to definitive care was anticipated to exceed one hour. If more than one unit of packed red blood cells (PBRC) was required, plasma was administered to achieve a RBC: Fresh Frozen Plasma (FFP) ratio of 1:1. A loading dose of 1g of tranexamic acid (TXA) was given to all transfused patients during initial resuscitation.

In the period from July 2008 to March 2011, 1153 casualties were retrieved from point of wounding to the MTF at Camp Bastion by the Medical Emergency Retrieval Team (Enhanced) (MERT-E); 310 casualties received a pre-hospital transfusion. 76.7% of recipients were severely injured (Injury Severity Score (ISS) of 16 or more), of which 48% of patients received pre-hospital transfusion. Almost one-half of patients required intra-osseous circulatory access and/or advanced airway management. The median (IQR) number of units of PRBC and FFP transfused pre-hospital was 2 (1-2). The

median (IQR) total transfusion volume was 8 units (range 3-18) of packed RBC (PRBC) and 7 units (range 2-16) of FFP. Nearly one-half of these patients required a massive transfusion (>10 units while at Camp Bastion), although one-fifth required no further transfusion after admission. The crude mortality of casualties who required pre-hospital transfusion was 20%.

Pre-hospital transfusion is an intuitively appealing intervention with considerable potential. The UK Armed Forces have successfully and safely implemented pre-hospital transfusion. Evidence for its use is currently limited although the first retrospective study suggests that DCR, including pre-hospital transfusion has a significant mortality benefit. The implications are important not only for future military practice but also for the wider civilian community.

4.3 The feasibility of group O LOw titre panels for small combat teams

Military elements increasingly operate in small teams in remote areas with no immediate blood product support. In this situation, planners may endorse the collection of whole blood from pretested donors in emergency situations. The biggest risk of this arrangement is the accidental use of ABO incompatible blood, which can be fatal. The risk may be mitigated by using only group O donors with plasma containing low levels of the naturally occurring antibody to group A and B red cells. This paper studies the ABO blood group distribution in potential blood donors from a high readiness UK medical regiment and explores the feasibility of using only Group O LOw titre (OLO) donors in very small teams.

We performed a retrospective review of routine volunteer blood donor samples at 6 monthly intervals during a 2-year period. Personnel were tested in random groups when available during training to create multiple donor panels to simulate small teams. 206 donation samples were collected from

157 potential donors. The testing protocol was the UK standard for donation which included transfusion microbiology, blood grouping (ABO, Rh and K) and screening for atypical antibodies. Plasma of all group O donors was screened for anti-A/B IgM using the Olympus PK7300® (Beckman Coulter) with a dilution of 1/85 against A_2B cells. Anti-A/B was defined as high titre (HT) positive if reactive at 1/128 (or equivalent dilution) by haemagglutination techniques and negative if reactive at 1:64 dilution.

All donors were acceptable based on the lifestyle questionnaire, serology and microbiology screen. Of the 206 samples reviewed, 85 (41%) were Group O (RhD positive and RhD negative). 14 Group O donors (16.5%) were shown to have a high titre of Anti-A or Anti-B. Therefore 71 donors, i.e. 34% overall were suitable as OLO donors. The individual donor 'panel' size varied from 15-44. The absolute number of OLO donors in each panel ranged from 4-17 and the number of group O RhD negative donors was 0-3. We concluded that a third of samples were suitable as group O low titre donors however, there were insufficient 'universal' donors within smaller subgroups (<10). In this situation, we recommend the careful use of both group O and group A donors or the use of a buddy-buddy blood group matrix.

4.4 A proposed field emergency donor panel questionnaire and triage tool

The aim of this short discussion paper was to raise and resolve some of the practical aspects for the non-specialist faced with the emergency collection of fresh whole blood (FWB) in the austere medical environment (AME). Examples include Military Special Operations, Humanitarian Missions, Remote Industry, the Cruise Industry and Scientific Exploration. Healthcare providers are not traditionally taught donor selection and care. We present a proposed Field Emergency Donor Panel Questionnaire and Triage Tool (QTT). It is designed for an isolated medical provider for use in a hostile,

remote or austere environment that falls outside normal regulated supply of cold stored blood products.

The initiative for this work followed the finding from a pre–conference exercise for the 2015 meeting of the Trauma, Hemostasis and Oxygenation Research (THOR) Network, which took place in Norway in June 2015. The work forms part of the 'Blood Far Forward' program - a whole blood research and training program for austere environments. The principal author reviewed various national and international, military and civilian donor screening guidelines to draft a generic Field Emergency Donor Panel (EDP) Questionnaire. A Triage Tool was developed to rapidly select donors, prioritising those that were previous donors. The tool and questionnaire were then refined by a group of practitioners with experience gained through responding to military and civilian events.

The tool serves as a point of reference for local guidelines and has been shown to be feasible to apply. In addition, the paper provides many useful top tips for the AME practitioner that may not be readily available in the general transfusion literature. We acknowledge that although the use of the EDP is associated with risk it may be the only local method of providing timely transfusion support. The best way to manage the risk is to brief and pre-select potential blood donors before overseas travel. An abbreviated donor questionnaire and triage tool can then be used as an aide to decision-making by the non-expert at the time of emergency donation. The tool should be tailored according to the perceived risks and underpinned by policy and training.

4.5 The evolution of a massive transfusion protocol for trauma in a single UK centre

Death from massive haemorrhage due to traumatic injury is potentially preventable after hospital admission using haemorrhage control and improved resuscitation techniques including Massive Transfusion Protocols (MTP). The introduction of MTPs was designed to provide a rapid response, however, the preparation of plasma may delay delivery of the initial pack. Emergency red cells are normally available in most hospitals and could be used to provide immediate blood-based resuscitation while waiting for a MTP. The purpose of this before-and-after study was to determine the impact of modifying a civilian protocol originally introduced in August 2008. The amendment was to include emergency red cells rather than delaying transfusion whilst waiting for plasma. In addition, we investigated whether massive transfusion prediction models could have been used to guide ongoing transfusion support.

We analysed all sequential MTP activations over three years, before and after the protocol revision. The percentage of MTP activation, component usage, and outcome data were compared. Trauma Associated Severe Haemorrhage (TASH) and Assessment of Blood Consumption (ABC) scores were derived and Receiver Operating Characteristic (ROC) analysis undertaken for an outcome defined as the use of > 6 red cell units. 52 and 66 MTP activations arose from the 216 and 495 major trauma cases, respectively. The protocol changes significantly reduced the MTP activation rate (p=0.0006) from 24% to 13%, and the number of activations requiring >10 RBC increased from 13% to 36% (p=0.006). However, the average emergency red cells usage in the second cohort increased from 0 to 4 units. The time to MTP pack issue and the outcome measures such as survival and coagulation parameters were unaffected by the protocol revision. The TASH score showed an area under ROC (AUROC) of 0.88 for ongoing transfusion requirements.

We concluded that the change in protocol improved the predictive value of starting the MTP without causing a delay or 'speed bump'. However, we suggested that methods should be developed to rapidly provide plasma and prevent a plasma deficit. In addition, we proposed that it was better to start the MTP early and then to step down once the patient was stabilised. The TASH score appeared to provide a useful predictive tool for ongoing transfusion support.

4.6 Massive Transfusion: changing practice in a single Norwegian centre 2002 – 2016

In this paper, we described the epidemiology of massive transfusion and the impact of a transfusion programme in a single Norwegian centre throughout the period 2002–2016. In 2007, Haukeland University Hospital introduced a massive transfusion (MT) programme incorporating education, thromboelastography and an Acute Transfusion Package (ATP). The ATP consisted of 6 units of RBC, 6 units of Octaplas solvent/detergent treated plasma *(Octapharma AG)* and 2 platelet concentrates (PC). A retrospective review was made of all MT episodes defined as $\geq$10 RBC in 24 hours. Searches were made using the laboratory information system (ProSang). Patient records were reviewed manually for: demographics, indication for transfusion, haemostatic drugs and mortality. Data was collated and analysed in SPSS.

410 MT episodes were identified in 410 patients. These episodes accounted for 2.8% of RBCs and 3.4% of PCs issued during the study period. The mean patient age was 60 (9-94) years, with a male predominance (64%). 87.1% of episodes were in support of surgery (cardiac services 42.7%; trauma 17.6%). 29.8% of all MT involved platelet inhibitors with 82.6% of these patients undergoing cardiac procedures. 25.1% of MT involved anticoagulants. The mean ratio of blood components RBC: plasma: platelets changed from

1.0:0.37:0.39 in 2002-2006 (n=149) to 1.0:0.79:0.85 in 2008-2015 (n=241, p<0,001). A sub-analysis showed that cardiac specialities used proportionally more plasma and platelets than other specialties. Survival appeared to be more improved in groups receiving 20 or more units. A sub-analysis of patients receiving ≥30 blood components within 24 hours showed that 30-day survival improved from 32.3% before 2007 to 54.9% after 2008 (p=0.027).

MT was primarily used in major surgery. The findings contrast with other studies showing that most red cells are used in medical specialities. The programme in 2007 successfully changed massive transfusion practice in that it delivered a more balanced treatment. The greater use of haemostatic components in cardiac surgery may reflect changes in anti-platelet medication or local management. These findings should inform future studies, demand planning and patient blood management programs.

4.7 MCEs: transfusion emergency preparedness across the continuum of care

The purpose of this descriptive study was to compare the support of two transfusion service systems to MCEs; one in Bergen, Norway and one in the UK. Traditionally, transfusion services have not been involved as part of the healthcare response. However, recent developments in haemostatic resuscitation have highlighted the importance of transfusion support in the care of the critically injured. In addition, the frequency of terror attacks in Europe has re-energised an interest in preparedness using lessons identified from recent military experience.

We reviewed the planning approaches used for MCEs such as the London bombings and mass gathering such as the Olympic Games. We summarised the recent military and civilian data and described the potential for computer modelling. We acknowledged the impact of military practice on pre-hospital

care, especially the early management of massive haemorrhage, which is key to controlling demand for blood. Demand is based on the supply of either multiple component therapy or whole blood, as both countries have introduced Massive Haemorrhage Protocols (MHPs) within their civilian hospital sectors. The challenge for the blood services is meeting the surge in demand for labile 'universal components' such as group O red cells and group A platelets, or whole blood. Supply options must be developed. It was this aspect of planning that was the focus for the study.

The English blood service has a network of manufacturing sites and stock holding units within a small but crowded geographical area. In contrast, Norway has hospital-based blood collection and preparation. Transport within Norway may be limited by geography and weather conditions. Therefore, different options may be considered for the emergency supply of blood. In the UK, preparedness has included appropriate stock management including repositioning and re-supply from other centres. In addition, integrated shortage plans exist with the hospitals to triage the use of blood components. However, the geography of Bergen is such that mutual aid from other Norwegian centres may not be immediately available. Bergen has recently established pre-tested emergency donor panels together with military aid. In addition, the manufacturing has been simplified to provide whole blood rather than component therapy.

In this paper we illustrated that transfusion demand and capability planning can be an integrated part of the wider medical planning process for emergency preparedness. We concluded that the chosen solutions should be tailored according to local resources and requirements.

5: DISCUSSION

Conflict continues to be a potent stimulus to innovation.[163] The multiple injuries sustained in recent warfare by combatants on all sides, as in Iraq and Afghanistan, have been horrific. However, the developments in military medicine have been extraordinary and have been presented as a revolution in military medical affairs.[1;2] Haemorrhage control and haemostatic resuscitation have been cited as critical determinants of outcome in the seriously injured.[8] Should and could the military philosophy of Damage Control Resuscitation doctrine be adopted by civilian healthcare? In this discussion, I address the four aims using the results of the papers presented in this thesis to describe the implementation and impact of the recent changes in military transfusion and explore the significance for civilian practice.

5.1 Implementation and impact of recent changes in UK military blood transfusion practice

Overview. The UK military Massive Transfusion Protocol (MTP) was introduced in 2007. The military transfusion capability was developed to rapidly resuscitate critically injured young people. The volume of blood required, and the survival have been extraordinary. Figure 5 in Chapter 1 illustrates the rapid rise in blood component demand from 2008 onwards peaking in 2011 before tailing off in 2014. Papers 1 and 2 explore the impact of changing policy and practice during this period.

The recent changes in UK military blood transfusion practice. Paper 1 described the blood use per patients admitted to the UK role 3 Medical Treatment Facility (MTF) during the period of 2008 – 2011. The paper included all patients presenting to the MTF and not just those arriving by helicopter. A total of 2618 patients was identified. Most patients were male (99%) and the median age was 22 years (range19-25). In broad planning

terms, one third of casualties received blood and fifty percent of these were Massive Transfusion (MT) i.e. ten or more units of red cell concentrates (RCC). The percentage transfused increased from 13 to 32%. The median blood component use per patient was 16 units of red blood cells (RBC), 15 units of Fresh Frozen Plasma (FFP), 2 adult therapeutic doses (ATD) of platelets and 1 pool (5 doses) of cryoprecipitate. The most striking changes in military practice, i.e. the increase in the use of haemostatic components, was seen for the more severely injured group. The findings are consistent with a US database analysis of multiple traumatic amputations published in 2017.[184] The US paper found that the average transfusion requirements in the period of 2009- 2012 were RBC 18.6 (0–142), FFP 17.3 (0–128), platelets 3.6 (0–26), and cryoprecipitate 5.6 (0–130). Godfrey *et al.* correlates the degree of injury and demand for transfusion with the change in the technology of improvised explosive devices (IED) from 2009 onwards.

Massive transfusion. In the period of 2008-2011, 13.7% of UK hospitalised military trauma patients received a MT. The proportion of military patients who received a MT doubled during the period of study increasing from 9% to 20%. Paper 1 does not convey the enormity of resuscitating these combat injuries. However, Allcock had highlighted that 7 out of 59, i.e.11.8% of massive transfusions during 2009 involved more than 100 components. Such cases not only required blood but also placed an enormous demand on all aspects of military healthcare. Allcock showed that 51 (86%) survived to be discharged from hospital in the UK.[116] It is difficult to compare this result directly with civilian healthcare practice and outcomes. An analysis of UK trauma registry data from 2005-2009 showed that only 0.4% of civilian casualties received massive transfusion. Such patients received on average 11 units of RBC but only 4 units of FFP and 2 single units each of platelets and cryoprecipitate. The mortality rate for civilian patients with MT was 40.3%[176] in contrast to the military survival rate of 93.1%. The improved survival of military patients may be related to the patient population which is almost exclusively male, younger,

assumed fitter with access to body armour. However, 74% of military patients had an injury severity score (ISS) > 15. The mean new injury severity score (NISS) of 22 hides the injury severity of patients with multiple amputations.

Changes in capability. Survival studies require careful consideration. The better survival of massively transfused casualties, compared with non-massively transfused casualties shown in paper 1 is probably explained by survival benefit – i.e. casualties had to survive long enough to receive a massive transfusion. Pre-hospital transfusion was introduced during 2008. Paper 2 suggests that the developments in pre-hospital rescue and en-route care led to more severely injured casualties being rescued which may account for the apparent fall in survival following arrival at the field hospital. The more severely injured casualties received proportionally more plasma, platelets and cryoprecipitate. Paper 1 proposes that the increased use of platelets from 2008 may be explained by the improved availability of this product following the development of a deployed apheresis capability.[53] The deployment of rotational thromboelastometry (ROTEM) in 2009 may explain the increased use of both platelets and cryoprecipitate. These findings are consistent with those reported by US colleagues, who also demonstrated that the introduction of ROTEM was associated with an increased use of all blood components other than RBC, and particularly cryoprecipitate (Cap, 2012 Personal Communication). Paper 1 also highlights the changes in the use of pharmaceutical adjuncts to transfusion. Tranexamic acid (TXA) was not used before 2009, but is now given to most patients requiring transfusion, and almost all patients requiring massive transfusion. In contrast, recombinant factor VIIa (rFVIIa) was used during the early years of the war, but not later. This change may reflect an increasing recognition of the limited effectiveness of rFVIIa and risks of thrombosis.[69] On reflection, the influence of the governance systems and pre-deployment training should also be recognised. The delivery of the massive transfusion capability (MTC) had a significant impact on all members of the clinical team, especially the nursing cadre. The

delivery of emergency transfusion was integrated into pre-deployment training designed to provide high fidelity mission specific training leading to well-orchestrated team-work. [50]

The development of pre-hospital transfusion for the MERT. The introduction of phase change materials revolutionised air-borne transfusion logistics for both pre-hospital emergency care and medical evacuation. Intra-osseous devices enabled vital circulatory access as part of the blood delivery systems. The Medical Emergency Retrieval Team (MERT) transfusion capability was developed in the context of severely injured patients recovered by physician-led helicopter borne medical teams with transfer times of 1-2 hours. Paper 2 by O'Reilly *et al.* in 2014[88] was the first of a pair of papers describing military pre-hospital blood transfusion. This Special Report covers the practical and clinical aspects of prehospital transfusion as practiced by the UK Armed Forces in Afghanistan and describes a cohort of patients who received pre-hospital transfusion. O'Reilly, in an additional paper, presented a matched cohort study of mortality outcomes after pre-hospital transfusion.[185] This was the first comparative study of military pre-hospital transfusion in a modern context. There are acknowledged confounders but, in the context of particularly accurate matching of injury profiles, that paper showed a halving of mortality among recipients. Paper 2 ends with a discussion of the rationale for pre-hospital transfusion and an exploration of future directions, especially for civilian practice.

Pre-hospital transfusion. The civilian context for the air ambulance may be different from that of the military. The transit times for most UK air ambulance transfers are shorter and the clinical capability en-route is restricted by the smaller airframes. The value of pre-hospital transfusion for short transfers is debated however; early blood product resuscitation is intuitively attractive. Several air ambulances have described their early experience.[185-188] These papers confirm feasibility and safe practice but do not confirm the survival

benefit suggested in military practice. The Midwinter group's systematic review of pre-hospital blood products (PHBP) resuscitation for trauma identified only low and very low-quality evidence and argued the case for prospective studies.[186] Other investigators in the field have stressed the importance of "high-quality prospective data collection".[187] In 2016, the Midwinter group, including this author, started the pilot phase of RePHILL. RePHILL is a two arm, open-label, parallel group randomised controlled trial (RCT), investigating the role of PHBP resuscitation using up to two units each of red blood cells and Lyoplas-N. The endpoint includes tissue perfusion as measured by lactate clearance. The pilot phase is finishing at the time of writing in 2017 and the methodology has been published.[188] The experience of the pilot phase has highlighted the feasibility of delivering combined component therapy in the civilian pre-hospital environment. However, they have also highlighted the importance of close collaboration with laboratory services.[189]

Impact on survival. Papers 1 and 2 have described the recent developments in military transfusion practice. Others have claimed that these developments have had a significant impact on survival.[1;8] Figure 7 shows the improved survival in UK combat casualties from Iraq and Afghanistan during the period 2003–2012.[8] Survival is the product of the entire system of care, which – in this setting of combat, the system of care incorporates the early control of external haemorrhage, hybrid resuscitation; rapid and physician-led recovery from the battlefield, early limited initial surgery including haemorrhage control, transfusion support and expert critical care. It is thus not possible to ascertain the individual contribution of the transfusion strategy employed, however, in Papers 1 and 2 we propose that it has been an important element.

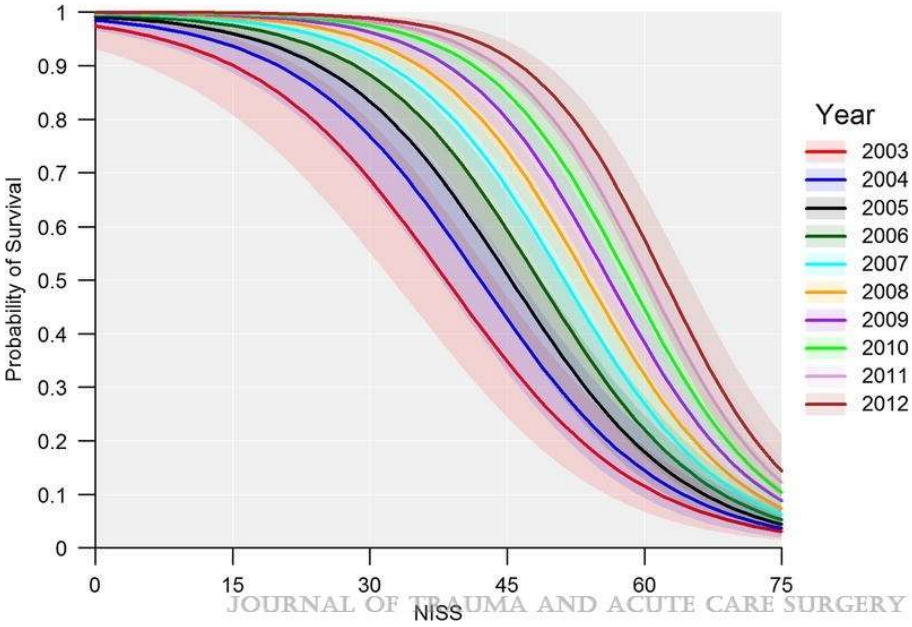

Figure 7. Plot of predicted probability of survival by NISS value for each year. Shaded regions indicate the 95% CIs for the predicted values obtained from the logistic regression model. Figure used with permission from the Journal of trauma and Acute Care Surgery.[8]

5.2 The development of donor selection for forward transfusion

Overview. The current use of whole blood in trauma is primarily motivated by the need for a resuscitative solution that treats both shock and coagulopathy for patients with life-threatening hemorrhagic shock.[137] In addition, whole blood offers simplified logistics, reduced donor exposure, reduced dilution by additive solutions and anticoagulants. It is an ideal candidate for the military and civilian pre-hospital environment and possibly for Mass Casualty Events (MCE). Whole blood collection as part of Remote Damage Control

Resuscitation (RDCR) is in the process of being developed in the UK. Papers 3 and 4 were studies designed to inform the selection of donors.

Group O Low titre whole blood donors. The Trauma Hemostasis and Oxygenation Research (THOR) network has advocated the use of group O donors who have been pre-tested, and shown to be negative, for low titre or clinically significant levels of anti-A/B antibodies.[154] The approach is pertinent to both military and civilian practice but is particularly important when there are risks associated with both emergency collection and administration. This approach was adopted and developed on a larger scale by the US 75th Ranger Regiment (Special Forces) as part of their 'Rangers O Low titre' or the ROLO initiative.[144] Paper 3 describes the feasibility of using this approach for the smaller UK airborne medical regiment to create a POLO (Parachute O Low titre) panel. We demonstrated in Paper 3 that for planning purposes, approximately one third of a military unit were suitable for a POLO panel. The findings were similar to those of the US.[144] However, we also demonstrated that the use of a group O donor only policy may need to be modified for small team work, i.e. less than 10 persons.[190] The UK medical doctrinal notes[157] were updated to reflect the optional use of a 'Blood Buddy' system for small groups. In this situation, planners are now advised to consider the use of both group O and group A donors (A to A and low-titre O for all others) or to use a prepared blood group matrix of donors and recipients (buddy-buddy blood group matrix). However, Group O whole blood with low anti-A/B titres should be used where the blood group of the recipient is unknown or there is uncertainty.[154]

Civilian use of plasma rich components. In civilian medical service, the problems related to the transfusion of group O whole blood to non-group O recipients disappeared with the introduction of component therapy, (RBC, plasma and platelet units) and the virtual elimination of whole blood transfusion in adults. However, platelet transfusions with ABO-incompatible

plasma continue to occur routinely in hospitals in the US and Europe due to inventory constraints. Each unit of apheresis platelets contains about 200-300 mL of plasma, which is similar to that of whole blood. A previous study by the Biomedical Excellence for Safer Transfusion (BEST) collaborative in 2010 concluded that there was considerable variation in the transfusion practice and testing of minor ABO-incompatible platelet concentrates.[191] In addition, few centres performed routine monitoring following such transfusions. Transfusion reactions are commonly reported and collated via hemovigilance systems. A total of 25 reports (mostly case reports) of haemolytic reactions in connection with platelet transfusions from 1975 to 2009 were evaluated in detail.[192] From 30 patient cases, of which 25 were malignancies, mostly leukaemia, there were only two fatalities that could be linked to a haemolytic transfusion reaction due to incompatible platelets in otherwise very sick cancer patients. The risk of haemolysis associated with platelets has been reduced through the introduction of Platelet Additive Solution (PAS). However, guidance for haemolysin testing will be required if whole blood is to be reintroduced into the civilian inventory.

The unscreened emergency donor. The context of Paper 4 by Doughty *et al.*, 2016[109] is access to blood for isolated military or civilian projects with extended lines of supply or limited logistical support, i.e. the austere medical environment (AME). The medical planning for remote activity should consider the requirements for resuscitation, including transfusion support. The emergency use of fresh whole blood (FWB) should be considered if medical evacuation is delayed and there is no capacity to provide cold stored blood products. Ideally, team members and staff should be pre-screened as members of an Emergency Donor Panel (EDP). However, the emergency screening and management of unknown additional blood donors may also be required. The aim of Paper 4 was to introduce a generic Field EDP Questionnaire and Triage Tool (QTT).[109] A review of the literature demonstrated that there was very little published about the assessment of

blood donors in the AME. The context and urgency may necessitate a rapid or focussed donor screen. However, relaxing donor acceptance criteria will introduce risk. Risks may need to be further managed using 'donor triage' and appropriate use of blood. The paper also addressed some of the practical aspects for the non-specialist faced with the donor selection in the austere medical environment. One of the novel considerations is the implication of donor selection and rejection within a close community.[109]

Implications for civilian practice. Transfusion is moving forward within the battlespace. Knowledge sharing from the THOR network has enabled new planning guidance to be developed for UK policy and practice as illustrated by Papers 2 and 3. However, the concept of the safe group O donor has also informed the wider transfusion community leading to the acceptance of group O Low titre by the American Association of Blood Banks in 2017.[193]

5.3 Introduction of Massive Transfusion Protocols in UK and Norwegian civilian centres

Overview. The theory of an acute coagulopathy of trauma together with retrospective evidence from analysis of military and civilian trauma databases led to new transfusion guidelines, including massive haemorrhage guidelines in Europe[166;197] and trauma guidelines in Scandinavia.[194] Early adopters in England and Scandinavia now have a decade of experience of using MTPs for massive haemorrhage. Papers 5 and 6 study different, but complementary, aspects of the introduction of MTPs.

The evolution of MTP*s in Birmingham.* The Birmingham massive haemorrhage protocol introduced in August 2008 was identical to the UK military protocol based on transfusion shock packs of four RBC and FFP followed by the early use of platelets and cryoprecipitate. The clinical

guideline is shown below in Figure 8. Features include pre-hospital notification, haemorrhage control and cell salvage.

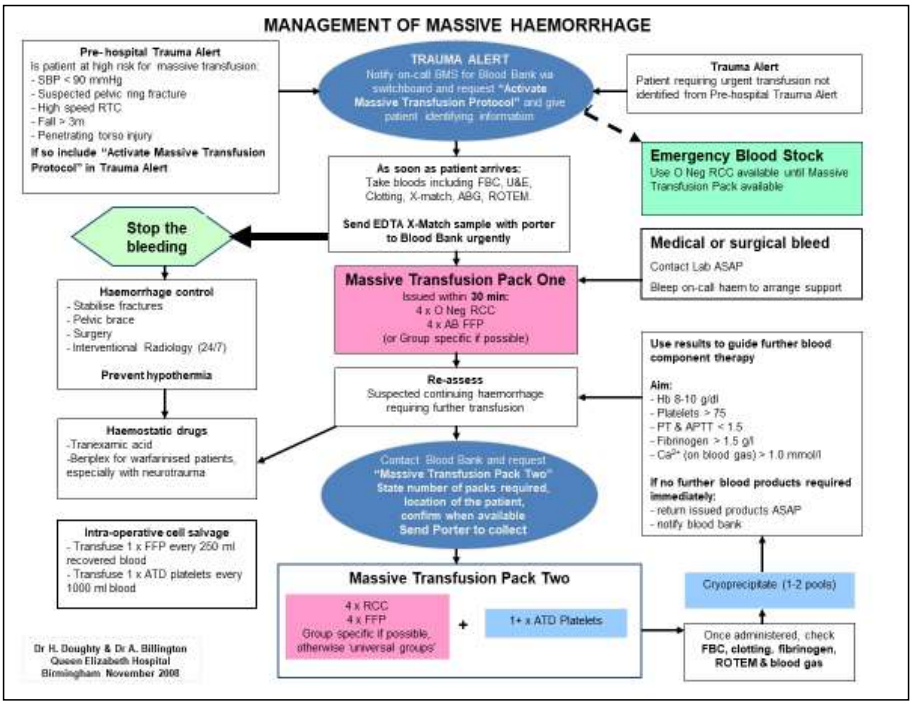

Figure 8. The 2008 version of the Massive Haemorrhage guidelines from the University Hospital Birmingham by Doughty and Billington.

The first audit of MT activations in Birmingham had highlighted concerns about delays due to the availability of thawed plasma. The average time from activation to issue of the packs was 30 min and this did not include transport time. The study tested the hypothesis that immediate access to red cells in the Emergency Department (ED) may reduce demand for Shock Packs and the waste of unused thawed plasma. The primary aim of this study was to study the impact of protocol change together with education. The study showed that the mean age of the patients was 40 years and 73 -80% were male. The main mechanism of injury was road traffic collision. The mean ISS

was similar in the two study periods, 25 and 30 and the mortality was 13% and 15%, i.e. unchanged. The use of emergency RBC reduced the MTP activation rate from 24 to 13% of all major trauma cases and the positive predictive rate for the use of Shock Packs improved from 13 to 36%. The main finding was that many patients only needed 4 units of red cells and did not require further blood-based resuscitation. However, this approach increased the use of group O RhD negative red cells and perhaps placed some patients at risk of plasma deficit.

Predictive scoring systems. Birmingham was an early adopter of MTPs and this audit was performed during the early days of practice. Over-activation of the MTP was common and perhaps desirable if there are perceived delays in transport of samples and blood. Over-activation provides patient safety but impacts on staffing and use of resources. Paper 5 attempts a retrospective application of massive transfusion predictive tools. Predictive modelling for massive haemorrhage has been designed for MTP activation and may support decision making.[195;196] However, Paper 5 argues that this is a limiting concept as the predictors are often not available at the time of admission. We proposed that if the scoring systems are applied later they can be used to determine the continued requirement for MT support. Using a prediction model in this novel way permits the use of data gathered during resuscitation and removes the gatekeeper effect. Greater accuracy can be gained through education, mentored clinical exposure[197] and ongoing audit.

Quality monitoring. A recent quality management audit of a mature system in a US level 1 trauma system during 2016 was described recently by Hess *et al.*[198] The MTP was activated 309 times during 2016 for a variety of conditions but mainly (77%) for trauma. The mean ISS was 32 and the mortality 15%. Over triage was minimal with 93% of all activations receiving blood and 83% receiving 3 or more units of red cell concentrates (RCC). Of note, only 19% of all activations fulfilled the traditional criteria of at least 10

units of RCC. The mode RCC use was 2 units, the median, 4 units and the mean 6.6 due to a small number of individuals requiring 20 or more units. The system in Harbourview Medical Centre in Seattle is unusual in that it operates a transfusion support system very similar to military field hospitals. The MTP activation results in a blood technician moving with components into ED to work closely with the clinical team. The target response time is 3 minutes. Such a model would be very attractive for MCEs.

Changing practice massive transfusion in a single Norwegian centre. Paper 6 is an early example of how the new transfusion paradigm has changed transfusion practice in relation to *all* patients with massive haemorrhage. The programme was based on established civilian practice in Copenhagen, and introduced as an integrated programme, including thromboelastography and education. More significantly, it was championed by the key stakeholder i.e. the Department of Anaesthesia and closely supported by the Department of Immunology and Transfusion Medicine. Only 410 MT episodes were identified in 410 patients during a 13-year period. This was due to the selection criteria of $\geq$ 10 units RCC. The mean ratio of blood components RCC: plasma: platelets used in massive transfusion changed in 2002-2006 from a red cell predominant mix of 1.0:0.37:0.39 (n=149) to a more balanced ratio of 1.0:0.79:0.85 (n=241) in 2008-2015 ($p<0.001$). The use of platelet concentrates, and plasma increased significantly after the introduction of the massive transfusion package in 2007, as seen in other studies.[199-203] The survival figures did not change, other than for those patients transfused greater than 30 components. The Halmin epidemiological study of 92,057 massive transfusions during a similar period showed a slight increase in the median plasma: RBC ratio over time but no marked changes in mortality.[204]

Patient demographics. The mean patient age in the Bergen study was 60, like other civilian MT studies[204;205] and more recent general trauma studies.[206] More importantly, it demonstrated that most (87.1%) episodes were in support

of surgery especially cardiac services (42.7%). Trauma accounted for only 17.6%. The figures may reflect the case-mix in an institution with a regional specialist unit in cardiac services. However, the findings are similar to other teaching hospitals.[205] Although the study numbers are small, there is a signal from the sub analysis that cardiac specialities used a greater proportion of plasma and platelets. We propose that this may be related to changes in pharmaceutical practice in this group especially anti-platelet medication. The paper concludes that MT remains an uncommon but serious complication of major surgery. The findings contrast with the general transfusion use studies from the UK, which show that most red cells (65%) are used for medical specialties, especially haemato-oncology and gastroenterology.[207;208] The findings are important for Patient Blood Management programmes and civilian blood component demand planning.

5.4 Transfusion support to Mass Casualty Events

Overview. Recent terrorist events remind us again that the UK and Norway are not immune from the traumatic injuries seen in military medicine. The care of the patient with traumatic haemorrhage is demanding, and this is further complicated in the mass casualty situation. Mass casualties may result in a demand for blood that cannot be immediately met. Paper 7 by Doughty *et al.* compared the UK and the Bergen systems and highlighted the need to work across the continuum of care, from the pre-hospital community to the blood providers.

Definitions. The terminology in Major Incident planning is complex; and civilian and military terminology differs. A Major Incident is any occurrence that presents a serious threat to the health of the community in such numbers or types of casualties to require special arrangements. The exact scale of an event and the resources required are often unknown when initially declared by the emergency services. For the purposes of this discussion, I have used the

term Mass Casualty Event (MCE) rather than Major Incident or Disaster. An MCE may be defined as a '*single or simultaneous event(s) or other circumstances where the normal major incident response of one or several health organisations must be augmented by extraordinary measures to maintain an efficient, suitable and sustainable response'*.[209] Glasgow argues that MCE is an appropriate term in the context of transfusion planning because it is healthcare specific and addresses healthcare load. I suggest it is a good fit because Blood Services commonly support several healthcare organisations and planning must address the requirement for sustainability.

Transfusion planning for the Olympics. Glasgow *et al.* described how the military concepts of pre-hospital care, registry reviews, standardised MTPs and emergency donor planning principles were successfully integrated into NHS Blood and Transplant's (NHSBT) planning for the 2012 Olympic Games.[177] Demand planning for the Olympic Games was based on a compromise between the available civilian and military data combined with the feasibility of achieving and maintaining the required stock level. Military experience had shown that a third of patients needed blood with a requirement for 15 units of RCC and FFP. In contrast, reviews of civilian MCEs with military type trauma suggested that few people need blood and the RBC demand was 2-3 units. The notable exception was the demand for blood following the London bombings described by Glasgow *et al.*[164] The mean RBC demand was 17 and the mode was 12. It is difficult to explain why the London bombing figures are so much greater than the civilian norm. Blood use after the Boston Marathon bombing of April 15, 2013 was summarised by Quillen and Luckey in 2014.[210] Thirteen percent of patients brought to the ED were transfused. The mean blood use per patient (24 hr) was 6.15 units. Only 1 patient of the 58 (2%) received $\geq$10 units. Quillen reflected on the greater blood use per patient transfused in London and suggested it was due to lack of tourniquets.[210] The point is well made and demonstrates the importance of early haemorrhage control.

Transfusion requirements for MCEs. Paper 7 highlights the requirement to estimate the proportion of casualties requiring blood following MCEs. Traditional planning by the North Atlantic Treaty Organisation (NATO) is based on a P1: P2: P3 ratio of 25:25:50 however, this does correlate well with civilian events and transfusion planning. A past Israeli survey of 1645 attacks involving 7497 casualties suggested 13% death at scene with 8% severe (P1) and 12% (P2) moderate casualties, i.e. a total of 20% who may need blood. Most blood is required within 6 hours. Current Israeli planning assumes early notice of the MCE and the provision of 3 RBC per casualty and 7 units for more severely injured. [211] These planning principles would have worked well for the Manchester bombing in 2017 where 20% were transfused with a median use of 3 units. However, the Manchester incident was characterised by many girls and young women. It is noted that one third of the blood used (31/89) was group O RhD negative, of which 90% was used as emergency group O RhD negative. The demand:use ratio was 3.5 for all red cells, which is similar to past attacks. However, the demand factor for group O RhD negative blood was 5.25.[212] The experience following the Manchester bombings, together with a recent review of blood use in civilian major incidents by Ramsey[213] has led to revised UK planning figures of 3 units per admitted casualty. However, if the methods and devices used in MCEs change, as noted by Godfrey, than these figures may require amendment. Quality data and reviews following each event are required to inform future planning.

Transfusion Emergency Preparedness in Norway. Planning in Norway has been shaped by their own tragedy of MCE. The paper from Gaarder *et al.*, 2012[214] following the twin terrorist attacks in Norway in 2011 describes the impact of MCE using two different mechanisms. The IED explosion in Oslo caused 8 deaths (8.1%) at the scene where 98 casualties were injured. Ten (11%) of the survivors were triaged to the major trauma centre. In contrast, the shooting on the island caused 68 dead (52%) at the scene and 61

survivors. 21 of these were triaged to trauma, i.e. 34%. The MTP was initiated in 7/149 injured cases (4.7%). The mean MTP blood use: RBC 7.6 units, Octaplas 5.6, platelets 2 ATD (pools of 4). The authors comment that the provision of blood was easily met though existing stocks. Despite this reassurance, the Norwegian Red Cross has engaged the author to advise on managing the donor response.

Transfusion resilience. Haukeland University Hospital has worked closely with the blood donor communities to develop a novel resilience plan based on the lessons identified from the Blood Far Forward (BFF) program. Transfusion support is based on an agile whole blood program using military and civilian donors. The demand planning for specific events has been developed further using more detailed modelling. An example would be the planning for the Bergen World Cycling Championships. The initial response is based on the use of existing stock however the urgent local donor panels are designed to replenish these. All blood is fully tested however it is not subject to separation into components. Irrespective of whether countries use blood components (UK) or whole blood (Bergen), transfusion must be part of an integrated healthcare plan. Pre-hospital care and haemorrhage control should be optimised and the use of blood in MCEs may need to be triaged and simplified. Most blood will be required within the first six hours but there may be an ongoing requirement . Paper 7 contends that blood supply should be part of civilian transfusion emergency preparedness. The author proposes that it is the principles of military planning and the resource constrained nature of RDCR that have the greatest potential to inform civilian practice. Bricknell, as one of the senior medical planners during this period argued that the absence of a mass casualty declaration is the best evidence for the effectiveness of the UK military medical planning process.[215]

5.5 The implications for civilian healthcare

In the introduction, I reflected that the UK Trauma Services would require considerable re-organisation to leverage the lessons learnt from developments in military trauma and transfusion. Trauma services are undergoing a transformation.

Major Trauma Networks. The UK Major Trauma Networks were created in 2010 and the regional Major Trauma Networks in 2012. The networks have adopted many of the military trauma organisational practices. Specific transfusion measures include the requirement to have a massive haemorrhage protocol (MHP) as in Paper 5. Protocols alone do not make a difference, it requires leadership[197] and local champions, as seen in Paper 6. Did these changes impact on survival? Results from the Trauma Audit and Research Network (TARN) national audit in 2013 showed that 1 in 5 patients who would have died before the networks, are now surviving severe injuries. A more detailed evaluation of the London Trauma System was published in the 2016 paper by Cole *et al.*[206] The team used the same core methodology used by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report described in Chapter 1. 344 severely injured patients were identified in a 3-month period and their outcome compared with the NCEPOD report. Survival had improved, with the greatest benefits seen in the most severely injured where the crude mortality rate reduced by 50% from 31% to 11%. The principle cause of death was Traumatic Brain Injury and not haemorrhage. Patients were noted to have increased use of pre-hospital services and were older than in previous studies (NCEPOD). The latter has also been demonstrated by Kehoe.[216] The authors conclude that inclusive trauma systems seem to deliver quality through organisational change. However, I suggest that it is further evidence that the civilian population is not the same as the military population and that the future configuration and capability of trauma services should be different.

National Institute for Health and Care Excellence (NICE) Trauma Guidelines.[217] Rapid and efficient safe transfusion support is now considered an essential element in the management of major haemorrhage.[218] Sadly, in 2015 a prospective UK observational study from 22 major hospitals showed that there were still delays in the delivery of blood.[219] The authors concluded that only 2% of patients with massive haemorrhage received optimal, i.e. timely, resuscitation. Further direction was required for the wider trauma community. In 2016, the changes in transfusion practice that began in 2006, were formally adopted within the UK NICE guidelines for trauma.[64] The early requirement for plasma had highlighted the delays in thawing FFP to order. The military had introduced pre-thawed plasma with an extended post thaw shelf-life in 2008. However, this was not introduced into UK civilian practice until after the NICE trauma guidelines in 2016.[220] The introduction of pre-thawed plasma has reduced one of the practical barriers to the timely delivery of plasma identified in Paper 6. It also appears to have reduced the wastage of plasma where there is a sufficient ongoing demand within the hospital. However, pre-thawed plasma may not be convenient for helicopter-based services deploying from airfields remote from their supporting blood banks as in Paper 2 and lyophilised plasma may be used.[188] The demand for 'plasma now' has also resulted in the blood service reviewing the development of new components including liquid plasma[221] and whole blood.[150]

Patient Blood Management. The civilian community has successfully reduced the demand for red cells through the Patient Blood Management (PBM) initiative.[35] Whereas, the demand for blood appears to have increased in military practice despite haemorrhage control. There is a perception that the opportunities for PBM are limited in the management of traumatic haemorrhage. However, this paradox can be resolved.[222] Patient Blood management is about optimising the care for patients rather than just reducing blood use. Paper 1 suggests that the use of goal directed transfusion therapy increased the demand for haemostatic components. However, these studies

also imply that some patients were under transfused in the past and that massive transfusion has contributed to the unexpected survival figures.[8] Classical PBM manoeuvres already being used by the military that reduced the demand for red cells included tourniquets, combat bandages and topical haemostats. The massive blood use after the London bombings may reflect the non-availability of these measures in civilian practice. Damage control surgery is the definitive method of haemorrhage control.[223] In addition, transfusion-sparing techniques can be learnt from civilian teams performing complex surgery without blood support, including cell salvage.[224] There is also valuable guidance for transfusion planning from Coupland and others who have worked with the International Committee of the Red Cross (ICRC) in resource constrained environments. [225;226]

Transfusion demand planning. Studies in this thesis have considerable implications for civilian demand planning. Demand management of blood components is challenging. Challenges arise from the limited shelf-life of blood components combined with providing sufficient stock whilst minimising blood wastage. Most blood components in the UK, especially red cells, are used by non-surgical patients[207;208] where it is harder to predict demand. In contrast, Doughty *et al*. and other investigators suggest that massive transfusion is associated with surgery[204;205;227] which can be managed through PBM principles. Whereas the use of red cells has fallen, the demand for other components has increased in the UK. The drivers for the increase in platelet use may include haemato-oncology, gastroenterology and the wider use of anti-platelet drugs as discussed in Paper 6.[228] The requirements for plasma and fibrinogen replacement have also increased in most European countries. This may be due to the inappropriate use of plasma in non-bleeding patients[229] but also in part to the wider use of MHPs as discussed in papers 1, 5 and 6. The wider use of pre-hospital transfusion in civilian practice is leading to an increased initial demand for 'universal' components such as Group O RhD negative RBC and Group AB FFP. The recent paper by Naumann *et al*., has

quantified the potential demand. Most of the patients attended by the air ambulance are male.[230] Consideration may need be given to the carriage of group O RhD positive blood in addition to Group O RhD negative. The trends for components use and the group mix should be factored into local and national demand planning as well as the planning for MCEs. Transfusion Emergency Preparedness for MCEs is underpinned by sound military planning principles together with the lessons learnt from taking transfusion forward.

5.6 Limitations of study

A general limitation of the study is the retrospective analysis of observational data collected during a period of considerable change. The source data for Papers 1 and 2 were extracted from the military Joint Theatre Trauma Registry (JTTR), which records details of all casualties who receive treatment in deployed UK military MTFs. The data for both blood and other fluids is thought to be complete for military papers 1 and 2. In contrast, the study-specific limitations for the civilian papers 5 and 6 include a lack of data on the volume of crystalloid and colloid solutions administered during resuscitation. The reason for lack of detail is that papers 3, 5 and 6 have used hospital LIMS data as a key source of primary data. The author recognises that clinical information provided to hospital blood transfusion laboratories with requests for transfusion may be limited. In addition, there may be difficulty in extracting the information required for retrospective studies from hospital IT systems. Of note, LIMS assumes that the time of blood administration equals that time of issue, which may not be correct.

The definition of 'massive transfusion' used for all the studies (Papers 1, 5 and 6) was ten units, or more, of RBC transfused in 24h. We recognise the limitation of this definition which has been used since the initial papers from the Holcomb team.[38] Green *et al.*[205] used several definitions including both MT $\geq$5 RBC units in 4 hours as well as the traditional $\geq$10 RBC units in 24 hours.

The former has been proposed by Mitra.[231;232] When the two definitions are used together they should capture approximately 95% of all cases. The MT ≥5 RBC units in 4 hours is a much more appropriate marker of active haemorrhage and resonates with the definitions used in the military protocols. In addition, it is useful for MI demand planning where it should be assumed that most blood will be required within the first 6 hours.

Despite these issues, these studies add to our understanding of modern resuscitation strategies in both military and civilian practice. The military studies complement analyses from the US JTTR.[233] The military studies in Papers 1 and 2 are based on a large and complete database collating contemporaneously collected data. The conclusions are applicable to similar military trauma systems. Likewise, the laboratory data from paper 3 is complete, being underpinned by both military and civilian LIMS. The civilian studies in papers 5 and 6 are subject to the limitations of retrospective studies at a single centre and the numbers are relatively small. Cardiac cases are over-represented in paper 6 and trauma is possibly underrepresented. The general observations from both would be applicable to other large medical centres dealing with massive haemorrhage. However, larger scale studies are needed from Norway. The Bergen team is currently designing these.

Retrospective studies cannot prove causation. Papers 1 and 2 suggest a temporal association between increased component use and improved survival, in combat casualties requiring transfusion as part of Damage Control Resuscitation (DCR). The higher survival in the military severely injured may be accounted for in part by the younger age and greater fitness of the military patient group. In addition, the military care system was optimised for trauma care with early care from point of wounding through to rehabilitation.[4;234;235] However, the small civilian studies in papers 5 and 6, have failed to demonstrate an improvement in 30-day mortality. Similar observations, i.e. no significant improvement in mortality, have been made in other retrospective

civilian studies such as that by Green *et al.*[205] The failure to demonstrate an improvement may be due to the sample size, the greater variance in co-morbidities or the challenge in demonstrating incremental improvement in a more controlled environment. The significance of these is considered in the future recommendations. Finally, the body of published literature for transfusion in the austere environment and in support of mass casualties was, and remains, limited.

The strength of the study is that it documents the entirety of a unique transformation programme with a continuity of clinical and academic leadership.

6: CONCLUSIONS

6.1 Summary of findings

*Aim 1. T*he paradigm of military transfusion has changed in the last decade. The developments have been credited with contributing to survival of the critically injured. Survival is the product of the entire system of care, which – in this setting of combat, incorporates the early external haemorrhage control, hybrid resuscitation; rapid and physician-led recovery from the battlefield, damage control surgery, transfusion support and expert critical care. It is not possible to ascertain the individual contribution of transfusion however, it has been an important element.

Aim 2. Transfusion support is increasingly being considered in the Austere Medical Environment. These are military and civilian environment where there is a risk of traumatic haemorrhage but minimal medical or logistic support. The collection of whole blood from a pre-tested Emergency Donor panel is a viable transfusion management option. Knowledge sharing from the Bergen based Blood Far Forward program has enabled the further development of UK military practice. In addition, the concept of the safe universal whole blood donor has informed the wider transfusion community leading to the acceptance of group O Low titre as a new standard.

Aim 3. Massive Transfusion Protocols have been successfully introduced into civilian practice for both trauma and other causes of massive haemorrhage. Massive Transfusion (MT) is a phenomenon of surgery not trauma and the organisational principles can be applied to all causes of haemorrhage. MT is resource intensive and has implications for both hospital and blood service organisation. However, the civilian studies have not demonstrated a survival advantage and the definitions of MT require standardisation to allow comparison of practice and the design of further studies.

Aim 4. The pattern of blood use in civilian Mass Casualty Events (MCE) differs from that seen in the recent military experience in Afghanistan and Iraq. Far fewer injured require blood and few require Massive Transfusion and haemostatic component support. However, military style planning has added value to the preparation for MCEs and the response to Major Incidents. Elements of military planning have included the optimisation of pre-hospital care, haemorrhage control, transfusion triage, MTPs and emergency donors. Transfusion Emergency Preparedness should become an integrated part of healthcare emergency planning.

6.2 Reflection on findings

Returning to the opening vignette, the recent developments in military transfusion practice have had a direct impact on civilian transfusion practice, including the planning and response for MCEs. Elements of new clinical practice include: pre-hospital control of haemorrhage, pre-hospital transfusion, trauma registries, standardised massive transfusion protocols and emergency donor planning. However, caution is required in extrapolating the blood demand for military trauma to current civilian hospital practice or emergency planning. I suggest that the lessons learnt for MCEs from the military are related to planning rather than the direct comparison of transfusion requirements. Military planning and transfusion practice together underpin the emerging discipline of Transfusion Emergency Preparedness.

Transfusion has emerged as an essential and successful element of combat care. The success must be placed in the context of the whole healthcare system, especially pre-hospital care. Combat has stimulated rapid innovation. Sometimes military developments have been based on emerging evidence together with pragmatism rather than randomised controlled trails. However, the thesis has presented evidence that lessons identified from military medical and transfusion care have been intelligently adopted into civilian practice and

planning. In turn combat care has benefitted from civilian transfusion regulatory and governance expertise. The continued military-civilian collaboration and international innovation in transfusion practice has the potential to benefit not only the armed forces, but also the wider healthcare community.

6.3 Recommendations and future works

The operations in Iraq and Afghanistan have been a stimulus to develop new paradigms of treatment. Developments in planning have led to transfusion emergency preparedness. However, preparedness for the future requires constant horizon scanning. A recent analysis of the implications of future operating environments for the defence medical services can be summarised as follows:[236]

- Preparedness: High readiness, humanitarian assistance, disaster relief
- Operations: Urban, distributed small mobile combat teams, sea basing
- Technology: Develop capability but reduce size and weight, telemedicine
- Economic: Need for evidence base and collaboration with academia and industry

The last statement is important. It emphasises the need for an evidence base developed together through partnerships. The North Atlantic Treaty Organization (NATO) Blood Panel exists to promote interoperability of transfusion practice between NATO partners. It was started as an informal ad hoc working group in 2005. In January 2011 it was formally integrated into the NATO Committee of Chiefs of Military Medical Services (COMEDS) structure as a permanent sub-element and expert panel under the Military Health Care Working Group (MHCWG). More recently, it has advised the United Nations on deployed transfusion support. The panel has served as an important forum for the development of pre-hospital transfusion and transfusion in the austere environment. In doing so, there are synergies with the Trauma, Hemostasis

and Oxygenation Research (THOR) community, especially in the areas of innovation and research.[131]

The collaborative work between Birmingham and Bergen has linked military and civilian teams from both organisations. We have achieved significant changes in emergency transfusion support especially very early transfusion support. Sometimes practice has preceded the evidence and has stretched regulatory and logistic constraints. Ethical and philosophical issues are also important and require us to question 'should we' and not just 'could we'. Conducting research in military[182] and civilian trauma, especially MCEs, is challenging especially where practice has become established and the numbers of patients required to power studies are great. In addition, this thesis has illustrated the caution required when extrapolating the lessons identified in one system to another. The challenge is for the combined communities to continue to optimise transfusion support with intelligent application of best evidence. To do this will require an ongoing commitment for data collection and management. In addition, quality quantitative and qualitative research should be embedded into routine clinical and planning practice.

Pilot and feasibility studies provide guidance for future studies. For instance, the CRYOSTAT feasibility study[58] signaled possible associations between higher fibrinogen levels following trauma and better outcomes and use of healthcare resources. The observations coupled with other reports[59] led to the current CRYOSTAT-2 study to determine the clinical benefit of early fibrinogen supplementation. Multi-centre randomised controlled trials are viewed as the gold standard however, such trials take a considerable time to prepare and are best done through clinical trials networks.[197] Such trials may not show significant improvements in mortality. An example is the PROPPR trial (Pragmatic, Randomized Optimal Platelets and Plasma Ratios Trial) published in 2015.[237] The large trial of transfusion in traumatic haemorrhage trial did not

achieve the primary objective. The use of a 1:1:1 ratio of RBC: FFP: platelets did not result in a significant reduction in mortality at 24hr or 30 days, however more patients achieved haemostasis and fewer experienced death by exsanguination. Despite perceived limitations[238] these trials appear to be the tipping point for the British Society of Haematologists[61] formally supporting the early use of plasma in haemorrhage in ratios of 3:2 to 1:1 and the National Institute for Health and Care Excellence (NICE) trauma guidelines of 1:1.[217]

Professor Hans Erik Heier from Oslo has suggested that a more philosophical approach should be applied to current and future development.[131] Increasing the resources and skills available may not lead to a linear improvement of results. The general law of decreasing marginal efficiency suggests that where the effect of additional resources and skills is progressively reduced, the better results are those which are obtained early. When few resources and skills are available, as in the far forward environment or mass casualties then small changes are likely to make a bigger difference than under optimal Damage Control Resuscitation (DCR) conditions.[131] For instance, the benefits of whole blood (WB) over component therapy may be of greater significance in Remote DCR and pre-hospital practice than within hospital conditions. New trials for whole blood are being introduced however, John Ioannidis warned that “the hotter the scientific field and with more scientific teams involved, the less likely the research findings are to be true”. [239] The clinical advantage of WB may prove impossible to show scientifically.

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APPENDICES

Appendix 1

Organisation of military healthcare

All military medical treatment facilities (MTF) are categorised into response capabilities Role 1 – 4. A brief description based on current medical doctrine is provided below.[76]

Role 1 MTF - Medical Response Capability. The initial medical response capability (Role 1 MTF) is a national responsibility and focuses on provision of primary health care, specialised first aid, triage, resuscitation and stabilisation. NATO doctrine assumes this will be a physician. The UK model is the use of a general practitioner with enhanced military medical skills. Transfusion is not traditionally offered in this Role.

Role 2 MTF - Initial Surgery Response Capability. Initial surgery response capability (Role 2 MTF) is characterised by its ability to perform surgical interventions in addition to perform reception / triage of casualties; resuscitation and treatment of shock to a higher level than Role 1 facilities. There are two main types of Role 2 MTFs: basic and enhanced (E). Examples of the enhanced hospital would be the high readiness field hospitals and their maritime equivalent, the Primary Casualty Receiving Facility (PCRF). Examples of basic Role 2 medical units are the Air Manoeuvre Surgical Group (AMSG) and the Commando Forward Surgical Group (CFSG). In some circumstances, it may be necessary to provide a mission-tailored medical treatment facility including a surgical module, the so called Forward Surgical Element (FSE).

Role 3 MTF - Hospital Response Capability. A hospital response capability provides secondary health care at theatre level. A Role 3 MTF must provide all

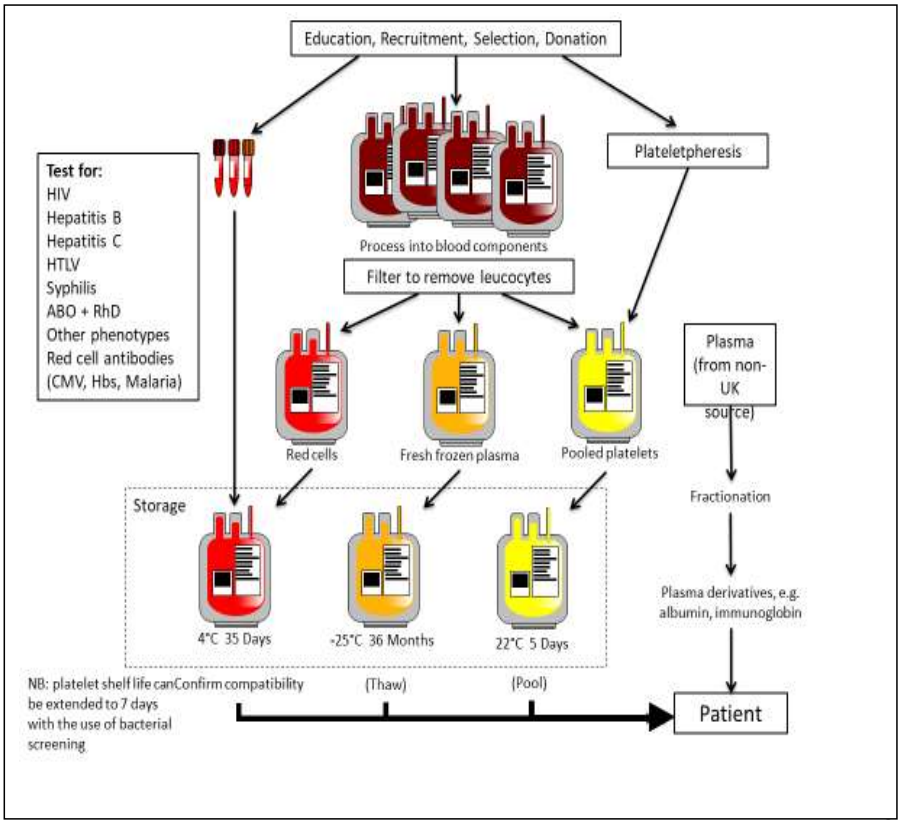
the capabilities of the Role 2E MTF and be able to conduct specialised surgery, care and additional services as dictated by mission and theatre requirements. The Role 3 facility may also act as a hub for medical logistics providing blood resupply and platelets. The field hospital at Bastion was an example of a Role 3 MTF which was subsequently stepped down to a Role 2E before closure.

Role 4. Role 4 is a base hospital capable of providing the full capability of a Major Trauma Centre. The Role 4 facility for the UK is the University Hospital Birmingham. The full care package from reception to rehabilitation is co-ordinated by the Royal Centre for Defence Medicine.

Appendix 2

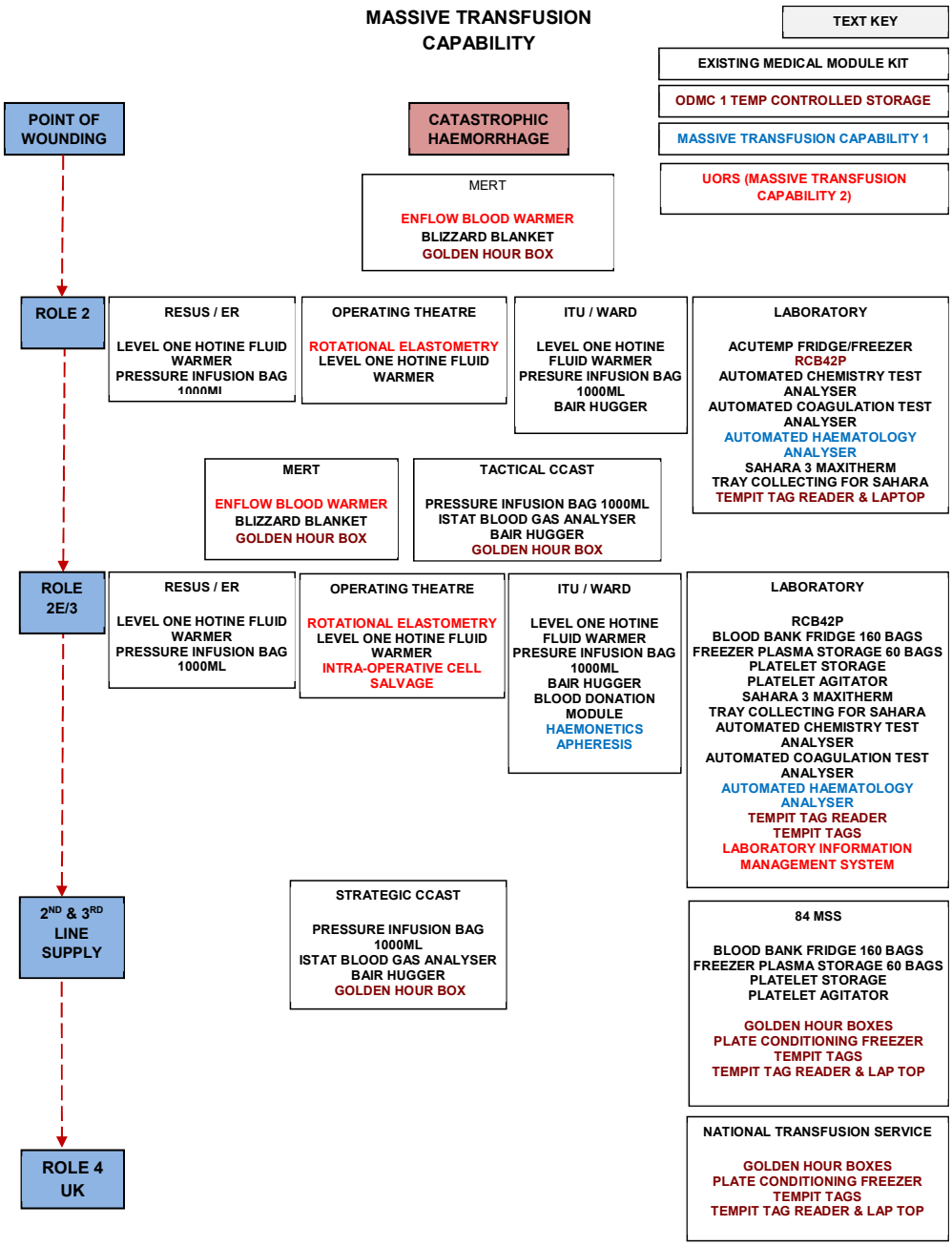
Vein to vein: An overview of the transfusion process

The figure provides an overview of the transfusion process from donor recruitment to administration of blood components to the patient. The process starts with the key step of donor selection before the collection by whole blood or apheresis. Testing of the samples and manufacturing of the collection are simultaneous activities. Whole blood is filtered before separation into components. Blood components are issued to the hospitals after a final validation check of the manufactured product together with the results of microbiological and serological testing. Source plasma may be used for clinical plasma or fractionation to produce plasma derivatives such as fibrinogen.



Appendix 3

An overview of the UK Massive Transfusion Capability



Appendix 4

Associated publications and selected presentations related to the thesis

PEER REVIEWED PAPERS

H. A. Doughty & S. Allard (2006) Responding to Major Incidents – Lessons Learnt from July 2005 London Bombings. *Blood Matters (NHS Blood and Transplant)*, **20**, 14 - 15.

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TRANSFUSION MEDICINE Official Journal of the British Blood Transfusion Society

Transfusion Medicine | ORIGINAL ARTICLE

Changes in blood transfusion practices in the UK role 3 medical treatment facility in Afghanistan, 2008–2011†

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SUMMARY

Objective: To document blood component usage in the UK medical treatment facility, Afghanistan, over a period of 4 years; and to examine the relationship with transfusion capability, injury pattern and survival.

Background: Haemostatic resuscitation is now firmly established in military medical practice, despite the challenges of providing such therapy in austere settings.

Materials and Methods: Retrospective study of blood component use in service personnel admitted for trauma. Data were extracted from the UK Joint Theatre Trauma Registry.

Results: A total of 2618 patients were identified. Survival increased from 76 to 84% despite no change in injury severity. The proportion of patients receiving blood components increased from 13 to 32% per annum; 417 casualties received massive transfusion (≥10 units of RCC), the proportion increasing from 40 to 62%. Use of all blood components increased significantly in severely injured casualties, to a median (IQR) of 16 (9–25) units of red cell concentrate ($P = 0{\cdot}006$), 15 (8–24) of plasma ($P = 0{\cdot}002$), 2 (0–5) of platelets ($P < 0{\cdot}001$) and 1 (0–3) of cryoprecipitate ($P < 0{\cdot}001$). Cryoprecipitate ($P = 0{\cdot}009$) and platelet use ($P = 0{\cdot}005$) also increased in moderately injured casualties.

Conclusions: The number of blood components transfused to individual combat casualties increased during the 4-year period, despite no change in injury severity or injury pattern. Survival also increased. Combat casualties requiring massive transfusion have a significantly higher chance of survival than civilian patients. Survival is the product of the entire system of care. However, we propose that the changes in military transfusion practice and capability have contributed to increased combat trauma survival.

Key words: haemostatic resuscitation, military transfusion, tranexamic acid, trauma resuscitation.

The past decade has seen remarkable changes in military trauma transfusion practices, brought about by the recognition that acute traumatic coagulopathy is associated with excess mortality (Brohi *et al.*, 2003; MacLeod *et al.*, 2003; Brohi *et al.*, 2007; Pidcoke *et al.*, 2012), and that combat casualties transfused with high plasma to red cell unit ratios had dramatically improved survival (Borgman *et al.*, 2007; Pidcoke *et al.*, 2012). Haemostatic resuscitation, comprising the administration of predetermined ratios of units of red cell concentrate (RCC), plasma (FFP) and platelets (PLT), is now firmly established, despite the inevitable challenges of providing such therapy on deployment, and in austere settings.

Two recent analyses from the United States have examined changes in military blood use over time. Pidcoke *et al.* (2012) have shown that the volume of blood transfused per casualty, and the ratio of the units of plasma and platelets to red cell concentrate has increased, and that these changes are correlated with improved survival. Rentas *et al.* (2012) have demonstrated similar trends. However, neither of these studies have examined the impact of changes in injury pattern and severity on blood use.

The aim of this study is, first, to analyse blood component usage in the UK medical treatment facility at Camp Bastion, Afghanistan, over a period of 4 years; and second, to examine the relationship between blood component usage, transfusion capability, injury pattern and survival.

MATERIALS AND METHODS

Design

This is a retrospective analysis of blood component use in a single combat support hospital. The study was approved by the Royal Centre for Defence Medicine (RCDM/Res/Audit/1036/12/0175). Eligible patients were British and coalition

† An abstract of this work has been presented at the annual meeting of the Association of Surgeons of Great Britain and Ireland (2013), and will be presented at BBTS (2013).

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(non-Afghan) service personnel admitted following injury, and transfused one or more units of blood components before and during admission to the UK medical treatment facility (MTF) at Camp Bastion, Helmand province, Afghanistan, between 1 January 2008 and 31 December 2011. Casualties who only received transfusions after discharge or transfer from the hospital were excluded.

Source data

Data were extracted from the Joint Theatre Trauma Registry (JTTR), which records details of all casualties who receive treatment in deployed UK military medical treatment facilities (MTF). UK service personnel are followed up to discharge from Queen Elizabeth Hospital, Birmingham. Coalition service personnel are followed up to aeromedical evacuation from the hospital at Camp Bastion. Extracted data included demographic details, injury severity scores, and the number of units of red cell concentrate, plasma, platelets, cryoprecipitate and fresh whole blood transfused. In addition, data on adjuncts to haemostasis management (recombinant factor VIIa and tranexamic acid) was extracted.

Setting

The retrieval of casualties in Helmand Province is almost invariably by helicopter, usually directly to the UK MTF at Camp Bastion. In-flight care is provided by paramedics or doctors. For casualties who are *in extremis*, transfusion with red cell concentrate and plasma may be initiated *en route*, but is more commonly administered at the hospital at Camp Bastion.

The MTF at Camp Bastion is a field hospital optimised for the management of trauma. Staffing is multi-national but comprises predominantly British and American military personnel. The hospital has increased in size and complexity over the period of this study, from a basic tented facility to a solid build. In late 2011, it had 4 operating tables, 12 intensive care beds and 2 CT scanners. The laboratory provided a basic transfusion and general pathology diagnostic service together with the ability to receive and re-distribute blood components. Blood components are provided by licensed blood services and imported by military logisticians. All UK components were leucodepleted. The principles of transfusion inventory management remained largely unchanged during the period of study. Red cells provided for resuscitation should be 'fresh'. In 2009, the policy further defined this as less than 14 days old where possible. Plasma was provided as pre-thawed FFP with a maximum post thaw shelf-life of 5 days. The laboratory also managed a pre-tested Emergency Blood Donor panel. This capability permits the donation of Fresh Whole Blood and the collection of platelets by apheresis.

Transfusion policy

Transfusion support for the severely injured was guided by a Massive Haemorrhage Policy, containing a Massive Transfusion Protocol (MTP) together with guidance for monitoring response to treatment (Surgeon General's Policy Letters, 2007, 2009). The key elements of the policies are shown in Box 1. The MTP may be initiated by clinical staff who are concerned that the patient has had or may be at risk from the effects of massive or rapid haemorrhage. Treatment is initially given as 'Shock Packs', based on the use of pre-thawed plasma (4 units) and red cell concentrate (4 units) in a 1 : 1 ratio. Shock packs may be used

Box 1. Key components of the massive transfusion protocol used by the Defence Medical Services (Surgeon General's Policy Letter, 2007).

Definition

Massive transfusion is defined as:

1. The replacement of an equivalent amount of blood to an entire circulating blood volume of the patient with 24 h; or
2. Administration of more than 10 units of red cell concentrate within 24 h (whichever comes first).

In the acute military operational setting, additional criteria include:

1. The transfusion of over 4 units of red cells in 1 h; or
2. The replacement of 50% of the total blood volume in 3 h; or
3. A rate of loss of >150 mL min^{-1}.

Principles of the DMS Operational Massive Transfusion Protocol (MTP).

The DMS operational MTP adopts an aggressive resuscitation approach in which the primary aim is to avoid a significant degree of coagulopathy. This approach requires:

1. Active avoidance of hypothermia by the use of fluid warmers and rapid infusion devices.
2. Maintain the Hct at 35%.
3. Use of FFP to RCC in a 1 : 1 ratio as soon as practicable.
4. Early use of cryoprecipitate in order to maintain the level of fibrinogen above 1·0 g L^{-1}.
5. Early intervention with platelet support to maintain the platelet count above 100×10^9 L^{-1} using UK (or more local source if appropriate) derived platelet components, or platelets donated using field apheresis, both in preference to whole blood from the Emergency Donor Panel (EDP).
6. Frequent measurement of FBC and coagulation studies to confirm successful application of the MTP.
7. Frequent measurement of potassium and calcium levels in order to identify the presence of hyperkalaemia or hypocalcaemia so that appropriate therapy can be commenced.
8. Appropriate intervention with rFVIIa in accordance with current military guidelines.
9. Regular assessments of the base deficit in order to monitor (along with hypothermia and coagulopathy) the lethal triad associated with massive trauma.

in both the hospital and pre-hospital setting (physician-staffed retrieval helicopters carry 4 units of red cell concentrate and 4 units of plasma). Subsequent transfusion support including the early use of cryoprecipitate and platelets is guided by the clinical response together with the results of laboratory and point of care testing. Pharmacological adjuncts have changed during the period of study with the decreasing use of recombinant factor VIIa (rFVIIa) and the increasing use of tranexamic acid (TXA) since 2009. The transfusion protocol has recently been updated to incorporate the evidence for the routine use of TXA (CRASH-2 trial collaborators, 2010; Morrison *et al.*, 2012) and a higher target for fibrinogen.

Transfusion capability

Transfusion capability increased over the period of the study, in line with operational requirements. The focus has been on both the capacity and capability to support haemostatic resuscitation. Plasma, cryoprecipitate and platelets have all been available since before the period of study. However, greater resilience was introduced in spring 2008 with the introduction of an operational apheresis capability to collect platelets (Doughty *et al.*, 2011). Pre-hospital transfusion was introduced in summer 2008, requiring investment in equipment and manpower. Laboratory staffing was increased, and services increasingly automated. The introduction of the Laboratory Information Management System in 2009, together with full bar coding, has transformed the speed and accuracy with which staff can respond to the call for large amounts of blood components. Walk away automated diagnostic technology has facilitated the processing of large numbers of samples, required to monitor resuscitation in critically injured patients. More recently, rotational thromboelastometry (ROTEM) was introduced, as a point-of-care test, to further optimise haemostasis management.

Data management and statistical analysis

Injury burden was quantified by injury severity score (ISS), stratified into mild (ISS: 1–8), moderate (ISS: 9–15) and severe (ISS $\geq$ 16); new injury severity score (NISS); and by body region, using abbreviated injury scales (AIS).

Demographic characteristics were compared using Kruskall–Wallis tests for continuous data and χ^2 tests for proportions. The number of units of individual blood components transfused were analysed by calendar year and injury severity strata, and compared using Kruskall–Wallis tests.

Transfused patients were furthermore analysed by volume of red cell concentrate transfused, dichotomised into massive and non-massive transfusion. For the purposes of this study, massive transfusion was defined as the administration of 10 or more units of red cell concentrates while at Camp Bastion. The definition was chosen due to ease of data collection and to permit comparison with other studies.

Mortality for UK personnel was defined as in-hospital mortality which occurred within 30 days either in Afghanistan or in the UK. For other coalition patients, in-hospital mortality included only that which occurred at the treatment facility in Afghanistan. This approach is pragmatic, and has been employed previously (Morrison *et al.*, 2012), as it is very difficult to track the progress of casualties from other countries through their respective evacuation chains. Furthermore, although some casualties succumb after transfer to role 4 care, this is unusual.

The ratios of plasma to red cell concentrate and platelet to red cell concentrate are presented as three-month moving averages. The frequency of use of tranexamic acid and FVIIa were calculated in all transfused and massively transfused patients. All analyses were performed using Microsoft Excel (Microsoft, Redmond, Washington, DC, USA).

RESULTS

Between 1 January 2008 and 31 December 2011, 2618 coalition service personnel were treated for trauma at the UK MTF Camp Bastion. 791 (30·2%) required a transfusion. The characteristics of this group are shown in Table 1. Nearly all (99%) were male. The median age was 22 years (range: 19–25). The median injury severity score and new injury severity score were 22 and 34, respectively, indicating a high burden of injury. Analysis of ISS strata reveals that 74·1% of transfused casualties were severely injured (ISS 16+) (Table 1).

Number and proportion of casualties transfused

The number of trauma patients per year has increased from 303 in 2008 to 794 in 2011, peaking at 849 in 2010 (Fig. 1). The number of trauma patients who required transfusion has also increased, from 68 in 2008, to 257 in 2011 (Fig. 1). In addition to an overall increase in the number of casualties, the proportions that were transfused have also risen, from 22% in 2008 to 32% in 2011 (Fig. 2). Four hundred and seventeen casualties (52·7% of all patients transfused) received a massive transfusion (10 or more units of red cell concentrate). The proportion of all trauma patients who received a massive transfusion (13·8% in total) increased from 9% in 2008 to 20% in 2011. The proportion of transfused patients who required a massive transfusion also increased, from 40% in 2008 to 62% 2011 (Fig. 3).

Injury severity

There has been little change in injury severity, as measured by ISS ($P = 0{\cdot}189$) or NISS ($P = 0{\cdot}104$) (Fig. 4). Similarly, there has been little discernible change in the pattern of injury, as measured by the proportion of casualties with a severe injury (defined as an AIS $\geq$3) (Fig. 4).

Blood component use

In terms of injury severity, the median number of units of red cell concentrate transfused to severely injured casualties increased from 2008 to 2011 ($P = 0{\cdot}006$). There was no corresponding

Table 1. Baseline characteristics, 1 January 2008 to 31 December 2011

	All patients transfused at R1/R2/R3		Patients who received massive transfusion at R1/R2/R3		Patients who received non-massive transfusion at R1/R2/R3	
Demographics						
Total number	791		417		374	
Male, *n* (%)	784	(99·1)	412	(98·8)	372	(99·5)
Age, years, median (IQR)	22	(19–25)	22	(19–25)	23	(20–26)
Injury severity						
NISS, median (IQR)	34	(18–52)	42	(30–54)	23	(9–37)
ISS, median (IQR)	22	(14–31)	27	(19–35)	17	(7–27)
by ISS strata						
ISS 1–8, *n* (%)	77	(9·7)	12	(2·9)	65	(17·4)
ISS 9–15, *n* (%)	113	(14·3)	30	(7·2)	83	(22·2)
ISS 16+, *n* (%)	586	(74·1)	368	(88·3)	218	(58·3)
Unknown, *n* (%)	15	(1·9)	7	(1·7)	8	(2·1)

NISS, new injury severity score; ISS, injury severity score.

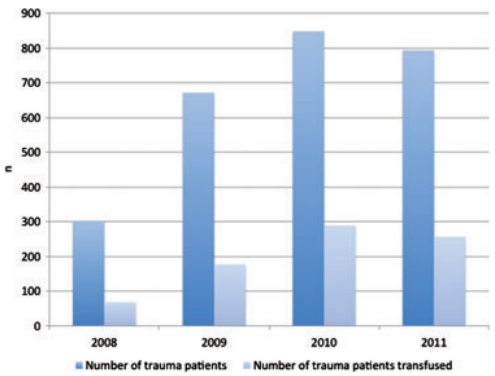

Fig. 1. Number of trauma patients, and number of trauma patients transfused, by year.

increase in casualties with mild and moderate injuries ($P = 0{\cdot}617$ and $P = 0{\cdot}283$, respectively) (Fig. 5). The median number of units of plasma transfused to severely injured casualties similarly increased over the same time period ($P = 0{\cdot}002$). Again, there was no corresponding increase in those with mild and moderate injuries ($P = 0{\cdot}350$ and $P = 0{\cdot}549$). The median number of units of cryoprecipitate and pools of platelets transfused, in contrast, increased in severely (both $P < 0{\cdot}001$) and moderately ($P = 0{\cdot}009$ and $P = 0{\cdot}005$, respectively) injured patients (Table 2).

In terms of total transfusion requirements, the median number of units of red cell concentrate administered to massively transfused casualties did not change ($P = 0{\cdot}699$), but the median

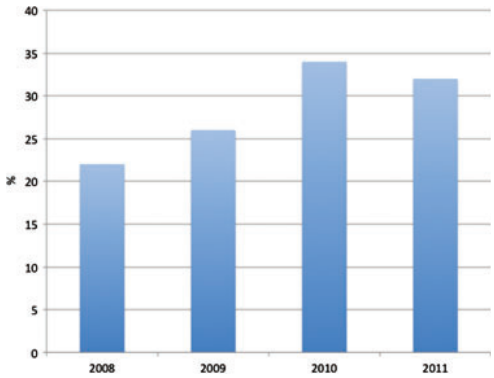

Fig. 2. Proportion of trauma patients transfused, by year.

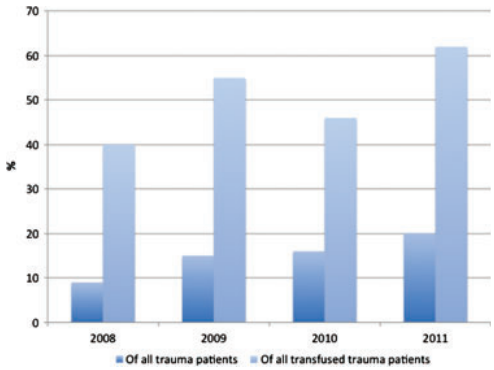

Fig. 3. Proportion of patients who received a massive transfusion, by year.

Table 2. Median (interquartile range) units of cryoprecipitate transfused, by year

Year	ISS>16		ISS 9-15		ISS1-8	
2008	0	(0–1)	0	(0–0)	0	(0–0)
2009	1	(0–3)	0	(0–0)	0	(0–0)
2010	1	(0–2)	0	(0–0)	0	(0–0)
2011	1	(0–3)	0	(0–2)	0	(0–0)
*P**	<0·001		0·009		0·551	

*Kruskall–Wallis test.

number of units of plasma and platelets increased ($P = 0{\cdot}046$ and $P < 0{\cdot}001$, respectively) (Fig. 7).

The average moving ratio of units of plasma to red cell concentrate and units of platelets to red cell concentrate administered to massively transfused patients has progressively increased (Fig. 8).

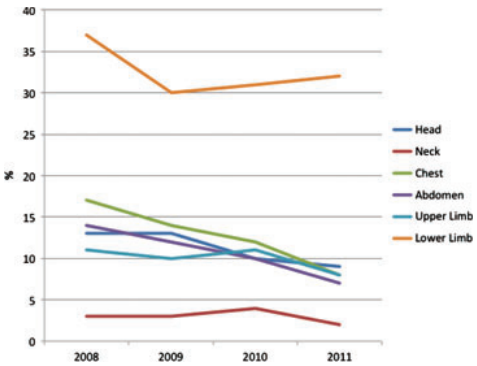

Fig. 4. Injury pattern: Proportion of patients with AIS≥3, by region and year.

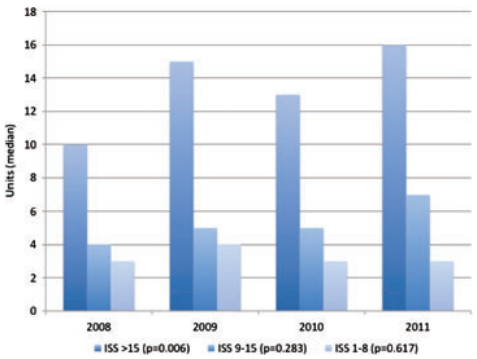

Fig. 5. Median number of units of red cell concentrate transfused, by injury severity and year.

Use of pharmaceutical adjuncts

Recombinant factor VIIa (rVIIa) was widely used until 2009, when approximately one-quarter of casualties who required red cell transfusions, and approximately one-half of those who required massive transfusion, received this product. By 2011, these proportions had decreased to 4·6 and 6·3%, respectively. Conversely, tranexamic acid was not used until 2009, but is now administered to two-thirds of casualties requiring blood transfusion, and 80% of those requiring massive transfusions (Fig. 9).

Survival

The overall survival of casualties who received any transfusion was 78·8%, ranging from 76·9% in 2008 to 84·8% in 2011. For casualties who received a massive transfusion, survival currently stands at 93·1%. Survival was lower for non-massively transfused than for massively transfused casualties (Fig. 10).

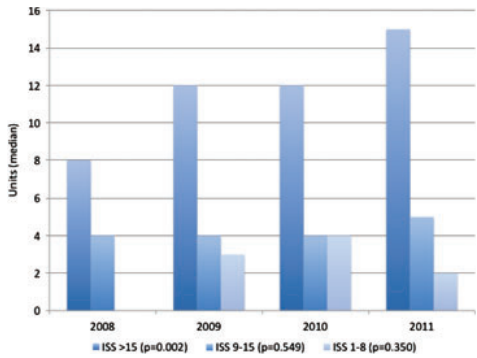

Fig. 6. Median number of units of plasma transfused, by injury severity and year.

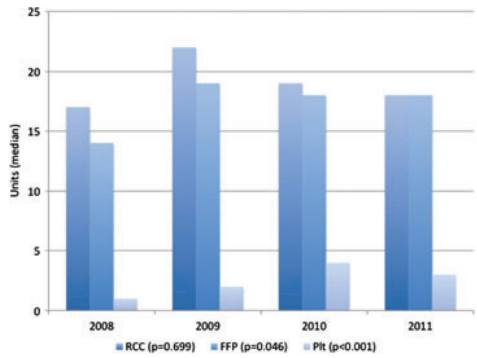

Fig. 7. Median number of units of red cell concentrate, plasma and pools of platelets administered to massively transfused casualties, by year.

DISCUSSION

This is the first comprehensive analysis of blood use by the UK Defence Medical Services, in a mature operational theatre. It provides an insight into current practice, its evolution, and the impact of policy and capability.

Conventional resuscitation of the bleeding trauma patient, as described in the 8th edition of the Advanced Trauma Life Support course, relies on the initial administration of large volumes of crystalloid solutions, followed by red cell concentrate and further crystalloid (American College of Surgeons, 2008). Products such as plasma, cryoprecipitate and platelets would only be introduced at a later stage, and usually once demonstrable abnormalities in coagulability or platelet numbers were present. The contemporary treatment of combat casualties differs: There is greater emphasis on controlling haemorrhage (Hodgetts *et al.*, 2006), hypotension during en-route care is permissible, and the use of crystalloid solutions

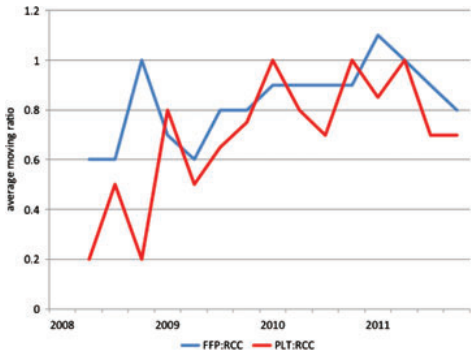

Fig. 8. Average moving ratio of units of plasma to red cell concentrate, and platelets (individual units) to red cell concentrate, by year.

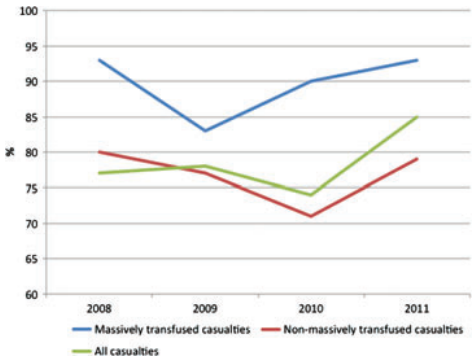

Fig. 10. Survival, by year and volume of transfusion.

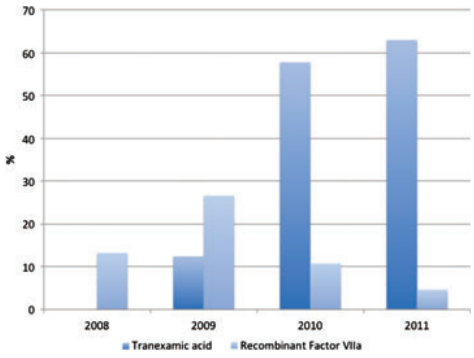

Fig. 9. Tranexamic acid and recombinant factor VIIa use, by year.

is limited to maintaining a palpable radial pulse, and only when blood is not available (Jansen *et al.*, 2009). Lost blood is replaced with a combination of products which approximate whole blood, and where necessary, transfusion support can be provided en route to definitive care.

As a result, the proportion of injured service personnel who were transfused blood products has increased, year on year. Approximately one-third of casualties now receive treatment with blood components. The proportion of casualties who received a massive transfusion has increased five-fold, to 20% of all casualties. This proportion is markedly higher than reported in civilian practice. A recent analysis of UK registry data has shown that only 0·4% of civilian casualties require massive transfusion (Fuller *et al.*, 2012). The proportion of transfused patients who received a massive transfusion has doubled. It is tempting to ascribe these changes to increasing injury severity or changing injury patterns, but this is not supported by our data. The observed trends therefore seem to reflect changes in practice.

The most striking changes are the increase in the number of units of red cell concentrate, plasma, cryoprecipitate and platelets transfused to severely injured patients. These findings suggest that severely injured patients may have been under-resuscitated in the past.

Changes in blood product use may also be accounted for by developments in policy and capability, which explain some of the differences in the UK and US approaches to combat casualty care in this setting. The Defence Medical Services employ physician-led medical emergency retrieval teams (MERT), which have the ability to transfuse up to 4 units of RCC and thawed plasma during the en-route phase of care. This capability, which has been shown to improve mortality in some groups of patients (Morrison *et al.*, 2013), results in earlier commencement of transfusion support, and may also be responsible for some of the overall increases in red cell concentrate and plasma seen over the duration of the study period.

Increased platelet use can be explained by the improved availability of this product, following the development of a deployed apheresis capability, in 2008 (Doughty *et al.*, 2011), and perhaps also the greater use of near-patient haemostatic testing. Point-of-care ROTEM has been available since 2009, and has facilitated the recognition of both coagulation factor deficiencies and platelet function abnormalities. Detection of these defects may explain the increased use of both platelets and cryoprecipitate, facilitating 'bespoke' component therapy. These findings are consistent with those recently reported by US colleagues, which demonstrated that the introduction of ROTEM was associated with an increase in the use of all blood components other than red cell concentrate, and particularly cryoprecipitate (Cap *et al.*, 2012).

There has also been a marked change in the use of pharmaceutical adjuncts to transfusion. Tranexamic acid was not used before 2009, but is now given to most patients requiring transfusion, and almost all patients requiring massive transfusion. Recombinant factor VIIa, in contrast, was widely used during the early years of the war, but is now only

infrequently administered. This latter change may reflect an increasing recognition of the limited effectiveness of rVIIa, but also points towards current strategies, including initial formula-driven component use, subsequent tailored therapy based on point-of-care-testing, and antifibrinolytic therapy, providing adequate microvascular haemostasis.

The introduction of new strategies such as formula-driven resuscitation and tranexamic acid, as well as capabilities such as apheresis and thromboelastometry, is – to some extent – a reflection of operational requirements. However, it also reflects the successful dissemination of clinical guidelines, which have been shown to change practice (Simmons *et al.*, 2010).

The better survival of massively compared with non-massively transfused casualties is perplexing at first, but probably explained by survival benefit – casualties had to survive long enough to receive a massive transfusion. Overall, the survival of massively transfused casualties is high (93·1%) compared with recent British civilian experience (59·7%) (Fuller *et al.*, 2012). The difference in survival may, in part, reflect variations in injury types and severity (civilian patients are more likely to have suffered blunt trauma, including neurological injury) and underlying co-morbidity (combat casualties are almost exclusively male, younger and fitter). Has transfusion practice and capability improved survival? Survival is the product of the entire system of care, which – in this setting – also incorporates the early control of external haemorrhage with tourniquets, the use of topical haemostatic agents, hypotensive resuscitation, rapid and physician-led recovery from the battlefield, early surgical haemorrhage control, limited initial surgery and expert critical care. It is thus not possible to ascertain the individual contribution of the transfusion strategy employed however; we propose that it has been an important element.

This study has limitations. It is a retrospective analysis. Injury severity scoring, and stratification into severe, moderate and mild injury, is known to be less useful when applied to combat casualties compared with civilian trauma victims. The definition of 'massive transfusion' used for this study was 10 units, or more, of red cell concentrate transfused in 24 h. We recognise the limitations of this definition. The transfusion strategies and outcomes employed in non-massively transfused patients are of considerable interest, but difficult to analyse because time-to-death data lacks granularity.

Despite these issues, this study adds to our understanding of modern resuscitation strategies, and complements recent analyses from the US Joint Theatre Trauma Registry. Retrospective studies cannot prove causation, but there nevertheless seems to be a temporal association between increased component use and improved survival, in combat casualties requiring transfusion as part of Damage Control Resuscitation. The underlying principles may be of benefit to other populations.

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CONFLICT OF INTEREST

The authors have no competing interests.

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II

III

IV

A proposed field emergency donor panel questionnaire and triage tool

Heidi Doughty,[1] Patrick Thompson,[2] Andrew P. Cap,[3] Philip C. Spinella,[4] Elon Glassberg,[5] Håkon Skogrand Eliassen,[6] Marc De Pasquale,[7] and Geir Strandenes[6]

BACKGROUND: The provision of transfusion support to isolated military or civilian projects may require the use of an emergency donor panel (EDP) for immediate warm fresh whole blood (WFWB). The aim of this short discussion article is to raise and resolve some of the practical aspects for the nonspecialist faced with the emergency collection of WFWB whole blood in the austere medical environment (AME).

METHODS AND RESULTS: A proposed field EDP questionnaire and triage tool (QTT) is presented. It is designed for the hostile, remote, or austere environment that falls outside normal regulated supply of cold-stored blood products or removed from trained blood collection personnel, where collection may fall to an isolated medical provider. The tool has been drafted based on review of existing guidelines and consultation with practitioners. It serves as a point of reference for local guidelines and has yet to be validated.

CONCLUSIONS: The use of the EDP is associated with risk; however, it remains the simplest method of providing rapid transfusion support. The best way to manage the risk is to brief and prescreen blood donors before deployment. An abbreviated donor QTT can be an aide to decision making at the time of donation. The tool should be tailored to requirements and underpinned by policy and training.

Massive hemorrhage is a medical emergency and an immediate threat to life. The resuscitation of patients with massive hemorrhage requires the early use of transfusion support. Military and civilian guidelines promote the use of transfusion strategies that recapitulate the functionality of whole blood (so-called "balanced transfusion") for both trauma and nontraumatic hemorrhage such as bleeding associated with childbirth and gastrointestinal bleeding.[1-4] Whole blood or blood components may not be available in a situation where they are required urgently. Team members and supporting staff may be asked to donate whole

ABBREVIATIONS: AME = austere medical environment; EDP = emergency donor panel; FWB = fresh whole blood; PoCT = point-of-care testing; QTT(s) = questionnaire and triage tool(s); WFWB = warm fresh whole blood.

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blood or collect blood from an otherwise uncharacterized donor pool. Cordova and colleagues[5] graphically describe such an event where 5 units of fresh whole blood (FWB) were transfused following a 12-hour battle during which building fires threatened the isolated aid station.

The context of this article is access to blood for isolated military or civilian projects with extended lines of supply or limited logistical support, that is, the austere medical environment (AME). Examples include military special operations, humanitarian missions, remote islands or industry, the cruise industry, and scientific exploration. The medical planning for remote activity should consider the requirements for resuscitation including transfusion support. If medical evacuation is delayed or prolonged and there is no capacity to provide cold stored blood products, then the emergency use of FWB should be considered. Team members and staff should be prescreened according to national standards for blood donation (e.g., transfusion-transmitted disease testing, blood typing, hemolysis titer assessment) as members of an emergency donor panel (EDP). However, the emergency screening and management of unknown additional blood donors may also be required. Blood donation for the healthy individual is safe; however, there are risks.[1,6] There may be a challenge in balancing the safety and management of both critically ill patients and their blood donors. Careful donor screening and care is essential to optimize the safety for both. However, the context may not support a conventional donor assessment, and a more rapid or focused donor screen may be required. Relaxing donor acceptance criteria will introduce risk; the decision will ultimately be one of risk–benefit analysis. Risks may need to be further managed using "donor triage" and careful consideration of the need for transfusion. The aim of this short discussion article is to introduce a field EDP questionnaire and triage tool (QTT). The article also addresses some of the practical aspects for the nonspecialist faced with donor selection in the AME.

MATERIALS AND METHODS

Initiative

The initiative for this work follows the preconference exercise of the Remote Damage Control Resuscitation Symposium, which took place in Norway in June 2015. The work forms part of the "Blood Far Forward" program—a whole blood–based research and training program for austere environments. During training exercises, participants were required to rapidly assess several potential blood donors for emergency donation. Staff and participants identified that there was little guidance for the rapid assessment and triage of blood donors for the nonexpert.

Literature review

The following donor screening guidelines were reviewed.

- Military: US Special Operations Command, Tactical Trauma protocols (TTP) 2013,[7] and the Journal of Special Operations Medicine Training supplement 2012.[8] Standard operating procedures for the collection of whole blood, Centre of Defence Pathology, UK.
- THOR guidance.[9]
- Civilian: UK Blood Transfusion Services,[10] American Association of Blood Banks (AABB),[11] and the World health Organization (WHO).[12]

  Literature searches: A search was performed of PubMed and CINAHL using the search terms: *emergency donor panels, collection of whole blood, austere medical environment,* and *special forces medicine*. The search covered articles published up until September 2015.

Development

The field EDP QTTs were developed on the basis of experience gained through responding to military and civilian events. Members of the multinational exercise group were invited to comment on the feasibility of applying the tools.

Scope

The scope of this article is to provide guidance for operational teams supporting the critically ill patient when working in an AME. The technical aspects of blood collection are outside the scope of this paper but are well covered in previously published reviews[9] and the Special Operations Command, Tactical Trauma protocols. Readers are also referred to national guidelines for full donor selection and their own standard operating procedures for emergency procedures.

PROPOSED FIELD EDP QTT

The proposed field emergency donor panel QTT is shown in Fig. 1. The safest donors for warm FWB (WFWB) are members of a team that have been questioned, screened, and tested as conventional donors to national standards. Such donors may have donor cards or other proof of status. In the absence of preselected team members or the presence of other prequalified donors who can verify their status, the field EDP QTT may be used to help select the most appropriate donors from a mixed donor pool. Past donors are those that are not in date according to national norms for the mandated testing; however, they are preferred over unknown donors because they are familiar with the procedure and standards required.

Blood donor brief

The aim of the donor brief is to inform and identify potential donors. The donors can then be triaged into current,

Field Emergency Donor Panel Questionnaire and Triage Tool

- **Give blood donor briefing to potential donor group**
- **Confirm blood group(s) required**
- **Exclude air crew, HGV drivers and key machinery operators**

Primary Triage (Question as a group)

Serial	Question	Yes	No	Action
1	**Do you want to give blood?**			Disqualify if NO
2	**Have you given blood before**			If yes - Consider early selection

Secondary Triage (Question individually)

Serial	Question	Yes	No	Action
3	**Are you unwell now?** New Fever/ Diarrhea / Vomiting Chronic medical condition and not well			Disqualify if YES
4	**Are you taking medication for blood pressure; stroke or heart, lung, kidney, cancer or blood conditions?**			Disqualify if YES
5	**Have you had a blood transfusion or blood products in the last year**			Disqualify if YES Accept after 1 year
6	**Are you living with HEP B,C / HIV / AIDS – OR living with anyone with these conditions**			Disqualify if YES
7	**Have you ever been refused as a donor or told not to donate blood** (a past history of treated anemia may be acceptable)			Disqualify if YES
8	**Male donors only.** Have you **ever** had sex with another male?			Disqualify if YES
9	**Have you ever taken illegal drugs with a needle (even steroids)**			Disqualify if YES
11	**Are you currently pregnant or breast-feeding?**			Disqualify if YES
12	**Conduct a physical examination** **Check: Temperature / Rash / Malnutrition, / Pallor / Jaundice / Cyanosis / Shortness of breath / Intoxication from alcohol or drugs / Veins**			Disqualify any potentially unwell donor or donors with very difficult veins

- **The remaining group form the Emergency Donor Panel (EDP)**
- **Use the Risk Triage Screen to risk score the potential donors**

Fig. 1. Field EDP QTT.

past, and new donors. An initial group brief should cover the following:

- State that WFWB may be required;
- Outline the blood groups and amount of blood required;
- Explain the process;
- The importance of the health check;
- The tests that will be performed and that these might be positive;
- Donor deferral and confidentiality;
- Potential adverse donor reactions;
- Confirm that donors are volunteers and consented;
- Identify individuals who have previously given blood and those that are in date.

At this point, current and past donors, if previously accepted, can be directed for rapid assessment and donation if urgent. All donors must be well on the day of donation.

Risk Triage (Question Individually)

Score	Questions	Subtotal	Notes
	Blood donation history		
1	Regular Donor		Optimum
2	Previous Donor		
3	Non Donor		
	Veins and body weight		
1	Good lateral (outer) vein		Optimum
3	Poor or difficult vein		
3	Under 60 kg		Risk of fainting
	Infection		
1	> 21 Days Well		Optimum
3	< 21 Days Well		
	Travel		
1	No travel in the countries below in the last 6 months		Optimum
2	South America		
4	Asia and Africa		
	Life style:		
1	Sex with one partner		Optimum
3	Sex with multiple partners but protected		
-	Sex with a sex worker or in exchange for money/drugs		Avoid for 12 months
	Serious medical conditions		
1	None		Optimum
3	Past or present serious medical conditions but managed and well		
3	Untreated current medical conditions but well		
	TOTAL		

- **Add up score and record: Lowest score = Lowest Risk**
- **Use Point of Care Test for TTI's – Eliminate and counsel any positives**
- **Blood type donors and document results**

Fig. 1. Continued

The field EDP QTT

The QTT is a highly abbreviated version of a donor questionnaire. It is designed to be used after the group briefing for all donors. Donated blood should be safe and, in particular, should not put the patient at risk of infectious disease. The question set may need to be tailored to the situation. Some questions that are commonly asked such as those about tattoo may be nondiscriminatory because the behavior may be common to most or all donors. Likewise travel history may be nugatory in some communities. Questions related to sexual behavior may initially need to be simplified and then triage applied, that is, prepare to accept all donors but use them in order of lowest risk first. Infectious risk is commonly related to lifestyle and location. However, in many parts of the world infectious disease may have been acquired at birth or after medical treatment and individuals may not be aware and cannot declare the risk when questioned. The risk of transfusion-transmitted infection in screened blood donors in different countries may be estimated using published national data.

The QTT

The QTT is broken into three sections: primary triage, secondary triage, and risk triage. These three stages help to rapidly identify the individuals that may participate in the EDP and eliminate the individuals that may pose a relatively less acceptable risk to the transfusion recipient. The field EDP QTT is designed to assist and act as an aide memoire. It is not designed to replace clinical judgement and experience.

Primary triage

Primary triage identifies those who will consent to donation and those who may be regular donors who can be rapidly progressed through screening as the optimum candidates.

Secondary triage

Secondary triage seeks to disqualify candidates on the grounds of high risk to either donor or recipient on the grounds of current health, risk of disease, and pregnancy. It must be remembered that in extremes these candidates

may be considered for donation if no other donors exist, and while only the attending clinician can make this difficult decision they may also be able to obtain consent from the injured.

Risk triage

Risk triage seeks to quantify the remaining risk, giving a numerical value for the clinician to work with. It is an abbreviated field expedient questionnaire and serves only to guide and remind an isolated practitioner who will use this in conjunction with clinical experience and advice from telemedicine or other trusted sources. The numerical value is not an absolute value of risk involved, but merely an aid to quantifying the risk. The value is proportional to the risk, so the lower the score the lower the risk. There is no "cut point" of acceptable risk given the emergency setting of the potential transfusion; the scoring is thus relative.

The risk triage bases the scoring system on:

- Past blood donation history;
- Ease and safety of venipuncture;
- Lifestyle;
- Travel history;
- Veins and body weight;
- Occupation/role.

Individuals that are potentially suitable may be further triaged based on nationality and blood group if required.

Female donors

A number of the questions relate to female donors. Women tend to have greater iron demands and lower total blood volume and are more likely to faint especially if young and at first donation.[13] Women may also have smaller or more deeply set veins—factors that may make them less suitable donors in emergency situations where speed is of the essence. Pregnancy is associated with changes in blood volume, iron demand, and the development of white blood cell antibodies. Women should not donate when pregnant and are conventionally deferred for a period of time after pregnancy and while breastfeeding.

DISCUSSION

Transfusion support remains an important element of medical planning for individuals traveling or working remotely. The problems with transfusion support in the AME include availability, transfusion-transmitted diseases, accurate testing, and a secure cold chain. All efforts should be made to ensure *blood safety* through the appropriate sourcing, supply, and storage of blood. Transfusion support can be provided using stored blood components projected from the home nation or provided by specialized commercial companies or host nation support. However, blood is a logistically challenging materiel to manage and resupply especially where there is minimal medical infrastructure.

The advent of commercially available storage systems using phase change together with lightweight temperature monitoring devices permits storage for dislocated teams for extended periods of time.[14] However, it imposes a logistic and training burden. Alternative options include the use of fluids, dried plasma, and early evacuation. Where early evacuation is not an option, and blood is not available, medical planners should consider emergency whole blood donation as a resilience measure.[1] FWB offers the best physiological replacement fluid for major blood loss and the emergency collection of whole blood requires very little equipment.[15] The remote damage control resuscitation pack designed for blood donation described by Strandenes and coworkers[9] includes all of the materiel required for donation including point-of-care testing (PoCT). The pack weighs 780 g including freeze-dried plasma and a lactate analyzer.

Potential donor screening and consent

The key to safe blood is donor selection. A review of the literature demonstrated that there was very little published about the assessment of blood donors in the AME. The small numbers of teams undertaking EDPs appear to be using national donor questionnaires. The questionnaire takes time to deliver properly and may exclude a large number of potential donors. The challenge is a rapid assessment of donors to find the best available. Despite the emergency, we still advise that donors should be volunteers and give informed consent. A description of the process is important for planning purposes. It should be clear whether blood is to be taken immediately or whether donors are to remain on standby to be called forward as required.

The potential donors must also understand the purpose of the health check and the reason for screening. Caution must be exercised if language is a barrier and an interpreter is used. Potential donors are asked about confidential and sensitive aspects of their medical history and lifestyle. Not all donors define "sex" or "sexual contact" in the same way and local guidance may be required. Therefore, potential donors should be consented in a way which offers privacy to get an honest response. Donors should be assured that the information they provide will be kept confidential to the degree possible, recognizing that this may be challenging in isolated and small-group settings.

Untested donors and screeners should be aware that both screening and testing may reveal unexpected and unwelcome results. "Rejecting" individuals in a small and close community requires careful handling. Test results

may include both false and true "positives" and the donor may need psychological support if given unexpected news and in possession of firearms. It is recommended that potential donors consent for follow-up testing if required and that pretransfusion blood samples be retained for confirmatory testing if possible. Some countries may require all "bled" donors to have formal testing through either samples taken at the time of donation or samples taken on return to base. This is often not feasible due to tactical situations (ongoing combat, prolonged evacuation on multiple platforms, etc.) and it may be easier to follow-up the patients who have received emergency transfusion.

Abbreviated donor history questionnaires

The assessment of donor suitability aims to exclude donations from individuals at risk, particularly those who have recently acquired infections, which may not be detected by routine screening tests or with infections for which no effective screening is available. Certain behaviors have been shown by surveillance data to be associated with a high risk of transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). These include skin piercing, IV drug use, exposure to treatment with blood and blood products, and unprotected sex especially with individuals in high-risk groups. High-risk groups include men who have sex with men and sex workers.

Donor history questionnaires are designed to identify risk and must be comprehensive. However, they need to be pertinent to the country and context. Questionnaires are constantly evolving and abbreviated questionnaires have been introduced by a number of blood transfusion services. Abbreviated questionnaires are designed to speed up the process but are used for known or repeat donors. An excellent civilian example of this is analysis of the Food and Drug Administration–approved 34-question abbreviated donor history questionnaire implemented in 2003 for repeat blood donors.[16] The travel, medication, and health history questions were decreased by 18 questions. Data were analyzed from more than 50,000 donations and showed that there was no significant difference in reactive screening and/or confirmatory tests. However, these results cannot readily be extrapolated to new donors. New donors may have to be accepted at risk in the AME with limited assessment tools.

Donor safety and performance

Blood donation should be a safe procedure in the healthy donor. The donor assessment not only enables a review of the donor's medical history but also provides an opportunity for a very basic health check, especially in unscreened individuals.

Physical assessment

Many countries do not include a physical assessment; however, it may add value in the context of a rapid questionnaire. Physical assessment on screening and before donation should look for clinical signs to exclude current infection, severe anemia, significant disease and intoxication such as temperature, rash, malnutrition, pallor, jaundice, cyanosis, shortness of breath, and intoxication from alcohol or drugs. The venipuncture site should be checked to see that the donor's veins are accessible and suitable for easy venipuncture.

It is essential that commanders have confidence that the operational performance of donors will not be compromised. Strandenes and coworkers[17] have demonstrated that the combat readiness skills of Special Forces soldiers are maintained immediately after donation of a single unit of whole blood. Despite this, caution must be applied to the use of certain occupational groups as donors. Avoid the use of donors operating key machinery or those responsible for transporting others. Do not bleed aircrew. Generally aircrew personnel should not fly within 4 days after blood donation. Flight personnel in combat or performing shipboard duties should not donate blood for 4 weeks before flying.

The impact of blood donation may be greater on less healthy individuals especially those with a smaller body mass and malnutrition. Blood donation leads to loss of iron. After whole blood donation, donors are required to be excluded from further whole blood donation for up to 12 weeks to permit natural recovery of iron stores. However, this can be safely shortened if hemoglobin (Hb) screening is available. Recommended satisfactory donor's Hb levels are more than 12.5 g/dL for females and more than 13.5 g/dL for males. It should be noted that Hb may not adequately characterize donor iron status, although this may be the only available metric in the AME setting. Recognized complications of donation include fainting and venipuncture-associated complications. These can be mitigated by predeployment training, selection of donors, including veins, and good donor care.

Blood group selection

Blood group selection

Group O whole blood with low anti-A/B titers from prescreened donors should be used where the blood group of the recipient is unknown or there is uncertainty.[18] The values cited by Strandenes in this article from the THOR group were an anti-A and -B titer less than 100 for IgM and 400 for IgG type. However, there is no international definition of high-titer hemolysin. The use of ABO-identical or -compatible blood may need to be considered if demand for group O/low titer exceeds supply or if no donors have been prescreened. The preferred nationality of donors may also be specified. The use of a

multinational donor panel is a policy decision based on preagreed standards. There are scientific and practical reasons to select donors within national lines such as population disease prevalence and blood groups.

ABO group

The use of incompatible blood may result in a hemolytic transfusion reaction and cause serious harm. It is essential that the blood group of the donor is known. ABO grouping is conventionally performed twice on new donors. In addition, formal ABO testing consists of both a cell group and a plasma group. Blood may need to be given on the basis of a pretested donor blood group alone where technical support is not available to fully confirm the blood group. Most teams using EDPs are using a PoCT (e.g., Eldon card for ABO and D). It should be noted that PoCT will only provide a forward group or a cell group, although this is acceptable in this setting. It is therefore recommended that the results of locally determined ABO types are compared with known results where available. The results should be the same and the donor should not be used until the group is confirmed. An additional safety check is to test the collected unit itself to confirm labeling and reduce the risk of error. If the donor pool is extended to include donors of other ABO groups besides O, a practical approach is the use of group A blood for group A recipients and group O for all others. If a preprepared donor panel is used for a small team, a "blood-buddy" matrix of ABO- and D-compatible personnel for small groups may be considered.[19]

D group

The distribution of blood groups varies between populations and may affect the choice of blood donors. Garcia Hejl and colleagues[20] observed that blood type frequencies in their "potential walking blood bank" were similar to those observed in European or American countries. However, they noted a low frequency of B blood group and D– in the "potential walking blood bank." Conventionally, D– blood can be used for all patients; however, it is often in short supply. The use of D– blood may need to be prioritized for females of childbearing potential (under the age of 50).

Disease screening

The risks to the patient associated with the emergency collection of FWB include blood group error and the risk of transfusion-transmitted disease and a rare risk of transfusion associated graft-versus-host disease. The risk of transfusion-transmitted disease is dependent on the prevalence of baseline blood-borne disease in the donor population and the risks associated with the location, such as malaria. In addition, donors should notify of any adverse events of illness within a 14-day period after donation. However, this may be impossible in the context of independent movement of donors, patients, and staff. Risks can be mitigated by vaccination, prophylaxis, vector exposure control, and similar measures but may have to be tolerated. Consideration should be given to follow-up of patients who have received emergency blood.

Prescreened donors are the safest donors in that they have been screened based on national donor selection guidelines and testing. WHO guidelines advise that all blood components should be fully screened to standards by an accredited blood service wherever possible. Mandatory tests include ABO and D blood group and tests for HIV, HBV, HCV, and syphilis. Positive screening results should ideally be forwarded to a specialist reference laboratory for confirmatory testing. PoCT may be used to screen locally collected units before release. However, the PoCT should be selected with the appropriate sensitivity and specificity for blood donation rather than disease screening.

Some organizations may also choose to take blood samples at the time of donation for later definitive testing. Samples must be packed and transported in IATA 650 packaging; most samples for confirmatory testing must be received within 5 days of sampling. Samples that cannot be tested within in this timeline should be separated and the plasma frozen until transport is available.

Training and recordkeeping

Training

Medical providers who anticipate the emergency collection of whole blood should consider the training of personnel. Personnel should know how to conduct an emergency donor session, store, issue, and account for any blood donated. Training should also address the indications for the collection of blood and the administration of blood. Transfusion training should be incorporated into predeployment training and include practical sessions in a high-fidelity environment. Strandenes and coworkers[21] demonstrated that nonmedic soldiers had a 100% success rate in both blood collection and blood reinfusion on fellow soldiers after a short introduction to the procedures.

Recordkeeping

National and international guidance requires a record of all blood donated and used. The standard of recordkeeping may be a simple entry in the field medical notes. The advantage of using a properly designed donor or resuscitation pack is that it should contain the paperwork for donation. Recordkeeping is designed to permit recall of donors and lookback exercises in the event of donors or patients found to have viral markers. Source tracing of infection across international boundaries and organizations may be challenging and consideration should be given to a local Point of Contact who would be responsible

for any donor follow-up. All procedures and the associated records related to the conduct of a field collection should be completed at the time of donation. It is recommended that the fate of all donations is recorded, both transfused and discarded. The use of EDP blood should also be recorded in the clinical notes and included in the handover.

DISCLAIMER

The discussion included in this article does not override the responsibility of health care professionals overseeing emergency donor programs to provide direction and training appropriate to the operational situation. All activities related to blood transfusion should be subject to appropriate legislation, quality, and clinical governance regulations. It is also advised that there is policy or authority for the use of emergency blood donation.

CONCLUSIONS

The use of the field EDP QTT is associated with risk; however, it remains the simplest local method of providing rapid transfusion support. The biggest risks are those associated with ABO mismatch and infection. It is very difficult to produce a satisfactory generic abbreviated donor history questionnaire. The best way to manage the risk of donation is to brief and prescreen donors before overseas travel. An abbreviated donor questionnaire can then be used to rapidly screen donors when required. Where donor selection is applied to a number of donors including untested donors, then a triage approach to donor management is recommended.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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Emergency red cells first: Rapid response or speed bump? The evolution of a massive transfusion protocol for trauma in a single UK centre

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ABSTRACT

Background: Death from massive haemorrhage due to traumatic injury is potentially preventable after hospital admission using haemorrhage control and improved resuscitation techniques including massive transfusion protocols. Massive transfusion protocols (MTP) are an essential element of damage control resuscitation and provide a coordinated clinical pathology response to massive haemorrhage after hospital admission. The decision to activate and de-activate a MTP is based on a number of patient and local factors. The purpose of this before-and-after study was to determine the impact of modifying a protocol to include emergency red cells. In addition, we investigated whether massive transfusion prediction models could have been used to guide on-going transfusion support.

Methods: Sequential MTP activations over three years, before and after protocol revision, were analysed. Percentage of MTP activation, component usage and outcome data were compared. Trauma associated severe haemorrhage (TASH) and assessment of blood consumption (ABC) scores were derived and receiver operating characteristic (ROC) analysis undertaken for an outcome defined as the use of >6 red cell units.

Results: 52 MTP1 and 66 MTP2 activations arose from 216 and 495 major trauma cases, respectively. Protocol change significantly reduced the MTP activation rate ($p = 0.0006$) from 24% to 13%, and the number of activations requiring >10 RCC increased from 13% to 36% ($p = 0.006$). Average emergency red cells usage in the second cohort increased to 4 units. Survival, coagulation parameters, and time to MTP pack issue were all unaffected by the protocol revision. The TASH score showed an area under ROC (AUROC) of 0.88 ongoing transfusion requirements.

Conclusion: The change in protocol increased the use of emergency red cells but reduced MTP activation and use of multiple blood components. The TASH score appears to provide a useful predictive tool for ongoing transfusion support and may be of value for the trauma clinicians.

Introduction

Rapid and efficient transfusion support is an essential component in the management of major haemorrhage (MH) [1]. This has been highlighted by the experiences gained during recent military conflicts, and has led many civilian trauma centres to adopt ratio-based major transfusion protocols (MTPs) within the framework of a massive haemorrhage protocol [2]. The introduction of protocols results in a better co-ordinated response, better outcomes and a reduction in complications [3,4]. Although the optimal ratio of blood product use is uncertain there has been a move in civilian centres to adopt RCC:FFP ratios of 3:2 or 2:1 [5]. It is probable that the early use of plasma and platelets should be even higher in the severely injured. The recently published study by Holcombe et al. showed that although that the use of a 1:1:1 ratio of RCC:FFP:Platelets did not result in a significant reduction in mortality at 24 h or 30 days, more patients achieved haemostasis and fewer experienced death by exsanguination.

Massive haemorrhage protocols including a massive transfusion protocol have increasingly become an integral part of damage control resuscitation (DCR) in order to prevent and manage posttraumatic coagulopathy in the first hour and beyond. The

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massive haemorrhage protocol should include the clinical, laboratory and logistic response [6]. Protocols should also address the immediate availability of un-crossmatched group O red cells for trauma patients with massive haemorrhage [7]. The decision to activate the local massive transfusion protocol is complex, must be made rapidly, and yet if not required may lead to unnecessary treatment, waste of resources or harm [8]. Scoring systems have been proposed to improve the prediction for massive transfusion support [9,10].

We introduced a fixed-ratio massive transfusion protocol in August 2008 based on transfusion shock packs of 1:1 red cell concentrates (RCC):fresh frozen plasma (FFP) followed by the early use of platelets and cryoprecipitate. The protocol included prompts for activation of the protocol which could be done either in the pre-hospital environment or on admission. Pre-hospital activation requires additional training and has subsequently been shown to be effective [11]. Transfusion packs were prepared when ordered with a target response time of 30 min. Ongoing monitoring established that packs were often ordered but not used [12]. In addition, there were occasional incidents where there appeared to be delay in emergency transfusion support despite reference to the use of emergency red cells within the protocol. We proposed that adding an additional step in the protocol prompting the use of emergency red cells during initial resuscitation may improve the emergency use of blood rather than crystalloids. Red cells could be given either during the pre-hospital or hospital period. Where red cells are given during the pre-hospital period then this step would be omitted. The final ratio of RCC to FFP following the introduction of the additional step of 2 RCC to the initial 4 plus 4 pack was designed to be RCC:FFP = 6:4.

The primary aim of this study is to describe the impact of changing the protocol. The secondary aim was to assess if existing scoring systems for the prediction of massive transfusion, normally used at the point of activation, could have been used to guide the subsequent requirement for component support beyond the first massive transfusion pack.

Materials and methods

Setting and MTP revisions

Setting

This study was a retrospective observational review of practice in a single institution, the Queen Elizabeth University Hospital Birmingham, UK. The hospital is the receiving facility for UK military trauma patients and equivalent to a US level 1 trauma centre. It serves a population of 1.2 million UK civilians. Following the UK wide reconfiguration of major trauma networks, the institution was designated a regional Major Trauma Centre during the period of study. Pre-hospital treatment for trauma included a 24 h physician led emergency response capability with day time helicopter support. Pre-hospital transfusion was not available. Patients admitted to the trauma unit who require trauma ward admission for $\geq$3 days, critical care admission or whose injury led to their death (30 days) are recorded in the UK Regional Trauma Audit Research Network (TARN) database. The unit receives approximately 300–400 such cases *per annum*, which satisfy this classification and are herein referred to as major trauma cases.

Implementation

The hospital implemented the first massive haemorrhage protocol containing a massive transfusion protocol (MTP) in 2008 following a review of the military experience, the literature and consultation with key stake-holders. This protocol was based on the UK military transfusion algorithm and is outlined in Fig. 1A. Activation of the massive haemorrhage protocol and the MTP were concurrent and was made at the discretion of the trauma team leader, a senior clinician, with consensus from the trauma team. MTP pack one consisted of 4 units of red cell concentrates (RCC) and 4 units of fresh frozen plasma (FPP) (thawed from frozen on request). The second, and all subsequent, transfusion packs also contained an adult therapeutic dose (ATD) of platelets (PLT). Cryoprecipitate was given as clinically directed on the basis of laboratory fibrinogen and thrombo-elastography results. Thrombo-elastography was available in theatres and the critical care unit. Clinicians were informed that all MTP activations would be prospectively recorded by the transfusion laboratory and would be subsequently reviewed in multi-disciplinary meetings.

Review

The first annual review of MTP1 activations highlighted a number of concerns. Concerns included delays in transfusion, despite access to emergency red cells, and the non-use of thawed FFP when provided. The transfusion protocol was therefore modified one year after implementation (Fig. 1B). The revised (MTP2) protocol algorithm included a short initial evaluation period during which clinicians were prompted to use emergency RCC transfusion if immediate transfusion support was required. The recommended maximum number of emergency RCC units was two. This amendment was not designed to stop massive haemorrhage protocol activation i.e. be a speed bump. It was designed to provide a rapid red cell response during resuscitation and assessment before proceeding to massive transfusion i.e. multi-component transfusion support. The initial massive haemorrhage activation continued to alert the laboratory to thaw frozen plasma just in case it was needed. However, a telephone call confirming full MTP activation was required to release the massive transfusion pack.

Change management

The roll-out of both MTPs was supported by specific training in the emergency department. Copies of the algorithm were present in all clinical areas for reference. The protocol also formed part of the trust's mandatory transfusion training for medical staff during which the continued requirement for baseline blood samples was emphasised. We anticipated that there would be a learning curve associated with the introduction and change of protocol. To reduce the impact of any learning curve associated with the introduction of protocols we have not included MTP cases occurring in the first 100 days after implementation of either.

Blood components

All blood components met UK specifications including leucodepletion. The estimated age of all RCC provided for transfusion packs was 18–21 days. Emergency RCC were group O RhD and Kell negative. Fresh frozen plasma was single donor, quarantined plasma from untransfused males. Plasma was thawed and issued to order. Thawed plasma maintained within temperature control was returned to stock and stored at 4 °C for 24 h before discard. Platelets were either prepared by apheresis or derived from whole blood (4 buffy coats). The adult therapeutic dose (ATD) of platelets was $>2.4 \times 10^{11}$.

Predictive scoring systems

The trauma associated severe haemorrhage (TASH) score and assessment of blood consumption (ABC) scores were both calculated in accordance with their original publications and subsequent validation [9,10,13]. (Appendix 1 outlines the constitution and details of clinical parameters required to measure these scores).

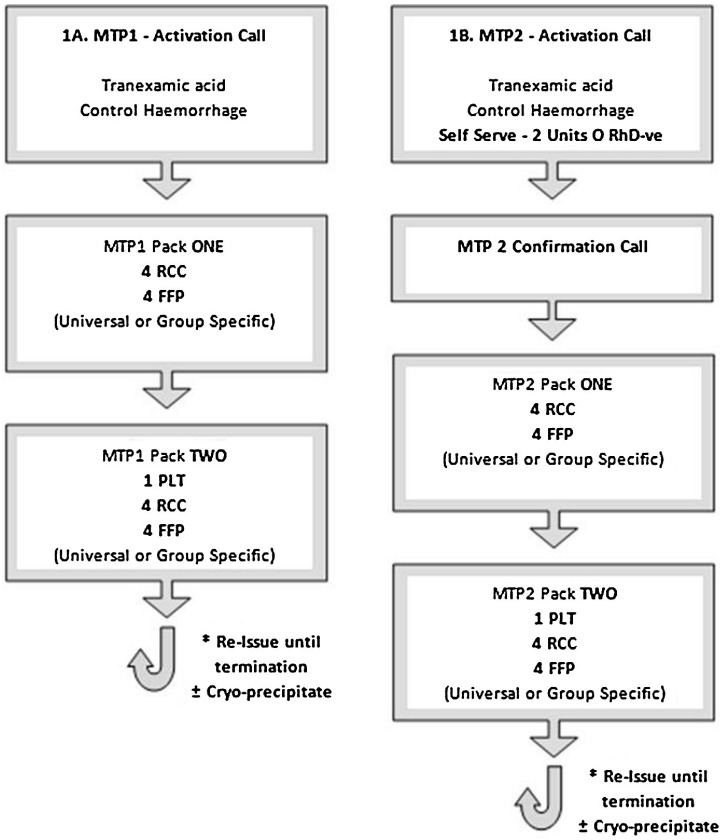

Fig. 1. MTP1 and MTP2 algorithm.

Outcome data: Transfusion support and clinical data

Transfusion support

All consecutive MTP activations throughout both periods were prospectively recorded. All timings in the following data, for both MTP1 and MTP2, were recorded from the initial activation call (rather than the confirmatory call in MTP2). Data registered at each MTP activation included: patients' demographics; the time and date of MTP activation; the environment in which MTP activation occurred (pre-hospital or emergency department); a summary of the clinical indications; the time of issue of the first and subsequent MTP packs; the total number of emergency RCC units used prior to MTP pack 1 arrival; the number of RCC, FFP, PLT and cryoprecipitate units requested; the proportion of requested blood components utilised until stand-down; and finally the time that the blood bank was contacted to de-activate the MTP.

Clinical outcome

Clinical outcome data were retrospectively collated from patients' electronic clinical record, laboratory results and TARN. The TARN database has been described elsewhere [14]. Data collected included: survival (60 min, 24 h and 30 days); Injury severity score (ISS); mechanism of injury; presence or absence of penetrating trauma; the presence of high-risk fractures (unstable pelvic fracture and displaced and/or open femoral fractures); baseline clinical observations; point of care haemoglobin; base deficit on arterial blood gas sampling at the point of admission; baseline and 24 h coagulation; and the presence of a positive focused assessment with sonography for trauma (FAST) scan or free fluid on trauma series computerised tomography (CT). All patients within the prospectively collected data were accounted for.

Analysis

All analysis was performed with version 6 of the Graph-Pad Prism statistical software package, GraphPad Software, Inc. San Diego, California. Data are presented as mean with standard deviation or median and interquartile range as appropriate. The unpaired *t*-test with Welch's correction was used for parametric data comparison. The Mann–Whitney *U* test was utilised for non-parametric comparisons. Frequency comparison of categorical data was undertaken with either the Chi square test or the Fishers exact test. Statistical significance was set at p value ≤ 0.05.

The association between the TASH and ABC score and the number of RCC units used was tested with linear regression analysis and the R^2 statistic. The area under the receiver operating characteristic (AUROC) analysis was undertaken to test the accuracy with which the need for >6 RCC could be predicted. This number of RCC units was chosen as it represents progression to MTP pack 2 in both our and others' protocol.

Results

The two periods of study for the use of MTP1 and MTP2 were 259 and 536 days respectively. Fifty-two MTP1 and 66 MTP2 activations took place from a respective total of 216 and 495 major trauma cases during these two periods. The key features of the two cohorts are outlined in Table 1. No significant difference in the demographic composition of the two cohorts was identified. The mean ISS was moderately higher during the second period 30.65 vs. 25.50 ($p = 0.14$) however this was not significant. The injury mechanism, baseline observations, point of care test results, frequency of penetrating injury and incidence of high-risk fracture (unstable pelvic fracture and displaced and/or open femoral fractures) had also failed to show any statistically significant differences.

MTP activation and blood component usage

MTP activation

The rate of massive transfusion protocol activation expressed as a percentage of the major trauma calls, was 24% (95% confidence interval [CI]: 19–30%) during the first period and then reduced to 13% (95% CI: 10–17%) following the change in protocol ($p = 0.0006$) (Table 2). In neither cohort did we see an association between 'unnecessary' activation and the place of activation, addressing concerns that pre-hospital activation may be 'less accurate'.

Blood component use

Thirteen percent (95% CI: 6–26%) of those in the initial cohort received ≥ 10 RCC in 24 h. Within the second cohort this increased to 36% (95% CI: 25–49%) ($p = 0.006$). Patients in the second cohort were significantly more likely to use the FFP supplied in MTP pack 1 and received more FFP throughout treatment (Table 2). The use of emergency RCC increased in the second observation period as expected. However, this increase was greater than that planned in the revised protocol (Median 2 units, IQR 0–3.25). When adjusted for the total number of trauma cases treated, the increase was from 0.26 units per major trauma in MTP1 to 0.34 units per major trauma in MTP2. The total median use of emergency red cells per case increased to a median of 4 (IQR 0–8).

Outcome data

Survival

Survival data before and after MTP revision was compared at intervals of 60 min, 24 h and 30 days (Table 3). No difference was identified both in crude mortality rates and mortality stratified by time of death. Red cell use correlated positively with mortality. Assessment of the group in whom ≥10 RCC were used in 24 h saw crude mortality rates of 45% (95% CI: 27–64%) compared with 23% (95% CI: 15–33%) in the group using <10 RCC in 24 h ($p = 0.04$). No difference in the outcome of the group in which ≥10 RCC were used was seen between the MTP1 and MTP2 cohorts. Two deaths occurred beyond 30 days, one from sepsis at 94 days post injury and the other, a 90 years old male, died from an acute coronary syndrome 128 days following the initial injury.

Laboratory support

Coagulation parameters at baseline and 24 h did not differ between cohorts. The introduction of the MTP2 protocol did not significantly increase the time from the initial activation call to the laboratory to the issue of the first MTP pack (Table 3).

Component ratio

In the present study, ratios of blood products are based on averages transfused per patient and comparison was carried out between the two groups. The aim of this analysis was to demonstrate the variation in product delivery frequency with a protocoled ratio based transfusion program rather than the quantity usage of blood products. We compared the ratio (RCC:FFP and RCC:PLT) transfused in MTP1 to those in MTP2 (Table 3). This analysis was only undertaken in patients transfused at least two units of RCC (total RCC including emergency group O RhD negative red cells). This exclusion was undertaken to prevent the high frequency of patients for whom MTP activation was followed by little or no RCC transfusion (in the MTP1 cohort) from influencing

Table 1
Patient characteristics of the MTP1 and MTP2 cohorts.

	MTP1 ($n = 52$)	MTP2 ($n = 66$)	p Value
Demographic data			
Age (years) (mean, SD)	40.8, 16.4	41.3, 19.8	0.88
Male (% total)	38 (73%)	53 (80%)	0.38
Mechanism of injury			0.98
Fall > 3 m (n)	7	10	
Stabbing (n)	8	11	
Gunshot wound (n)	1	2	
Road traffic collision (n)	36	43	
Injury severity			
ISS (mean, SD)	25.50, 13.03	30.65, 14.21	0.14
Unstable pelvic fracture (n)	9	17	0.37
Open/compound femur (n)	5	16	0.05
Penetrating mechanism (n)	10	13	>0.99

Table 2
Summary of MTP activation rates and blood components usage for MTP1 and MTP2 cohorts.

	MTP1	MTP2	p Value
Total major trauma calls (MTC) (n)	216	495	
MTP activation (% total MTC)	52 (24%)	66 (13%)	0.0006
≥10 RCC (total) n, %	7 (13%)	24 (36%)	0.006
Group O RhD negative use pre MTP pack 1 (median, IQR)	0 (0–2)	4 (2–5.25)	<0.0001
Total FFP use per patient (median units, IQR)	0 (0–4)	2.5 (0–8)	0.0004
Patients not transfused FFP from MTP pack 1 (n, %)	33 (63%)	21 (32%)	0.001
Proportion of MTP pack 1 FFP used (median, IQR)	0% (0–50%)	50% (0–76%)	0.0007

Table 3
Survival data, coagulation data, RCC:FFP ratio and time to MTP pack issue.

	MTP1	MTP2	p Value
Mortality, n (%)	13 (25%)	15 (23%)	>0.99
24 h – 30 day	4	3	
60 min – <24 h	3	5	
<60 min	6	7	
Coagulation median (IQR)			
Baseline PT	1 (1–1.2)	1 (1–1.2)	0.55
24 h PT	1 (0.9–1.1)	1 (0.9–1.1)	0.77
Baseline APTT ratio	1.2 (1–1.3)	1.2 (1–1.3)	0.91
24 h APTT ratio	1 (0.9–1.1)	1 (0.9–1.2)	0.78
Blood component ratios[a] (mean, SD)			
RCC:FFP	2.24, 1.18	2.22, 1.54	0.95
RCC:PLT	7.86, 3.02	9.38, 5.13	0.34
Time to MTP issue[b]			
Minutes (mean, SD)	28, 10	25, 8	0.13

[a] Calculated (mean and SD) of products usage ratios: mean of ratio blood products transfused per patient. This analysis was only undertaken in patients transfused at least total two units of RCC and followed by blood components (FFP/PLT).
[b] Time to MTP issue is time taken to issue from the time of confirmatory call to blood bank.

the results. The mean RCC:FFP ratio was 2.2 with no significant difference between the first and second cohorts. The ratio for both groups was notable for its deviation from the ratio specified by the protocol. Four patients in the MTP1 cohort and 10 in MTP2 were given >2 RCC and received no FFP. The number was therefore relatively higher in the second group and the median number of RCC transfused for these patients was 4 and 4.5 respectively. These 14 patients were also excluded from the original analysis of component ratios since their mean and SD becomes indefinable. Of these patients, 1 in MTP1 and 5 in MTP2 had died within 60 min of arrival at the ED. In order to determine whether the latter group of patients had an impact on ratio deviation, the ratios of the mean blood products transfused, all patients included were also calculated for each group. The ratios of mean blood products transfused were RCC:FFP 1:2 and RCC:PLT 1:10.5 in MTP1 and RCC:FFP 1:2 and RCC:PLT 1:11 in MTP2. These results demonstrated analogous distribution of blood product ratios with the original analysis. This can be explained by the fact that the group of patients excluded represents the two extremities of the MT spectrum i.e. patients at high risk of early death owing to sever injuries and patients with minor injuries not requiring MT.

TASH and ABC score

Despite alteration of the pre-test probability, both the ABC and TASH scores retained a correlation with the total number of RCC used. In particular, the TASH score retained a good correlation with the number of RCC used (R^2 0.6) (Fig. 2). We tested the performance of the ABC and TASH scores to discriminate the need for transfusion of >6 units of RCC in other terms progress beyond the first massive transfusion pack. At this cut-off point the TASH score had an AUROC of 0.88 (95% CI: 0.81–0.93). The AUROC of the ABC score was 0.81 (95% CI: 0.72–0.87) (Fig. 3).

Discussion

Massive transfusion protocols (MTP) provide a valuable framework for the co-ordinated and timely response to massive haemorrhage. The very nature of the context means that MTP are activated in highly stressful circumstances. Under-treatment of trauma casualties with MH, a group whose mortality approaches 40%, is catastrophic [15]. Confronted with a potential massive haemorrhage, especially where there may be perceived delays in transfusion support and conscious of the devastating consequences of under-treatment, an inexperienced clinician may justifiably apply a liberal approach to MTP activation. Whilst proportionate MTP over-activation may mitigate the risk of under-treatment, a low predictive accuracy for MT may challenge the sustainable supply of 'universal' components and platelets. The provision of blood in the emergency setting of a patient with massive haemorrhage requires the use of a transfusion protocol designed for the local situation taking into account pre-hospital care and local constraints. We suggest that protocols and the outcome should be subject to constant review and amended as required. Amendment of our MTP protocol was associated with a reduction in activations, a greater percentage use of plasma and platelets when ordered and no adverse outcomes. However, it led to a greater use of emergency red cells than expected. The risk of this is plasma deficit and needs addressing. The results are not surprising but demonstrate the impact of changing protocols.

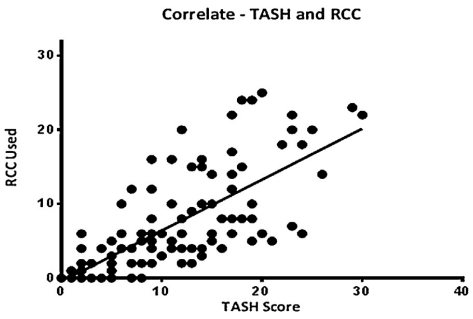

Fig. 2. Correlation of TASH score with the total number of RCC used.

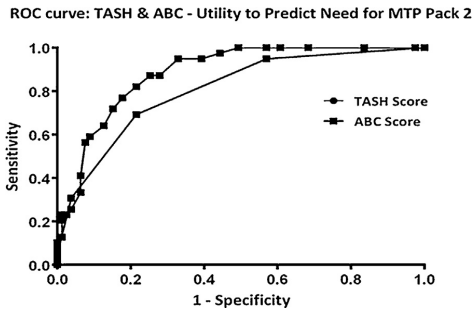

Fig. 3. Receiver operating characteristics curve for TASH and ABC scores.

MTP over-activations may reduce the risk of under-treatment but has the inevitable consequence of exposing patients with non-major haemorrhage to unnecessary blood components. The full risks of using an MTP in this latter group remain unclear. The risk of human error remains the greatest danger in any transfusion and the risks may be greater in the emergency situation. Specific concerns relate to the unnecessary use of plasma, with recent reports of acute lung injury in non-massively transfused patients exposed to high volumes of FFP exemplifying the need for caution [16]. However, more recently the PROPPR trial has demonstrated there was no increase in complications when higher blood product ratios are used [17]. MTP over-activation is also unappealing when one considers its potential impact on blood component stocks. Achieving a safe and sustainable rate of MTP activation, which balances both the risks of under-recognition of MH as well as those of over-activation, will be highly desirable. Activation is inextricably linked with the ability of clinicians to accurately predict MH and knowledge of the local logistic and laboratory response time. Until now it has been difficult to discern from the literature how accurately clinicians predict massive haemorrhage, target transfusion use, and what factors influence these issues. This lack of clarity has arisen from the practice of excluding cases where an MTP has been activated for patients requiring little or no transfusion [4,18] and a general paucity of information about the size and composition of the denominator groups [3,19]. The only brief insights into this issue have been provided by Hendrickson et al. [20] Morse et al. [21] and Sinha et al. [22] who, in their respective paediatric, adult non-trauma and mixed MTP groups, have all noted MTP activation can be followed by little or no transfusion.

In this present study we also found that massive transfusion packs were called for patients who, although bleeding, did not have 'massive haemorrhage'. This contention was supported by a number of surrogate markers. For example, the mortality rate in the initial cohort (MTP1) was 25%, far lower than the 40–50% mortality rate which is widely reported for patients who require MT [15,23]. Likewise, analysis of blood component use in this group showed that over half (63%) of the initial group had not

received emergency RCC and or plasma (63%). Only seven cases (13%) from the first cohort ultimately met the definition of ≥10 units of RCC. Activation of the massive transfusion protocol during the first period had a predictive accuracy (positive predictive value) for MT of just 13%. The modification of the protocol resulted in a reduction in the demand for massive transfusion packs from 24% of major trauma cases to 13% ($p = 0.0006$). The positive prediction of MT improved, increasing from 13% to 36% ($p = 0.006$). Analysis of blood component usage showed that a greater percentage of the plasma was used and fewer of the MTP2 packs were returned with the FFP unused. Any concerns that the protocol may impede FFP delivery and impair outcomes proved unfounded. Survival, coagulation parameters, time to transfusion pack issue and final RCC:FFP ratio were all unaffected by the protocol revision. It should be noted that the second period in this study overlapped with the re-designation of the unit as a Major Trauma Centre. The impact of this has led to an increase in patients with poly-trauma and a moderately increased injury severity score (mean, SD 30.6, 14.2) in the second group. However, there was no significant change in mortality among in the second group following introduction of the amended protocol.

The use of emergency RCC Group O RhD negative in the second cohort increased from a median of 0–4. The findings, although greater than expected, were consistent with recent reports of pre-MTP emergency RCC use [18]. A median of two additional emergency RCC units was used i.e. a total of 4 units of RCC (Table 1) resulting in a final RCC:FFP ratio of 2:1 rather than 3:2. We appreciate that there is a debate with regards to a hierarchy of resuscitation vs. the immediate use of plasma and that some authors may be concerned that the initial use of RCC may lead to a potential plasma deficit. Where practitioners would prefer early access to plasma, a more rapid access to liquid plasma through the use of pre-thawed or reconstituted lyophilised would address this concern the reasons for the greater use of emergency red cells than expected were not explained by injury severity or delay in plasma provision. However, we subsequently introduced the use of pre-thawed plasma which improved the mean initial laboratory response time to 15 min for the initial pack. It is plausible that there was improved 'targeting' and treatment of patients. The mechanics of transfusion may have changed during this period with the introduction of a new generation of rapid infusers, i.e. blood was transfused more rapidly before the laboratory could respond. It is also possible that the first (MTP1) cohort may have been under-transfused. Under transfusion has been highlighted by the UK haemovigilance Scheme [24] and the National Patient Safety Agency [7]. Whatever the reasons for the increased use, the increase in emergency red cell use is important for transfusion service planning. Current practice in the UK is to use O RhD negative cells for emergency transfusion although these should be prioritised for women of child bearing age. There is a risk that males may be alloimmunised however the risks are less than expected [25]. Consideration should be given to further restricting the emergency use of O RhD negative blood.

Aggressively pursuing further reductions in the rate of over-activation increases the risk of under-treatment of massive haemorrhage. It is better to start transfusion treatment early followed by safe and rapid MTP de-escalation if not required. The process becomes even more valuable in the context of multiple casualties where blood component use may need to be prioritised [26]. Some investigators have developed predictive models for massive transfusion to aid clinical decision making [9,10,27,28]. Whilst conceptually attractive, these models have several limitations. Importantly they all serve as a 'gatekeeper' at the point of activation. This is a very limiting concept because, for many clinicians, unless the sensitivity approaches 100% they represent an unacceptably high risk to use in clinical practice [29]. Equally, the parameters required for the accurate measurement of such predictors are often unavailable at the point of activation. The nature of our data has allowed us to explore the utility of MT prediction models later in the course of a MH, beyond the point of MTP activation. Our casualties were all clinically judged to be at high risk of MH and had been commenced on MTP which contrasts with the original development of these scores in large unscreened trauma cohorts. Despite altering the pre-test probability, the models we tested (and in particular the TASH score) retained a positive correlation with RCC use. We therefore tested the TASH score within a model designed to predict who, after clinician-led MTP activation, may require continued MTP support. We chose a cut point of >6 units RCC units for this model, reflecting the need for MTP continuation beyond pack 1 in our (and others') protocols. Using a MT prediction model in this manner removes the 'gatekeeper' effect and places the emphasis on objectively deciding if MTP support can be safely de-escalated or stopped. It also addresses concerns that a predictive score may take time to calculate. The time to TASH is less than 8 min [30], and all the parameters required for the TASH score calculation should already be available when scoring is used later in the course of resuscitation. The TASH score performed well in this new role (AUROC 0.88). We suggest that such scoring systems may have a value in not only to predict the individual's probability for massive transfusion but also in identifying patients with a continuing need for further transfusion.

This study is subject to limitations of a retrospective before-and-after study at a single UK centre and the numbers are relatively small. However, the general observations would be applicable to other centres dealing with trauma. Study-specific limitations include a lack of data on the volume of crystalloid and colloid solutions administered during resuscitation. We recognise the limitations of the use of ≥10 units RCC as a definition of MT, a definition which was chosen to allow comparison with other studies. The authors assumed the impact of a learning curve on the delivery of the protocols which reduced the numbers of activations available for study. Despite these limitations our study confirms the findings of others that massive transfusion protocol 'over-activation' is common and perhaps desirable. Although an independent analysis of individual operators of MTP is beyond the scope of this study, we suggest that reflection of individual practice, together with multi-disciplinary review, constitutes an important element in optimising the use of MTPs.

Conclusions

The introduction of a step with emergency red cells first has resulted in rapid response rather than a speed bump. We suggest that a prompt for the early use of red cells in MTPs during assessment may provide sufficient transfusion support for the less severely injured and reduce the subsequent requirement for additional blood components. However, measures should be taken to ensure that the momentum to treat the severely injured is not compromised and that the inappropriate use of O RhD negative red cells is minimised. Finally, scoring systems traditionally used to predict the individual's probability for massive haemorrhage and used to initiate massive transfusion may also have a role in predicting the requirement for further transfusion support.

Disclosure and competing interests statements

None of the authors have financial or competing interests to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.injury.2015.05.046.

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VI

Massive Transfusion: Changing practice in a single Norwegian centre 2002 – 2015

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Running title
Component therapy in massive transfusion

Abstract

Objectives: To describe the impact of a Massive Transfusion (MT) programme in a single Norwegian centre throughout the period 2002–2015.
Background: Transfusion support for massive haemorrhage has changed since the mid-2000s, with protocolled use of haemostatic components. Haukeland University Hospital (HUS) introduced a MT programme during 2007 including education, Acute Transfusion Package (ATP) and point-of-care measurements (thromboelastography).
Methods/Materials: A retrospective review was made of all MT episodes defined as ≥10 red cell concentrates (RCC) in 24 hours. Episodes were identified using the laboratory information system. Patient records were reviewed manually for demographics, transfusion indication, haemostatic drugs and mortality. The ATPs contained 6 units RCC, 6 units Octaplas and 2 platelet concentrates (4 buffy coats/ apheresis in PAS).
Results: 410 episodes were identified in 410 patients. These accounted for 2.8% of all RCCs and 3.4% of PCs issued. The mean patient age was 60 (9-94) with a male predominance (64%). 87.1% of MT episodes were in support of surgery (cardiac services 42.7%; trauma 17.6%). 29.8% of MTs involved platelet inhibitors with 82.6% of these undergoing cardiac procedures. The mean ratio of blood components RCC: plasma: platelets changed from 1.0:0.37:0.39 in 2002-2006 (n=149) to 1.0:0.79:0.85 in 2008-2015 (n=241, p<0,001). A sub-analysis showed that cardiac specialities used proportionally more plasma and platelets.
Conclusion: Massive transfusion was primarily used in major surgery. The programme changed MT practice and delivered a more balanced use of components. The greater use of haemostatic components in cardiac surgery may reflect changes in anti-platelet medication.

Key Words: Massive transfusion, blood component therapy, acute transfusion package, red cell: plasma: platelet ratio

Introduction

Massive haemorrhage is a medical emergency requiring transfusion. Epidemiological studies of massive transfusion show that this may occur in most acute medical and surgical specialities (Halmin, et al. 2016) . Traditional practice was to use red cells only once 40 % of estimated blood volume was lost. Haemostatic components were commonly considered if the transfusion was likely to be massive, i.e. 10 or more units in 24 hours. However, since 2004 there has been increasing evidence that balanced transfusion support or Haemostatic Resuscitation should be introduced as soon as the risk of life-threatening uncompressible haemorrhage is identified (Holcomb, et al. 2007). Transfusion support has become an integrated part of resuscitation designed to provide haemostatic support in addition to red cell replacement. This approach has led to the increasing initial use of standardised Acute Transfusion Packages (ATP) or 'Shock Packs' which contain a fixed ratio of red cells, plasma and platelets (Malone, et al. 2006). Subsequent management is commonly goal directed with tailored transfusion support in which the use of haemostatic components is guided by laboratory and point of care monitoring (Doran, et al. 2012, Rossaint, et al. 2016). The acceptance and introduction of haemostatic resuscitation has varied across the globe during the last decade. However, there has been increasing refinement and endorsement of this approach to Massive Transfusion despite the continuing uncertainty and resource implications (Hunt, et al. 2015, Rossaint, et al. 2016). Early adopters in Scandinavia now have a decade of experience. Haukeland University Hospital (HUS) introduced a massive transfusion (MT) programme during 2007 including education, Acute Transfusion Package (ATP), and point-of-care measurements (thromboelastography). We describe the use and impact of the programme in a single Norwegian centre during the period of 2002 – 2015.

Setting

Bergen is a city on the Western Coast of Norway. The city population is approximately 278,000 and the Bergen metropolitan region has about 420,000 inhabitants. Although geographically isolated by road, it is a popular centre for tourism, giving rise to periods of expanded population. The Haukeland University Hospital is a 790-bedded secondary care facility providing regional specialist cardiothoracic service. It is also a regional trauma receiving hospital. The Department of Immunology and Transfusion Medicine provides the hospital transfusion and

regional diagnostic services. In addition, the department collects and processes blood components for the local hospitals.

Implementation

The hospital implemented an ATP on 17 December 2007. However, clinical practice had started to change following a visit to Copenhagen in Jan 2007 by representatives from the haematology and anaesthetic departments. Thromboelastography *(TEG 5000, Haemonetics Corporation; Braintree, MA, USA)* was introduced into clinical practice in April 2007. The instruments were originally available in theatres and the critical care unit, and then later the blood bank. There was an ongoing education programme throughout the year within the Department of Anaesthesia. The request for an ATP was made at the discretion of the senior anaesthetist. Transfusion packs were prepared on-demand with a target preparation time of 30 minutes. Each ATP consisted of 6 units of RCC and 6 units of Octaplas solvent/detergent treated plasma *(Octapharma AG, Lachen, Switzerland)*, and two platelet concentrates (pool of 4 buffy coats or apheresis collected in 65-70 % platelet additive solution). The total plasma from the platelet concentrates, together with the plasma from Octaplas, provided a red cell to plasma ratio of 1:1. Fibrinogen replacement, using cryoprecipitate until 2014 and then fibrinogen concentrate, was given as clinically directed guided by laboratory fibrinogen and thromboelastography results.

Materials and Methods

Methodology

A retrospective review was conducted of all episodes of patients receiving a massive transfusion during the period of Jan 1st, 2002 and Dec 31st, 2015, i.e. 13 years. Massive transfusions were defined as 10 or more RCC given during the first 24 hours after insult (Malone *et al.*, 2006). An initial search was made using the ProSang laboratory information system (LIMS) *(Databyrån AB, Stockholm, Sweden)*. Patient records were then reviewed manually for demographics, transfusion support, principal indication for transfusion, haemostatic drugs and mortality. The principal indication for transfusion was encoded using ICD-10. The total RCC use for the period was calculated as a denominator.

Blood components

All RCC were prepared from whole blood and processed in SAGM with a residual plasma volume of 10-30 ml. Leucodepletion was introduced in 1996 and applied to all red cell and platelet concentrates. The plasma used throughout this study was Octaplas solvent/detergent treated plasma *(Octapharma AG, Lachen, Switzerland)* with a standardised unit volume of 200 ml. The production method for recovered platelets changed during the study period from manual preparation to automation using the OrbiSac, TACSI and Reveos systems *(Terumo BCT, Inc., Lakewood, CO, USA)*. Most of the platelets included in the ATP were issued as a pool recovered from 4 whole blood donations resuspended to give an average total volume of 309 ml in 30-35% plasma and 65-70% platelet additive solution. In addition, during the years 2003-10 40% of the platelet concentrates were pathogen inactivated by the Intercept psoralen-based technology *(Cerus Corp., Concord, CA, USA)* in 2003-2012. The routine use of tranexamic acid was advocated with the introduction of the ATP in 2007. Tranexamic acid was given as an initial bolus dose of 1 gm within 3 hours of insult, followed by a second dose as infusion.

Statistical analyses

The ratios for the number and volume of plasma and PCs to RCCs were calculated. Standardized volumes of 276 ml for RCCs and 309 ml for PCs were used. The total amount of plasma transfused was also calculated to include the 35% plasma in PCs. PC volume ratios were multiplied by 4 to account for the pooling of four donors per concentrate.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0 *(IBM Corp., Armonk, NY, USA)*. Descriptive statistics were used to summarize the number of components by year, speciality, and patient demographics. The Student's t-test was used to compare the mean number of RCC, plasma and platelet concentrates transfused per episode pre-2007 and post-2007. Differences in platelet inhibitor and anticoagulant use between cardiac and non-cardiac episodes were tested using Chi-squared tests. A p-value <0.05 was considered statistically significant. Excel 2010 *(Microsoft Corp., Redmond, WA, USA)* was used to produce graphs.

Results

We identified 410 massive transfusion episodes in 410 patients during the 13-year period from 1 Jan 2002 to 31 Dec 2015.

Overall blood component usage

The total blood component use in this period was 225,455 RCCs, 84,101 plasma units and 28,885 PCs. Of these, 6,363 RCCs (2.8%), 992 PCs (3.4%) and 5,046 units of plasma (6.0%) were used for massive transfusions. The total number of units transfused per episode varied greatly, but most were closer to 10, with 80% of episodes using 18 or fewer. The summary of component use per transfusion episode is shown in table 1. The pattern of component use by year is shown in Figure 1.

RCC usage remained essentially unchanged before and after 2007, whilst the number of plasma units and PCs doubled ($p<0.001$). Figure 1 shows the mean annual use of each component over the study period. The mean total number of component units increased from 25 to 30. The total volume of blood components used in resuscitation increased by 1887 ml with most of this accounted for by plasma.

Patient characteristics

The number of transfusion episodes by age and gender is shown in Figure 2. 262 (64%) of the episodes involved males and 148 (36%) females. The mean age was 60 (9-90) for males and 59 (17-94) for females with highest numbers in the age groups of 60-79 for males and 70-79 for females.

The blood use by specialty is shown in Table 2. Most of the episodes (42.7%) were in support of cardiothoracic surgery. In total, surgery accounted for 87.1% of all episodes including surgery for trauma.

Full information on medication was available for 386 patients (94%). Of these, 115 were on platelet inhibitors and 97 on anticoagulants. The majority of platelet inhibited patients were cardiac (82.6% vs 17.4% in the non-cardiac group, $p<0.001$). Anticoagulant use was more evenly distributed (55.7% cardiac, 44.3% non-cardiac, $p=0.008$). In the cardiac group, 55.9% of patients used platelet inhibitors, compared

with 9.3% of non-cardiac patients (n=170, p<0.001). Anticoagulant use was greater in the non-cardiac group (31.8 vs 19.9%, n=216, p=0.008).

Blood component ratios

The pattern of components use throughout the period of study is shown in figure 1. The aim of the programme was to move towards 1:1:1 ratio of RCC: plasma: PC. The use of plasma and platelets rapidly increased during the period of 2007-2009. The mean component ratio of RCC: plasma: PC changed from 1.0:0.37:0.39 (n=149) in the period 2002 – 2006 to 1.0:0.79:0.85 (n=241) during 2008 – 2015. In summary, there has been a more balanced use of haemostatic components since the 2007 programme and this practice has endured.

A sub analysis illustrated in Figure 3 showed that the cardiac patients have made greater use of haemostatic components compared to other patient groups. The volume use of plasma has increased from 2014 onwards and now exceeds the use of RCC.

Survival

Table 3 shows that both for 24 hours and 30 days registration points, the survival increased significantly in the 2008-2015 group receiving a total of 30 or more blood components. However, no apparent survival advantage is demonstrated in the groups receiving less than 30 blood components or when analysed only by red cell transfusion.

Blood collection

Whole blood collection figures for Haukeland University Hospital fell slightly from 20,991 in 2006 to 19,751 in 2015. Platelet apheresis increased from 199 to 543. Red cell issues fell from 16,914 to 14,056, whereas platelet issues increased from 1608 to 2635.

Discussion

The mortality rate after massive haemorrhage is high unless actively managed. Haemorrhagic shock also results in a complex disturbance of coagulation which may be further exacerbated by crystalloids and colloids (Holcomb, et al. 2007). Coagulopathy in shock is a marker of poor survival and must be addressed (Brohi, et

al. 2003). The pathophysiology in traumatic haemorrhage has been actively explored. Hypoperfusion, hyperfibrinolysis, activation of protein C and upregulation of thrombomodulin pathways are all thought to contribute significantly to this early coagulopathy (Brohi, et al. 2003) In addition the integrity of the vascular endothelium may be lost in hypoxia (Ganter, et al. 2008). The theory of an acute coagulopathy of trauma together with retrospective evidence from analysis of military and civilian trauma databases led to new transfusion guidelines including massive haemorrhage guidelines in Europe (Spahn, et al. 2007, Rossaint, et al. 2016) and trauma guidelines in Scandinavia (Gaarder, et al. 2008).

This study is an example on how these new ideas have changed transfusion practice in relation to *all* patients with massive haemorrhage. After the introduction of the massive transfusion package in 2007, the use of platelet concentrates, and plasma increased significantly as seen in other studies (Johansson, et al. 2005, Davenport, et al. 2011, Bhangu, et al. 2013, Holcomb, et al. 2015, Padhi, et al. 2015). The mean ratio of blood components RCC: plasma: platelets used in massive transfusion changed in 2002-2006 from a red cell predominant mix of 1.0:0.37:0.39 (n=149) to a more balanced ratio of 1.0:0.79:0.85 (n=241) in 2008-2015 ($p<0.001$). The survival figures did not change other than for those patients transfused greater than 30 components. The Halmin epidemiological study of 92,057 massive transfusions during a similar period showed a slight increase in the median plasma: RBC ratio over time but no marked changes in mortality. The 30-day mortality for all causes of massive transfusion was 24.8% giving a survival rate of 75.2%. Mortality varied with age and indication however, they stressed that MT is independently associated with high mortality at 5 years (Halmin, et al. 2016). A small study from the Royal London group has shown that a major haemorrhage protocol introduced in 2008 improved the delivery of blood components. The outcome again did not show a change in mortality but there was a reduced length of stay (Khan, et al. 2013). Later, Green from the same institution shows that the overall mortality rate was 33% with transfusion of $\geq$10 RBC in 24 hours being associated with higher odds of death (Green, et al. 2017). Cardiac surgery had the lowest mortality rate.

In our institution 87.1% of episodes were in support of surgery. Trauma accounted for only 17.6%. The figures probably reflect the case-mix in the institution as a regional

specialist unit in cardiac services. Cardiac services encompass interventional radiological procedures which are increasingly used to replace open surgical procedures. Anti-platelet medications are often continued. The plasma: RBC ratios for cardiac and non-cardiac blood use are shown separately. Although, the figures are small there is a signal from the sub-analysis shown in Figure 4 that cardiac specialities used a greater proportion of plasma and platelets. We propose that this may be related to changes in pharmaceutical practice in this group especially anti-platelet medication as shown in Table 5. It is well known that antiplatelet drugs increase risk of bleeding, and this risk is significantly increased when dual platelet inhibition is applied (Shehab, et al. 2010, Giustino, et al. 2016, Grodzinsky, et al. 2016, Kim, et al. 2016, Ferraris 2017). However, it is also noted that a large proportion (31.8%) of the non-cardiac group in this study were on anti-coagulants. The figure is high and may not be representative of the general population. In contrast, the overall use in Norway is 98 daily doses/1000 inhabitants (Statens legemiddelverk 2017). However, the study does highlight the importance of recognizing the risk of bleeding associated with use of anticoagulants. The importance of recognition and correct treatment is addressed in several publications (Ufer 2010, Connolly, et al. 2016, Connolly, et al. 2016).

We suggest that massive transfusion remains an uncommon but serious complication of major surgery. It occurs predominantly in the older population in both men and women. The median age was 60 (9-94) with a male predominance of 64%. Our study shows similar age distribution to that seen in both the Halmin and Green papers (Halmin, et al. 2016, Green, et al. 2017). Green showed the median age was 61 (42-74) with a male predominance. We designed our study to be comparable with the seminal epidemiology paper from Denmark and Sweden (Halmin, et al. 2016). This study is a descriptive cohort study of all patients receiving 10 or more RCC in the equivalence of 24 hr. 92,057 patients were identified over a 16-year period. The incidence of MT was 4.5 per 10,000 in Denmark and 2.5 per 10,000 in Sweden. The authors identified that the most common indication for MT was major surgery (61.2%), followed by trauma (15.4%). Prevalence is determined by the definition of massive transfusion and these needs to be standardised using clinically relevant definitions. Green's study identified an impressive 710 MT cases in a three-year period (Green, et al. 2017). This was achieved this using two definitions of Massive Transfusion. These were MT $\geq$5 RBC units in 4 hours as well as the traditional $\geq$10

RBC units in 24 hours. The former has been proposed by Mitra *et al*., and when used together should capture 95% of all cases (Mitra, et al. 2011, Zatta, et al. 2014). All three studies have also shown that overall surgical cases account for the majority of MT. The findings contrast with the general transfusion use studies from the UK which show that most red cells (65%) are used for medical specialties especially haemato-oncology and gastroenterology (Tinegate, et al. 2014, Wells, et al. 2002). The findings from the MT studies are important for Patient Blood Management programmes and transfusion demand planning.

Limitations

This study is subject to the limitations of a retrospective study at a single centre and the numbers are relatively small. Cardiac cases are over-represented, and trauma is possibly underrepresented. However, the general observations would be applicable to other large medical centres dealing with massive haemorrhage. The study inclusion criterion requiring 10 or more RCC in 24 hours has excluded some patients with significant haemorrhage. We recognise the limitations of this traditional definition of massive transfusion however this was chosen to allow comparison with previous studies in Scandinavia. The definition of MT $\geq$5 RBC units in 4 hours proposed by Mitra *et al*., is a much more appropriate marker of active haemorrhage and resonates with the definitions used in the military protocols. However, the use of this time dependent definition requires a different approach to data collection, i.e. contemporaneous digital capture within the clinical space. Finally, we recognise the limited clinical information provided to hospital blood transfusion laboratories with requests for transfusion and the difficulty in extracting the information from hospital IT systems. However, the strengths of the study include the use of the same ICD version and LIMS throughout the 13-year period of study.

Conclusions

The MT programme implemented at Haukeland University Hospital, Bergen, Norway, in 2007 successfully changed massive transfusion practice in that it delivered a more balanced treatment. A trend towards improved survival was seen in the multi-transfused following the programme. We have shown that Massive Transfusion ($\geq$10RBC) was primarily used in major surgery, especially cardiothoracic surgery. The findings contrast with studies showing that most red cells are used in medical

specialities. The proportionally greater use of haemostatic components in cardiac surgery may reflect changes in anti-platelet medication. These findings should inform future studies, blood service demand planning and patient blood management programs especially in cardiac services.

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Table 1. Number of blood components per transfusion episode (mean ± SD (mode))

Blood component	2002-2006	2008-2015	2002-2015	P*
Red cell concentrate (SAGM)	16 ± 10 (10)	15 ± 9 (10)	16 ± 9 (10)	0.507
Plasma (Octaplas/Octaplasma)	8 ± 8 (4)	16 ± 13 (8)	12 ± 12 (6)	<0.001
Platelet concentrate (65% PAS)	1 ± 2 (0)	3 ± 3 (2)	2 ± 3 (0)	<0.001
All components	25 ± 18 (15)	30 ± 23 (20)	30 ± 21 (21)	<0.001

* p-value for difference between the period 2002-2006 versus 2008-2015

Table 2. Transfusion episodes and blood component use by specialty (%)

Specialty	Episodes	Red cell concentrate (SAGM)	Plasma (Octaplas/ Octaplasma)	Platelet Concentrate (65% PAS)
Cardiac/vascular surgery	42.7	41.8	49.2	50.7
Trauma	17.6	20.1	18.3	18.1
Other surgery	16.3	15.4	11.0	8.8
Cancer surgery	10.5	10.2	10.3	9.7
Obstetric care	6.6	6.0	5.7	7.6
Other hospital care	5.6	5.8	5.1	4.8
Hematologic malignancy	0.5	0.4	0.2	0.3
Other malignant disease	0.2	0.2	0.2	0.0

Table 3. Patient survival by total number of products transfused

Blood products	24 hours			30 days		
	2002-2006	2008-2015	p	2002-2006	2008-2015	P
10-29 (n=256)	77.1%	77.5%	0.937	67.8%	71.0%	0.577
20+ (n=270)	59.7%	70.5%	0.090	53.2%	63.7%	0.111
30+ (n=133)	45.2%	61.8%	0.101	32.3%	54.9%	0.027

Figures

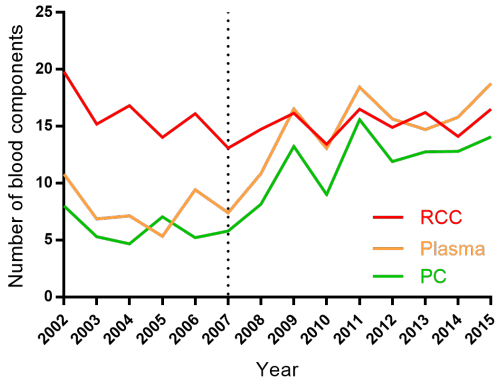

Figure 1. Mean blood component use by year. Vertical line indicates transition year for transfusion program including Acute Transfusion Pack

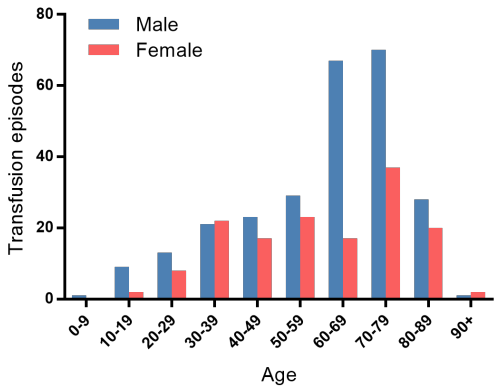

Figure 2. Number of transfusion episodes by ten-year age intervals and gender

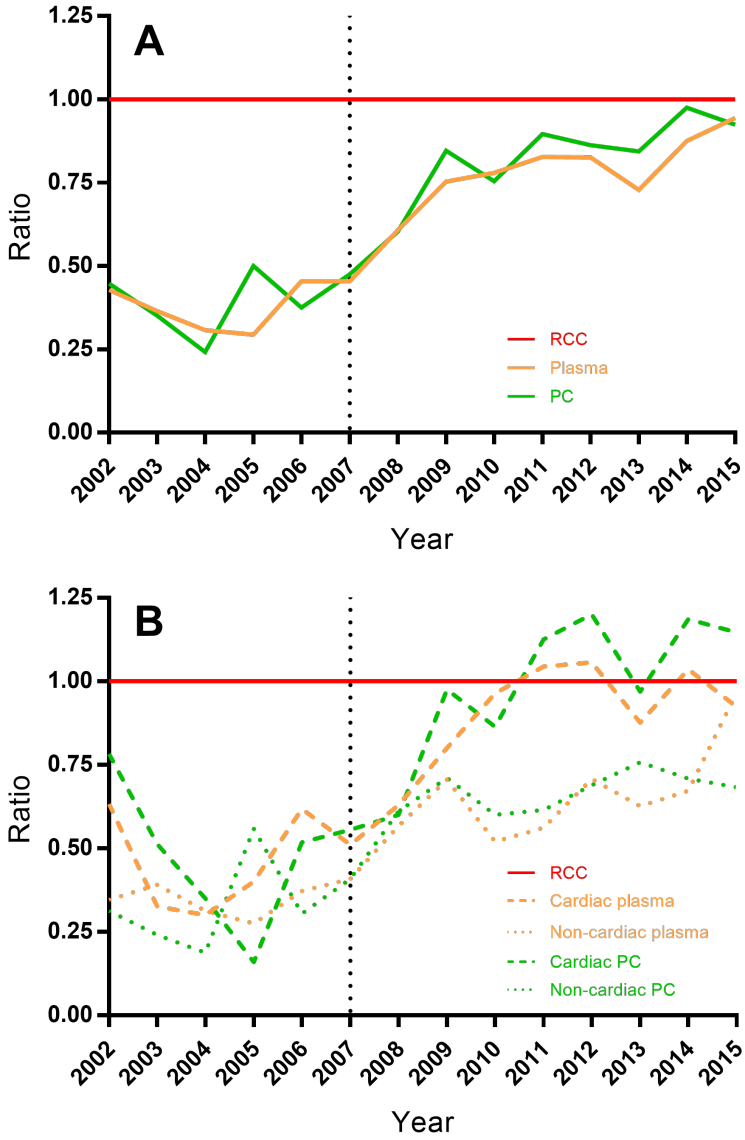

Figure 3. (A) Plasma and platelet concentrate volume as a ratio of red cell concentrate volume. (B) Ratios divided into cardiac and non-cardiac patients. Dotted vertical line indicates transition year

VII

Mass casualty events: blood transfusion emergency preparedness across the continuum of care

Heidi Doughty,[1] Simon Glasgow,[2] and Einar Kristoffersen[3]

Transfusion support is a key enabler to the response to mass casualty events (MCEs). Transfusion demand and capability planning should be an integrated part of the medical planning process for emergency system preparedness. Historical reviews have recently supported demand planning for MCEs and mass gatherings; however, computer modeling offers greater insights for resource management. The challenge remains balancing demand and supply especially the demand for universal components such as group O red blood cells. The current prehospital and hospital capability has benefited from investment in the management of massive hemorrhage. The management of massive hemorrhage should address both hemorrhage control and hemostatic support. Labile blood components cannot be stockpiled and a large surge in demand is a challenge for transfusion providers. The use of blood components may need to be triaged and demand managed. Two contrasting models of transfusion planning for MCEs are described. Both illustrate an integrated approach to preparedness where blood transfusion services work closely with health care providers and the donor community. Preparedness includes appropriate stock management and resupply from other centers. However, the introduction of alternative transfusion products, transfusion triage, and the greater use of an emergency donor panel to provide whole blood may permit greater resilience.

Mass casualty events (MCEs) in medical terms are "single or simultaneous event(s) where the normal major incident response of one or several health organisations must be augmented by extraordinary measures in order to maintain an efficient, suitable and sustainable response."[1] Most are marked by a relatively sudden and dramatic event that causes a surge in numbers of patients. MCEs are an important health care issue. Despite a plateau in the rate of all types of disasters recorded worldwide in the past 8 years, there has been a continued increase in man-made disasters and MCEs. The mortality from terrorist incidents alone has more than doubled since 2007.[2,3] Planned mass gatherings such as sporting and religious events also provide the potential for MCEs. Massive casualty events have the potential to generate many trauma

ABBREVIATIONS: DCR = damage control resuscitation; EDP(s) = emergency donor panel(s); MCE(s) = mass casualty event(s); MHP(s) = major hemorrhage protocol(s); NHSBT = NHS Blood and Transplant; RDCR = remote damage control resuscitation.

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victims; therefore, health care services must be prepared across the continuum of care.

The medical response to the multisite terrorist attacks in Paris in November 2015 was elegantly described by Hirsch and colleagues.[4] The medical response was described as the civil application of war medicine and included prehospital and hospital-based damage control resuscitation (DCR). DCR assumes hemorrhage control, restricted use of crystalloid, and access to blood. MCE and disaster planning has traditionally relied on stockpiles of virtually indestructible crystalloid with a shelf life measured in decades. Disaster planning reliant on perishable blood and blood components is clearly more problematic. A cross-sectional approach to transfusion planning that is nested within wider health care emergency management is required.

The delivery of transfusion support in the context of these incidents has received increasing interest. The appropriate management of severe hemorrhage offers a window of opportunity for improving MCE outcomes.[5-13] This opportunity has developed primarily through our further understanding of the role blood and, more specifically, coagulation therapy, plays in DCR.[14-17] Driving the focus on optimal transfusion support in DCR is the increasing use of major hemorrhage protocols (MHPs) to ensure early delivery of red blood cells (RBCs) and hemostatic components.[18,19] In addition, there has been a wider acceptance of the restricted use of prehospital non–blood-based fluids, in favor of waiting until MHPs can be provided within hospitals.[20-23] The early provision of blood has driven an international movement toward the delivery of these products in the prehospital environment in an effort to further improve trauma outcomes.[24-26] The practice of prehospital blood transfusion combined with additional hemostatic adjuncts such as tourniquets and tranexamic acid form part of the new overall paradigm of remote DCR (RDCR).[27,28]

Providing DCR and RDCR in the setting of an MCE is still relatively untested. The prospect of delivering blood components in the volumes now expected in major hemorrhage already presents a recognized challenge to MCE planners. Previous studies have illustrated the effect of applying modern-day MHPs during previously reported MCEs, showing a possible three to four times increase in the demand for hemostatic components in certain events.[13] The addition of delivering this in the prehospital setting further complicates the issue and is an aspect of transfusion service preparedness for MCEs that has not been previously discussed. The objective of this short article is to review the variation in the landscape of transfusion response to MCEs internationally, through the comparison of two northern European countries with similar systems of government-funded health care deliverance.

Transfusion service delivery for MCEs in the United Kingdom

The United Kingdom has a population of approximately 64.5 million with a land mass of just under 250,000 km^2.[29] Less than 20% of this area consists of mountains, moorlands, or similar terrain, which would present a challenge to an emergency service MCE response and the distribution of emergency blood products.[30] Approximately 85% of the nation's transfusion needs are provided by the English Blood Service, NHS Blood and Transplant (NHSBT). NHSBT undertook a review of its MCE transfusion response plans in preparation for the 2012 London Olympic Games[31] and is currently reviewing the implications of the Paris MCE.

NHSBT applies a policy of maintaining blood stocks at levels appropriate for the current risk level utilizing planned donor drives in preparation for periods of potential or expected surge in demand such as winter supply shortages. Currently, whole blood is not utilized in the United Kingdom. Transfusion support is based on components. This system aims to rapidly deliver the principal blood components: RBCs, fresh-frozen plasma (FFP), platelets (PLTs), and cryoprecipitate.[31] After an MCE there is no reliance on emergency donation for the immediate provision of blood products to casualties; instead, the response to such incidents is based on optimizing supply from existing stock and the forward planning of replacement donation.

During the lead-up to a period of expected heightened demand, NHSBT calibrates stock levels through a process of both bottom-up and top-down planning. Bottom-up plans are based on establishing a range of potential scenarios and therefore casualty load to which both a transfusion per casualty requirement and a hospital demand factor are applied to give an overall stock demand for an event. This is performed for all four of the major components. In addition, top-down plans, similar to business continuity planning for day-to-day needs, rely on the recent evidence from previous MCE transfusion responses to ensure the quantities applied in the bottom-up stage are appropriate and justified.[31] International blood demand prediction tools in trauma have focused predominantly on early individual casualty physiology and laboratory results to predict a "dichotomous outcome" of whether or not a massive transfusion will be required.[32-35] However, UK plans assume wider use of all blood components.

Prediction and planning tools for transfusion service and hospital deliverance are now going further with the use of computer modeling techniques. Simulation models have been developed to improve our understanding of blood provision following MCEs, as well as test potential strategies for managing instances of overwhelming demand in future events.[36] The standard blood stock

levels held at individual hospitals and within networks are determined based on the average daily blood use and can be increased when required. This is controlled and managed centrally through a hub-and-spoke approach that informs rapid resupply after an MCE. The overall component availability can also be manipulated through alterations to the central manufacturing processes. For example, increased plasma and PLT production can be generated from whole blood.[31]

The aim of in-hospital management of MCEs in the United Kingdom is to provide as close to the gold standard level of care as possible within the resource constraints generated by the surge casualty demands. Major trauma centers form the focus of the response for the most severely injured casualties providing DCR through MHPs with the aim of minimizing further blood loss, restoring circulating volume and preventing or treating trauma-induced coagulopathy.[18,37] The current approach to prehospital care delivery in the United Kingdom in terms of transfusion support focuses primarily on prevention of further blood loss and the development of trauma-induced coagulopathy through hemostatic adjuncts and restrictive transfusion protocols. Hemostasis is led through compression of active bleeding, the use of tourniquets, and application of pelvic binders where appropriate. Topical hemostatic agents such as factor concentrators, mucoadhesives, and procoagulant dressings are not widely used within the civilian setting.

Current practice advocates the use of tranexamic acid within 3 hours of injury combined with restrictive use of nonhematologic fluids to maintain a central pulse. Other pharmaceutical adjuncts such as recombinant activated factor (F)VII, while showing some benefit in reducing RBC requirements after trauma, are not in routine use within the UK system. However, it has been employed for major hemorrhage at certain UK hospitals after previous MCEs.[38-40] The use of prehospital blood is a relatively new concept in the United Kingdom. The London Air Ambulance was the first to begin carrying RBCs out into the field in 2012. Since then, a number of regional and national air ambulance services in the United Kingdom have introduced a range of capabilities including lyophilized plasma and tranexamic acid.

Transfusion service delivery for MCEs in the Kingdom of Norway

The Kingdom of Norway's population is less than 1/10th of the United Kingdom at just over five million people; however, this populace is spread over an area 1.4 times larger than the United Kingdom at nearly 350,000 km^2. In addition and in contrast to the United Kingdom, half of this land is mountainous terrain or moorland with difficult access, numerous transportation barriers, and seasonal challenges, especially with prolonged winter periods.[41] Blood and products from blood banks located and run by local and regional hospitals meet the transfusion needs. The hospital blood bank will maintain bloodstock levels to match ordinary hospital activity usage for 10 to 14 days for RBCs, approximately 30 days for plasma, and 4 days for PLTs. Only larger hospitals make PLT concentrates.

In one of the four health regions in Norway the hospital blood banks have plans to meet minor surges of blood and blood products. At times of larger crisis these may be extended to any affected regional hospital, although on an ad hoc basis. Single hospitals have their own contingency plans, but none are scaled to cope with MCEs. There is no control or coordination of the transfusion needs at a national level and no government body evaluating national blood stock levels related to current risk levels or expected potential surges. In the aftermath of the most severe civilian MCE in Norway on July 22, 2011,[42] improved contingency plans have been made to improve obvious shortcomings in nearly all areas except transfusion. In this incident, blood product needs were largely met, and any need for a change in national civilian transfusion strategies was therefore deemed unwarranted. There is presently no national policy in place on how to meet transfusion needs after an MCE in Norway.

Trauma teams are located at regional hospitals and will rely on a balanced transfusion policy of RBCs, FFP, and PLTs provided by the hospital blood bank as one "trauma package" containing a balanced quantity of the three components. No regional hospital provides whole blood as a part of its DCR program. Most regional air ambulance services now fly with lyophilized plasma, but only a few with RBCs and, as of December 2015, one with PLT-sparing, leukoreduced whole blood. As in the United Kingdom, there is no reliance on donation following an MCE for the rapid provision of blood components to casualties; indeed the regional blood bank involved in the July 22, 2011, terrorist incident managed successfully to stem the flow of nonregistered donors at an early time.[11]

However, one regional blood bank (Bergen) is in the process of implementing contingency plans that will involve prescreened group O low-titer emergency donors. The donors will be recruited from three locations, at a local naval base, among the regional hospital employees, and from city suburbs, and called to donate whole blood to be fully tested and utilized as soon as possible. These plans are coordinated with the Norwegian Armed Forces Medical Services contingency plans for blood product needs in emergencies. Donated blood is to be leukoreduced with PLT-sparing filters, tested, and dispensed as whole blood for immediate use or cold storage. The plan is based on a projected initial demand of 50 units of whole blood to meet the demand of five immediate massive transfusion cases; however, the scheme is easily upscaleable.

Literature review

We have briefly described the organization and planned response to MCEs by transfusion providers in two countries. One blood bank in Norway is redeveloping the use of whole blood as a part of its resilience plan. It is a novel approach for Europe and stimulates debate. Many countries have faced MCEs but the literature concerning transfusion support is limited. Blood demand in MCEs has been comprehensively reviewed by Glasgow and colleagues.[13] The publications and reports of transfusion service deliverance for MCEs in North America and Israel are particularly valuable. These nations have significant experience with a wide range of MCEs and face their own environmental and logistical challenges in mounting an effective response.[13] Hess and Thomas[43] and Schmidt[44] both highlighted the issues associated with the US experiences of emergency donation in the immediate aftermath of such events during their reviews of blood and disaster. Colleagues in Israel have also described their substantial experience with delivering transfusion support in MCEs, both providing detailed plans of their transfusion response and offering planning estimates for future MCE blood needs.[5]

Dann and coworkers[5] stated in a review of the response to nine individual terrorist MCEs in Israel that the established protocol is to prepare three RBC units for each patient "likely to require blood." In comparison, Shinar and coworkers[45] reviewed 1645 terrorist attacks, again in Israel, from 2000 to 2005, involving 7497 casualties. These authors, from the Magen David Adom (MDA), the national supplier of blood products to Israel, reported a mean number of units supplied per MCE casualty of 1.3 U of RBCs and 0.9 U of other components. Using the total number of casualties as a denominator, that is, "per casualty," is a much broader descriptor for planners than the units per individual casualty expected to require blood. However, the volume of casualties actually requiring blood is relatively small compared to the overall injury burden from an event.[13,43,44]

Most recently, another group from Israel reported the use of just over 3 units of RBCs "per casualty admitted to hospital," therefore negating the issues of accounting for all casualties with very minor injuries who may be dealt with at the scene or in minor injury units. The 3 RBC units per admission figure is supported by a separate report from a combat hospital in Iraq,[46] which describes their response to three separate civilian MCEs. The most recent report also stands out in its detailed discussion of component use and attainment of modern-day transfusion ratio deliverance after MCEs affecting civilian communities.[9] Blood use is greatest in casualties involved in terrorist MCEs with injury severity scores greater than 15 (ISS $>$ 15). Blood use in the most severely injured was 7 to 8 units of RBCs supported by components. UK military and civilian experience suggested even greater requirements for the most severely injured by improvised explosive devices, with median requirements of 16 (9-25) units of RBCs and proportionate amounts of components.[40,47]

The proportion of injured requiring blood varies enormously and is dependent on the event, hemorrhage control, and availability of blood. After the London bombings, only 23 patients received blood during the first 24 hours out of an estimated 700 injured.[40] The planning for the Olympics assumed a similarly small proportion. The Paris attacks in 2015 with shootings at four sites and three explosions have highlighted the requirement to support many more severely injured. However, there was good blood component availability during the crisis, demonstrating that large volumes of components can be rapidly mobilized if already stocked.

DISCUSSION

MCEs continue to challenge health care emergency preparedness. The definition of MCEs implies that critical sufficiency and supply of resources will be constrained. MCEs involving improvised explosive devices are characterized by massive bleeding. The widespread adoption of lessons learned on the battlefield has led to a more aggressive approach to hemorrhage control. However, the same paradigm has also led to the introduction of cautious fluid resuscitation and the early use of blood components in resuscitation. Such an expectation challenges health care planners and developed blood transfusion services especially when a large surge of patients is involved. Effective prehospital care and emergency system preparedness across the continuum of care has the potential to reduce morbidity and mortality as well as reduce the demand for blood.

Transfusion planning has not traditionally been a part of MCE planning; however, we suggest that integration is essential for both blood demand and supply management. The two European examples presented illustrate two complimentary approaches currently being used to prepare for MCEs. Both countries have recently responded to terrorist bombings. The UK example is a national example based on component therapy with access to redistributed stock. The Norwegian example (Bergen) is that of a relatively geographically isolated community using a whole blood program to supplement existing stocks of blood components. The two transfusion services' support to MCE is summarized in Table 1.

Continuity of care

The UK has dealt with a number of civilian disasters but it was the response to the July 7, 2005, London bombings that led to the first transfusion service review.[40] The review highlighted a number of issues that have been incorporated into subsequent planning. These include the provision of a large volume of universal components. The

TABLE 1. Comparison summary of MCE transfusion preparedness

Transfusion preparedness	England	Norway
MCE response planning		
Historical experience of MCEs	Periodic	Limited
Integrated military and civilian responses	No	Yes*
Blood stock management and redeployment	Coordinated at national level	Regional
Donor management systems	National call center	Local call-up
In hospital		
Whole blood available to civilian community	No	Regional initiative. Use of leukoreduced PLT spared whole blood.*
Principal blood components held within standard inventories	RBCs, FFP, PLTs, and cryoprecipitate	RBCs, FFP, and PLTs
Emergency blood donation program	National blood service	Local pool of emergency volunteer donors*
Routine use of tranexamic acid	Yes (within 3 hr)	Yes
Routine use of recombinant activated FVII for massive hemorrhage	No†	No
Prehospital		
Tranexamic acid	Increasing use	Yes
Tourniquets	Yes	Yes
Routine access to hemostatic dressings	No	No
Prehospital transfusion	RBCs with limited availability of lyophilized plasma	Lyophilized plasma with limited availability of RBCs and leukoreduced PLT-spared whole blood

* Recent initiative or currently in development.
† Reports of occasional use in response to MCEs.

demand was three times greater than the actual amount of RBCs used during the first 24 hours. This ratio of overordering has previously been described.[5,7] The proportion of group O RBCs ordered during July 7, 2005, was 80% whereas the proportion of group O in the UK population is 45%. In addition, there was a demand for hemostatic components including FFP, PLTs, and cryoprecipitate. Despite overordering, there was very little reported wastage due to the amendment of hospital blood bank standing orders and the subsequent use of blood. The subsequent use of blood is due to the ongoing care required for the severely injured. Early revision surgery leads to demand for both theater time and blood. The care of the severely injured may continue for many years and transfusion support should be mindful of the continuity of care. The other reason for continued blood use is the return to planned health care activity.

The impact of military practice on civilian care

Military practice has left a legacy across the continuum of care. It has changed trauma care and planning and has stimulated collaborative research. It has also contributed to MCE planning. MCE planning is facilitated by trauma networks with shared policies and massive hemorrhage protocols. A series of guidelines for the management of massive hemorrhage have developed over the past 5 years.[17,48,49] All have been underpinned by military transfusion practice and enhanced by the developing evidence. Transfusion guidelines now promote hemorrhage control, early use of tranexamic acid, and a foundation of RBCs and FFP in a 1:1 to 3:2 ratio followed by goal-directed therapy.[23,50] Good organization is essential to success with the early involvement of senior experienced clinicians, well-rehearsed teams, and trauma registries.[17,48,51] The concepts of prehospital care, registry reviews, standardized massive transfusion protocols, cross-sector planning principles were successfully integrated into the blood transfusion service for the 2012 London Olympics.[31]

The use of whole blood has traditionally been used by defense medical services and offers considerable logistic advantages in the austere medical environment.[52,53] The Bergen team has spearheaded the concepts of RDCR with the use of emergency donor panels (EDPs) and the introduction of cold whole blood for military units.[54] The use of emergency whole blood is not restricted to the military community but may be lifesaving in civilian situations such as the cruise industry.[55] The Bergen model for transfusion support demonstrates a further example of military practice used in wider support of the civilian community, that is, the use of EDPs for whole blood. EDPs are pretested donors who are prepared to give in emergencies. Donors are required to maintain their currency as donors and are normally screened at the time of donation. It represents the most agile of systems and is an ideal solution for a geographically isolated population with a low prevalence of transfusion transmitted infection. However, it also requires careful preparation and demand planning.

Transfusion triage and demand planning

Transfusion demand planning is primarily designed to meet the normal needs of the population at risk. In addition, consideration must be given to emergency-

TABLE 2. Guidance for blood component use during the 2012 London Olympics

Priority	RBCs (U)	FFP (U)	PLTs*	Cryoprecipitate (pool of 5 donations)	Category definition
P1	10	6	1	1-2	Immediate, requiring immediate intervention
P2	4	0	0	0	Urgent, requiring intervention < 6 hr
P3	0	0	0	0	Delayed, walking wounded

* PLT minimum dose of 2.4×10^{11} per adult therapeutic dose (Ref: internal reporting to NHSBT by H. Doughty).

preparedness. Emergency-preparedness must respond to not only the emergency but also ensure the continuity of critical services. The primary role of the blood transfusion services and hospital blood banks is to provide blood components. The wider use of "massive transfusion" protocols has led to an increased initial demand for "universal" components such as group O D– RBCs and AB FFP. Alternative universal components can be substituted. Examples are the use of group A plasma for all and group O D+ RBCs for males and women over 50.[48] Military experience has demonstrated that hemostatic resuscitation and the introduction of point-of-care testing may increase the demand for PLTs and cryoprecipitate.[47] Resuscitation teams have become accustomed to large volumes of components for individual patients. Such trends must be factored into local and national demand planning.

Stock management of labile components such as blood and PLTs is a challenge when there is unpredictable demand. Large stock holding in blood services or blood banks is associated with wastage due to time expiry, whereas insufficient stocks may lead to clinical disaster. It should be assumed that in the unplanned event the demand for blood components may exceed supply. The use of preprepared blood shortage plans provides valuable guidance in the event of RBC and PLT shortages.[56,57] In addition, transfusion triage can provide guidance for both clinicians and the blood transfusion services. The guidance issued for the Olympics is shown in Table 2. While such schemes are applicable to individual casualties where information may be in abundance, in an MCE scenario such detail is often unavailable, both at the planning stage and early in the course of the event. Historically, it has been repeatedly shown that blood demand is greatest within the first few hours of an event and that expectedly this period correlates with the arrival of the most severely injured casualties.[58,59] Experimental simulation modeling has recently explored the impact of restricting both the total number of RBCs and emergency group O blood in MCEs.[36] Restrictive transfusion protocols appear to increase the overall treatment rates where there are large casualty loads.

Transfusion safety

Demand planning and stock management should consider blood group mix. There will be considerable pressure on the universal components. Demand management of group O blood may promote the early use of group specific or ABO-compatible blood. However, the greatest risk associated with transfusion especially in the context of MCEs is the use of ABO-incompatible blood and the initial use of group O may be the safest option. Note that the use of group O before blood grouping may lead to "mixed fields" and staff should have guidance as to when to revert to group specific blood. Identification bands should be worn by patients receiving blood. Emergency identification should use gender and be compatible with laboratory information management systems. Attention must also be paid to cold chain management especially during the transport of blood between organizations and departments. Transfusion is a highly regulated area of health care. The European Blood Directive 2002/98/EC sets standards for the collection, testing, processing, storage, and distribution of human blood and blood components.[60] Requirements of the legislation include the traceability of blood used and hemovigilance. These are potentially challenging within the context of MCEs but must be managed.

Back to whole blood

Most national blood services have developed component programs designed to meet civilian patient requirements. The drivers for transfusion support in the UK are medical patients, in particular, those requiring hematooncology support.[61,62] Components permit not only optimal care of individual patient groups but also optimal storage. National component development programs have focused on targeted safety measures such as those designed to reduce the risk of transfusion-related acute lung injury and prion disease rather than MCEs.[63] The current management of traumatic hemorrhage requires hemostatic components. Frozen products can be stockpiled but must be thawed to be used which takes time unless prethawed. Component development such as liquid and lyophilized plasma may address some of the logistic constraints and permits treatment in the prehospital space. However, labile products such as RBCs and PLTs cannot be stockpiled. For instance PLTs have a shelf life of 5 to 7 days unless cryopreserved. Another method of delivery of PLTs is whole blood.

Few European civilian blood services provide whole blood either routinely or as part of their emergency response. However, the use of whole blood for hemostatic resuscitation is predicted to become more mainstream as evidenced by its inclusion as a research priority in the NHLBI Transfusion Medicine State of the Science Symposium Summary Statement.[64] Fresh whole blood not only addresses the concerns about the storage lesion, but also provides a supply of both liquid plasma and a small dose of PLTs with less anticoagulant than component therapy. PLT function is normally related to posttransfusion circulation time and PLTs stored at 1 to 6°C have reduced circulation time. However, whole blood stored cold has the potential to provide some hemostatic effect over a longer period.[54,65] Whole blood availability may be limited due to other barriers including leukoreduction. However, there is now an FDA-approved PLT-sparing filter.[66] Well-rehearsed collection, testing, and release can yield a continuous flow of whole blood bags. The use of whole blood is a potentially more agile and responsive approach and should be considered as a part of resilience measures. Indeed, as of December 2015 cold-stored, leukoreduced, PLT-containing whole blood has been offered to the Emergency Department at the Mayo Clinic in Rochester, Minnesota.

CONCLUSIONS

Transfusion support is a key enabler in the health care response to MCEs. Historical reviews have recently supported MCE blood demand planning; however, each new event offers further insights for resource management. The challenge remains balancing demand and supply. The intervention priority to reduce demand is hemorrhage control. However prehospital and hospital care has benefited from early access to transfusion support. A surge in demand for blood components remains a challenge for any blood provider and transfusion may need to be triaged and demand managed. The options for increasing supply include redeployment of existing stock, altered manufacturing, and careful donor management. The introduction of alternative transfusion products and rapid access to pretested emergency donor panels may also offer resilience. In conclusion, transfusion support in MCEs is important and should be an integrated part of health care emergency-preparedness.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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