Massive Transfusion

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Abstract

Massive Transfusion is a part of Damage Control Resuscitation. The aim of transfusion therapy is to restore oxygen delivery to poorly perfused tissues and to treat the acute coagulopathy of trauma. The severity and complexity of modern injuries have led to the use of swift, protocol-driven care with the use of 'Shock Packs' and management of metabolic complications. The pro-active treatment of the coagulopathy has been termed Haemostatic Resuscitation. The delivery of this transfusion capability has required an increasingly sophisticated logistic and laboratory response. New operational capabilities have included cold chain solutions; laboratory management information systems; platelet apheresis and ROTEM®. This investment in the massive transfusion capability has delivered rapid resuscitation. It has also enabled clinicians to direct individualised transfusion support following initial resuscitation i.e. goal directed therapy. Future technical solutions should further support the pre-hospital delivery of transfusion while addressing the logistic tail. However, the key to success is the knowledge and skills of frontline staff to deliver safe and appropriate blood transfusion.

Introduction

In 2006, the entry into the Helmand province heralded an era of medical response to increasingly complex and severe injuries. At the time of writing, massive transfusion in Camp Bastion involves a well rehearsed, complex clinical and laboratory response to the critically injured. The facilities equate to those of a civilian major trauma centre. Massive Transfusion is part of the integrated management of traumatic massive haemorrhage [1]. The resuscitative response starts with pre-hospital care and continues through to reception in the UK. The aim of transfusion therapy is to restore oxygen transport capacity and treat acquired coagulopathy. The early, proactive treatment of the post traumatic coagulopathy is termed 'haemostatic resuscitation' (HR) [2]. Transfusion is one of many treatment modalities provided to the critically injured. However, it is unique in that it relies on donated biological materiel. Safety is paramount. As a consequence, the last decade has seen an increase in legislative and regulatory measures [3]. These regulations and the increase in demand have required an increasingly sophisticated logistic response. Despite these constraints, the military transfusion community has developed and delivered a highly successful service in an austere environment. The aims of this paper are to describe the clinical and logistic aspects of Massive Transfusion support to current operations.

Principles and Clinical Practice

Definition and Demand

Massive transfusion is arbitrarily defined as 10 or more Red Cell Concentrates (RCC) within 24hr [4]. A search of the Joint Theatre Trauma Registry (JTTR) of all UK personnel admitted for trauma to the UK Field Hospital at Camp Bastion, Afghanistan from 1 Apr 08 – 30 Mar 10 was commissioned by the lead author. The search identified that 27% required transfusion; and that 11% received 10 or more RCC i.e. massive transfusion. The figures are similar to published US figures [5]. Further audits have identified that the mean component use per patient was approximately 22 units in 2008-2010 and 12% of patients receiving massive transfusion at the field hospital received more than 100 units of blood components [6].

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Trauma Induced Coagulopathy

Trauma results in a complex disturbance of coagulation. The concept of the 'Bloody Vicious Cycle' of shock has long been recognised [7]. However, our understanding of the complexities of early trauma coagulation continues to evolve. Current opinion is that this is tri-modal, with an immediate hypercoagulable state, followed by a hypocoagulable period, and ending in a hypercoagulable state [8]. The cause of the early coagulopathy is now no longer thought to be only due to consumption, dilution of clotting factors and platelet dysfunction [8]. Recent work has introduced the concept that hypoperfusion, hyperfibrinolysis, activation of protein C and up-regulation of thrombomodulin pathways contribute significantly to this early coagulopathy [9]. This process, as well as endothelial activation and subsequent coagulation changes, is thought to be mediated by hypoperfusion and tissue hypoxia [8, 10]. The integrity of the hypoxic vascular endothelium controls fluid shift and coagulation but the details have yet to be determined. What is agreed is that coagulopathy is a marker of poor survival and must be addressed [11]. The haematological challenge is supporting haemostasis to stop bleeding without exacerbating hypercoagulability.

The Use of Plasma

The paradigm change in massive transfusion management is the proactive treatment of the coagulopathy associated with trauma [12], i.e. haemostatic resuscitation (HR). The management of coagulopathy includes the pre-emptive early use of plasma and platelets. The outcome of this practice is limited to retrospective studies, as there are no randomised controlled trials of this therapeutic process. The largest study is the collation of US experience in Iraq [5] which led to the initial use of red cells

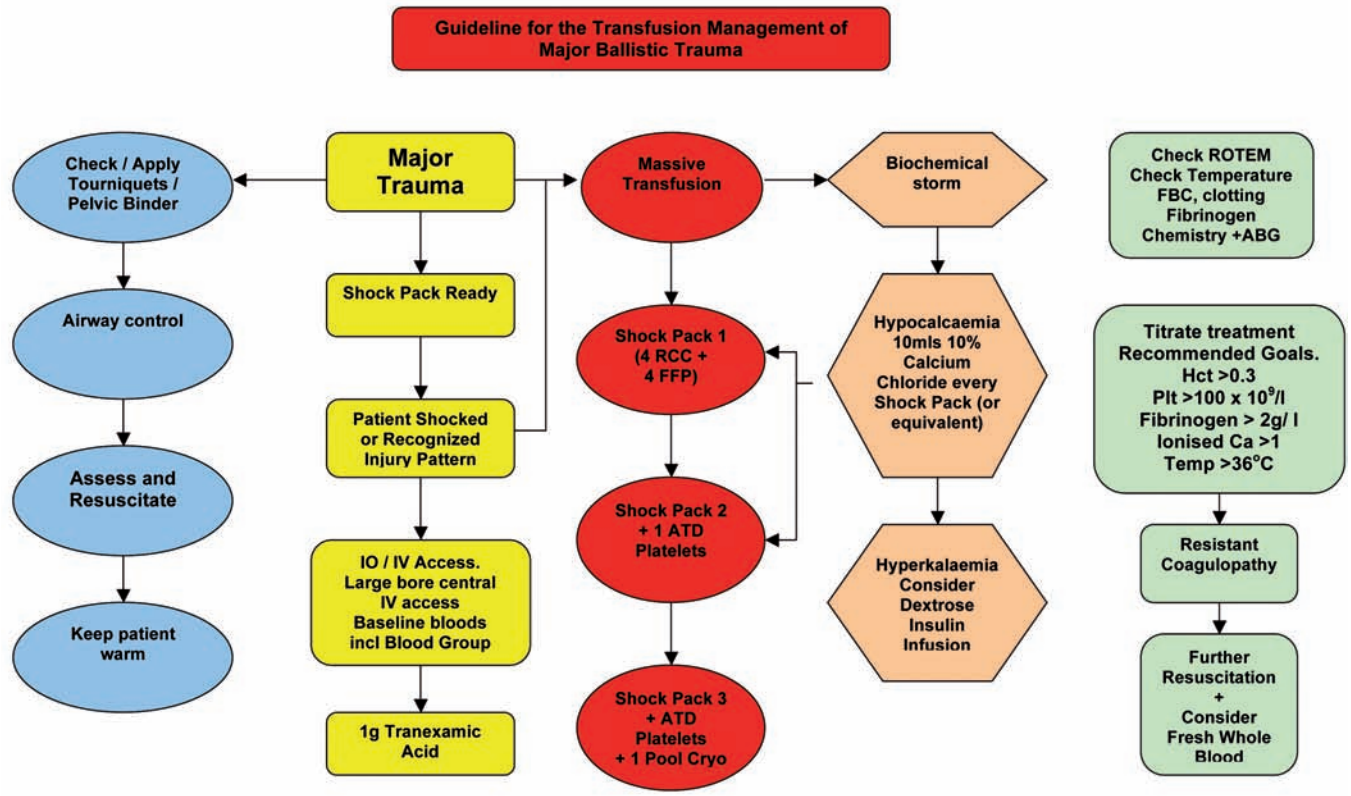

Figure 1. Guidelines for the transfusion management of major ballistic trauma

(RCC) and fresh frozen plasma (FFP) in a 1:1 ratio. A more recent review of UK military massive transfusion practice has confirmed that a plasma rich protocol as part of DCR is associated with high survival rates [6]. Civilian trauma centres have reviewed their own data and increasingly support the early use of plasma [13-15]. The direct translation of military practice into civilian trauma [16] has been challenged and prospective studies of FFP use in trauma are required. The optimal use and ratio of FFP may depend on a number of factors, ranging from patient genetics and injury type to whether or not the hypocalcaemia induced by citrate in FFP is treated [17]. The development of the UK massive haemorrhage policy of 2007, and revised in 2009, recognised the limitations of evidence but provided the rationale for transfusion treatment [2]. Current practice is shown in Figure 1. Initial transfusion support uses RCC and FFP in a 1:1 ratio, together with other components and tranexamic acid.

Indications for Massive Transfusion

The decision to start and to stop transfusion may be difficult. Definitions of massive transfusion are traditionally retrospective and not always appropriate for this context. The UK military policy [1] allows for initiation of the massive transfusion protocol based on:

- Injury severity
- Clinical evidence of haemorrhagic shock
- Rate of blood loss

Massive transfusion should be started as early as possible however many casualties only need rapid transfusion and haemorrhage control. Blood components are a precious resource and must not be used inappropriately. It is a judgement call and the early involvement of senior experienced clinicians is essential. Generally, it is recommended that the fixed formula protocol is used during the early phase of resuscitation. Staff should then move to a more goal directed response once the situation is under control and monitored. Transfusion care should continue during surgery and further care as required. Transfusion may be initiated before admission. The Medical Emergency Response Team (MERT) now carries RCC and thawed FFP permitting pre-hospital transfusion support. The MERT doctor can also alert the hospital that the patient may require massive transfusion allowing them time to prepare to continue transfusion as soon as the patient arrives in the resuscitation room.

Shock Packs

The implementation of the massive haemorrhage protocol, or the call for a 'Shock Pack', triggers a chain of events in the field hospital. Shock Packs are pre-prepared packs of group O RhD negative RBC and group AB thawed FFP in insulated containers. Each of the components are pre-labelled with a three-part traceability label, and stored for rapid issue with a corresponding issue slip. The patient details are added later. Components are initially released as universal groups, although group specific components are issued as soon as the patient's blood group is confirmed. Platelets and cryoprecipitate are automatically prepared by the laboratory but are not allocated to the patient until requested by the clinician.

Administration of Blood

Blood components are administered by designated staff who are also responsible for record keeping. Massive transfusion should always be delivered through a fluid warmer at the correct infusion rate for the condition of the patient. Consideration must be given to the size and location of circulatory access and compatibility with other resuscitation fluids. Rapid administration of large quantities of stored blood components will result in a profound metabolic disturbance. The severity of this metabolic disturbance is unpredictable but must be anticipated and managed to prevent avoidable morbidity and mortality.

Monitoring Treatment

Close monitoring is essential to guide therapy and minimise the potential complications of massive transfusion. Pathology monitoring may be via the laboratory or through the use of Point of Care Testing (POCT). POCT supports rapid clinical decision-making but requires a quality framework and good record keeping. Treatment targets commonly in use are shown in Table 1. The two most significant biochemical disturbances complicating massive transfusion are hyperkalaemia and hypocalcaemia.

Physiology	Haematology	Biochemistry
Systolic Blood pressure of 90mmHg	Haemoglobin >9 g/l	Base Deficit <2
Urine output of at least 0.5ml/kg/hr	Haematocrit > 3%	K^+ < 5.0 mmol/l
Core Temp > 36°C	Platelet count > 100 x 10^9/l	Ionised Ca^{2+} >1.0 mmol/l
	PT and APTT < 1.5	Lactate < 2 mmol/l
	ROTEM (Figure 1)	pH >7.3

Table 1. Treatment targets for Massive Transfusion.

Hyperkalaemia

Hyperkalaemia during massive transfusion is not uncommon and may prove fatal [18]. Postulated mechanisms include shock, older stored RCC, 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. Treatment involves intravenous calcium, delivered as calcium chloride or gluconate to protect the myocardium, and an insulin/dextrose infusion to maintain serum potassium below 5 mmol/l (infusion of 50mls 50% dextrose with 15 IU insulin).

Hypocalcaemia

Donated blood is collected in a citrate containing anticoagulant which chelates ionised calcium [19, 20] and magnesium. Rapid transfusion of citrate will overcome the liver's ability to metabolise citrate with resulting citrate toxicity. Hypocalcaemia may cause death [21] due to a decrease in cardiac contractility and a predisposition to arrhythmia [22]. Calcium is also critical for coagulation [22,23], and platelet activity [24]. Ionised calcium levels should be monitored closely and kept above 1.0mmol /l by the administration of 10ml of 10% calcium chloride with each shock pack or by the use of calcium gluconate.

Component Support

The optimal use of components, including the ratio of RCC:FFP, remains contentious. The early use of RCC and the avoidance of crystalloid solutions accelerates clot formation and may improve survival [25]. However, the optimal red cell mass is unclear. Civilian non-trauma guidelines suggest a target Hb of 7-9/dl. This is consistent with the concept that a haematocrit of 0.3 is the minimum level necessary to ensure enough 'shear stress' within a blood vessel to force platelets to the periphery. This in turn supports the formation of primary haemostatic plugs and initiates coagulation. Platelets are important but the optimal platelet mass is unknown. A platelet count of 100x10^9/L is readily achievable with current access to platelet support. However, blast trauma in itself may compromise platelet function and therefore a functional test may be more appropriate to guide replacement therapy. Functional fibrinogen is important in providing clot strength and in securing haemostasis [26]. Cryoprecipitate is used to provide additional fibrinogen and factor XIII to achieve a plasma fibrinogen level of >1.0g/l and optimal clot strength. However, it is anticipated that this fibrinogen target will be increased to >1.5g/l with the availability of a licensed fibrinogen concentrate in the UK. Early and aggressive resuscitation and haemorrhage control should reduce further demand for components.

Goal Directed Therapy

Since 2008 there has been an increasing effort to optimise transfusion support for the individual rather than follow a pre-designated sequence. The use of viscoelastic methodology or thromboelastometry is more likely to give a dynamic interpretation of whole blood clotting and diagnose specific issues such as hyperfibrinolysis [27]. A benefit of bespoke treatment is minimising the unnecessary use of blood components thereby reducing donor exposure[6] and preserving blood stocks.

Thromboelastometry

Thromboelastometry (TE) offers assessment of the whole clotting process including coagulation, thrombosis and lysis. It also evaluates platelet function and probably correlates more closely with the cell based model of haemostasis [28]. TE has been assessed as a valuable clinical and cost-effective intervention in surgery, and may have a place in trauma. The use of TE in the UK military has now been described [29], and recent reports have suggested that ROTEM® can be used to guide therapy [30-32]. The ROTEM® Delta Whole Blood Haemostasis Analyser is designed for *in vitro* diagnostic use. The operating principle of the analyser and a schematic representation of the output are shown in Figures 2A&B.

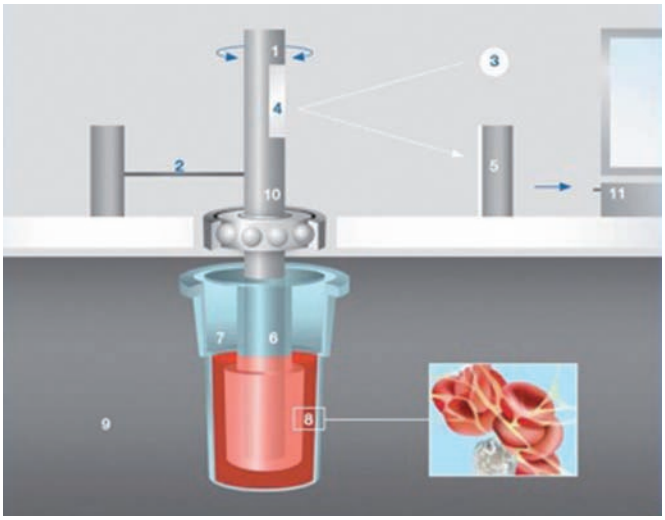

Figure 2A. Commercial representation of the ROTEM® system principle. 1- Oscillating axis; 2-counterforce springs; 3- Light beam from LED; 4- mirror; 5-detector (electric camera); 6- sensor pin; 7-cuvette with blood sample; 8- fibrin strands & platelet aggregates; 9- heated cuvette holder; 10- ball bearing; 11- data processing unit

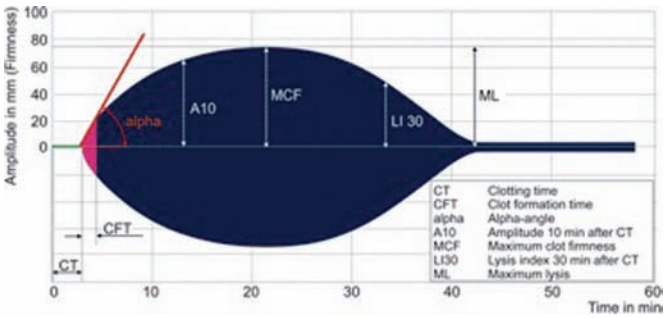

Figure 2B. A schematic representation of ROTEM® test output and associated interpretation

ROTEM® Field Trial

ROTEM® was deployed to Afghanistan as a field trial in 2009 to determine its usefulness and reliability [29]. The investigators concluded that the machine was robust enough to be used in a field environment, and was useful in detecting coagulopathy. Further work investigated the appropriateness of an abnormal ROTEM result in determining clinical coagulopathy, and the speed that this result was available to the clinician. The investigators proposed that two abnormalities in any of the three standard domains of the trace (clot initiation (CT), clot dynamics (alpha angle and CFT) or clot strength (MCF)) represents hypocoagulability and puts a casualty at risk of coagulopathy and bleeding. The ROTEM displays interim values of the amplitude of the trace at 5 and 10 minutes after clot initiation [A5 and A10]. The field trials demonstrated that the A5 and A10 values were able to predict hypocoagulation with sensitivities and specificities of 0.98/0.69 (A5) and 0.97/0.78 (A10). The use of ROTEM can be used to detect casualties at risk of coagulopathy in a clinically relevant time [33].

Recombinant Activated Factor VII (rFVIIa)

The use of rFVIIa remains contentious. rFVIIa is licensed to control bleeding in patients with haemophilia and those with clotting factor inhibitors. The promotion of haemostasis at the site of injury infers possible use in trauma [34, 35], although there is also a risk of provoking unwanted thrombosis [36]. A multicentre RCT examined the efficacy of rFVIIa [37], and found that treatment with rFVIIa in blunt trauma produced a significant reduction in massive transfusion requirement in patients surviving for more than 48 hours, and reduced the incidence of adult respiratory distress syndrome (ARDS). However, a Cochrane review recently concluded that the use of rFVIIa as a haemostatic drug remains unproven [38]. Currently, rFVIIa is considered only after first line therapy has failed. When used, it is given alongside haemostatic substrate and normalisation of physiology.

Tranexamic Acid (TXA)

Pathological fibrinolysis has long been recognised as a potential response in trauma [39]. Antifibrinolytic agents have been shown to reduce blood loss in surgery without the risk of thrombotic complications [40]. The CRASH-2 trial [41], a huge global randomised controlled trial, found that TXA safely reduced the risk of death in bleeding trauma patients. All cause mortality was reduced and the risk of death from bleeding was reduced by 0.8%. Further analysis suggests that it is the early use of TXA that delivers benefit [41]. Military clinicians have adopted the use of TXA within 3 hours, repeated if there is ROTEM® evidence of fibrinolysis [42].

Resource Implications

Despite the move to goal directed therapy, massive transfusion is a resource-intensive intervention. The survival rate has recently been reported as greater than 85% [6] and there appears to be no upper limit of blood use associated with survival. These outcomes are impressive and far exceed previously published figures. However, in a resourced-constrained environment, massive transfusion support for an individual with poor likelihood of survival may compromise the transfusion support available for others.

Laboratory and Logistic Support

The delivery of safe, effective and timely massive transfusion places extraordinary demands on both the biomedical scientist (BMS) cadre and medical logisticians. The last decade has seen an increase in volume and complexity of the operational workload. However, the period has been marked by successful innovation, increased quality assurance, and regulatory compliance.

Blood Supply and Planning

The military transfusion supply is successfully contracted to NHS Blood and Transplant. Operational supplies are issued from a designated centre working under the direction of a small military Blood Supply Team (BST). The BST is licensed by the MHRA as a blood establishment. Alternative supply options are: coalition partners; host nation support (HNS); and Emergency Donor Panels (EDP). Where HNS is used, quality assurance is fundamental. Transfusion inter-operability and co-ordinating the contribution from each partner is essential for successful planning. Planning includes assessment of the populations at risk, including civilians. The implications of caring for a local population present a number of challenges for transfusion provision including those of patient identification, blood group mix (since ABO distribution varies between populations), support for children, co-morbidity and the need for extended care.

Blood Demand

The current red cell use in Camp Bastion equates to that of a large district general hospital, but there are significant differences. Firstly, the demand for universal components, such as group O RhD negative RCC and group AB FFP, is greater. Secondly, blood is mostly used in the context of trauma, in contrast to civilian practice where 65% of blood is used for medical patients. Despite excellent stock management, ABO and RhD substitutions may be required [1]. Red cell age is emerging as a challenge for blood inventory. Koch et al suggested that transfusion of RCC that had been stored for greater than 14 days may be associated with a significantly increased post-operative complications and survival [43]. Currently, all shock pack RCCs are less than 14 days old. A reduced shelf-life risks shortfall in availability and increased outdating [44].

Cold Chain Management

Blood components are a valuable temperature-sensitive resource that requires carefully monitored transport and storage within specified temperature ranges. Transport packaging must be capable of maintaining the temperature range for blood products from the UK to the end user. One of the significant advances in cold chain capability has been the introduction of a new generation of insulated containers, Golden Hour® (Minnesota sciences and Credo). These, combined with a range of continuous temperature monitoring devices, have revolutionised the management of the three cold chains over the extended Lines of Communication (LOC).

Lyophilised Products

Haemostatic support in the current transfusion protocol is provided by plasma, cryoprecipitate and platelets. However, logistic re-supply to any Role 2 facility is challenging, and frozen materiel is costly and cumbersome to support. Lyophilised or freeze dried products offer 'freedom from frozen' and would lighten the logistic and regulatory burden permitting forward resuscitation. Two products are currently being explored; lyophilised plasma and fibrinogen. Other potential candidates include Prothrombin Complex Concentrates. Lyophilised whole plasma has existed for many years but a commercially available product has only relatively recently become available in Europe [45]. Cryoprecipitate could be replaced by fibrinogen concentrates. Fibrinogen is not identical to cryoprecipitate but it is effective, pathogen-inactivated and provides standardised fibrinogen content [46].

Emergency Donor Panels (EDP)

The EDP is a group of pre-screened volunteer donors who may be called upon at short notice to give fresh whole blood (FWB) or platelets by cell separator (apheresis). All donors are re-screened and tested by POCT at the time of each donation. However, the donation will be used before the results are confirmed in a reference laboratory. There is a risk of transfusion transmitted infection and the usual risks of donation. The benefits must be weighed against those risks. The US approach has been more robust. Over 6000 units of FWB were transfused between March 2003 and July 2007 [47]. It is a medical command decision which has few counterparts in civilian practice. The use of EDP or FWB remains one of the most difficult decisions for the UK deployed medical director (DMD).

Platelet Apheresis

Platelets have a shelf life of 5-7 days and it is an enormous supply challenge to provide a continual supply of platelets to the battlefield. An operational platelet apheresis capability was introduced in early 2008 to support the supply of platelets; the platform is the Haemonetics MCS® (Figure 3). Apheresis permits the collection of plasma and platelets whilst returning the red cells to the donor. Donors can give repeatedly providing a safer pool of repeatedly tested donors. The key part of the capability is the staff, who receive pre-deployment training and competency assessment. The capability has been integrated within the activities of a deployed field hospital but, as apheresis is currently a secondary duty, it may impact on operational workload priorities.

Staff and Training

Massive transfusion is the start point to a resource consuming capability. An individual's knowledge and technical competence have been addressed through a number of operationally focussed courses. Courses such as the Military Operational Surgical Training (MOST) course provide DCR training for teams with a focus on the MTP, Haemostatic Resuscitation and goal directed therapy. The greatest success has been the integration of all aspects of Massive Transfusion, including apheresis, into the collective pre-deployment validation exercises.

Conclusions

Massive Transfusion is credited with contributing to the improved survival of the severely injured. It is, however, one part of a carefully considered and co-ordinated approach to the battlefield casualty. Protocols and practice are based on current evidence and a degree of pragmatism. A rapid response is essential however; one size does not fit all. Trauma may require rapid transfusion but not always 'massive transfusion'. Patients should benefit from a more tailored approach where possible. It is this individualisation that allows massive transfusion and DCR to be bespoke, effective and successful.

Logistic and pathology developments have permitted intensive component support and goal directed therapy. However, the developments have presented an increasing training and logistic burden. Forward operations and future entry operations will require staff to move from the comfort of a trauma centre and go back to basics. Technical solutions such as: portable cold chain devices; light weight near patient testing; the ability to safely collect FWB; lyophilised products and anti-fibrinolytics offer forward haemostatic resuscitation whilst addressing the logistic tail. The key to success will be the continued excellence of frontline care, and the quality of trained personnel throughout the evacuation chain.

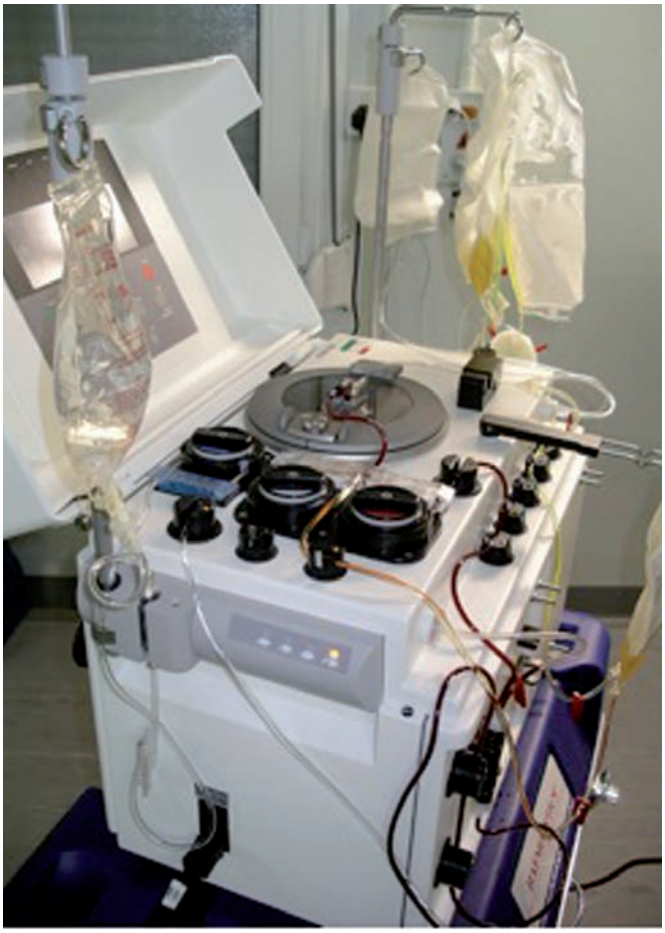

Figure 3. Collection of platelets in the field using the Haemonetics MCS+.

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Lessons Learned . . . on the Jebel Dhofar (Oman) in 1972

Good first aid should be provided by medical orderlies on the ground and by trained helicopter crewmen during casualty evacuation. Every combatant should be trained in the ABC (airway, bleeding, chest) treatments for their friends. A medical officer should be placed on the helicopter when the evacuation time is longer than 1 hour. Strategic positioning of the skilled first-aider with air-ambulance mobility and the ability to perform early airway control with suction, intubation, infusion, occlusion of chest wounds with intercostal drainage and control of external blood loss is paramount. Rapid evacuation saves lives. A helicopter crew on 24hr standby that can be airborne in 2-3 minutes is mandated. Casualty evacuation should be controlled by a simple radio communication net. There must also be a direct link with the incident point and the surgical centre. This allows the surgical team to be called out at the time of casualty notification. Trauma does not respect specialist boundaries. Trauma teams who are immediately available for resuscitation and surgical care (and able to take on management of the patient as a whole) show many intangible benefits. Abnormalities of clotting and fibrinolytic factors will occur but will be difficult to detect. Treat this empirically with fresh blood and fibrinogen infused in a 1:1 ratio. Do not forget to add calcium. Supplement this with fresh frozen plasma if available. If oozing occurs – assume fibrinolysis and treat with epsilon-aminocaproic acid* and be prepared to repeat. Full laboratory support is required. Miniaturization of diagnostic and treatment aids is required to fulfil the requirement for mobility. There must be the ability to place surgical facilities forward of the base hospital.

**An anti-fibrinolytic lysine derivative (C6H13NO2) – a weaker analogue precursor of tranexamic acid (C8H15NO2)*

Melsom MA, Farrar MD, Volkers RC. Battle Casualties. *Ann R Coll Surg Eng* 1975; 56: 289-303

Lessons Learned . . . on Operation CORPORATE (Falkland Islands) in1982

Surgeons and anaesthetists must be physically fit and psychologically able to function under conditions of extreme stress. The South Atlantic experience strengthened the case for greater tri-service co-operation in the training of surgeons and anaesthetists and in the training exercises of forward units. Surgeons must also know field-craft and their Operating Department Practitioner (ODP) team. They must know their equipment and how to look after it. As such a professional army needs professional surgical teams to support its operations worldwide. These surgeons must be able to operate on the head, chest, abdomen and limbs. Scales of equipment can always be improved. Rapid evacuation from the point of injury saves lives; early antibiotic administration prevents infection. The case for specialist care in a base hospital or hospital ship for burns was proven. The appointment of a Consultant Surgeon to the force, with the specific duty of monitoring treatment and outcomes would have provided much valuable information - which is now lost.

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