# BLOOD ISSUES

February 2010, Issue 23 A Transfusion Medicine Newsletter

## Revisiting the Role of Fresh Frozen Plasma in Massive Transfusion Situations

There are a number of definitions of massive transfusion. These include:

- a situation involving the loss of at least one total blood volume within a 24 hour period.
- the loss of 50% of blood volume within a 3 hour period.
- a rate of blood loss of at least 150mL/minute.

Such situations are not uncommon and in larger hospitals in New Zealand might occur several times each week. In some cases the volume of blood lost will be significantly higher and each year a number of patients will receive in excess of 100 units of red cells associated with massive trauma, surgery or post partum haemorrhage.

The British Committee for Standards in Haematology (BCSH) guidelines on the management of massive blood loss identify a number of therapeutic goals. These are:

- Maintenance of tissue perfusion and oxygenation by restoration of blood volume and haemoglobin.
- Arrest of bleeding by treatment of any traumatic, surgical or obstetric source, and
- Judicious use of blood component therapy to correct coagulopathy.

The Blood Bank will play an important role in the management of these clinical situations. Effective and timely communication between Blood Bank and clinical staff will impact significantly on clinical outcomes. Problems with communication undoubtedly leads to poor outcomes. This is particularly important when transfusion requirements are complex with patients requiring a mix of blood components. Blood component support, particularly the thawing of frozen components, takes time to organise.

Recent evidence coming from the treatment of injured soldiers in Iraq and Afghanistan has led to considerable debate on the most appropriate mix of blood components used to treat massive transfusion. This data involves predominantly management of penetrating traumatic injuries arising in battlefield settings. Nonetheless the lessons learned can likely be applied more widely in the management of massive transfusion.

Two particular developments are noteworthy and considered in more detail in this edition of *Blood Issues*. The first development involves a more proactive approach to the use of Fresh Frozen Plasma (FFP) in the early period of transfusion support. Essentially this approach aims to ensure that normal haemostasis is maintained during this period and ensuring that a progressive fall in coagulation factor levels, and platelets, do not contribute to the rate of bleeding. The second development involves the use of Massive Transfusion Protocols (MTP). This provides a system for improving communication between the clinical team responsible for management of the patient and the Blood Bank providing the transfusion support. These two strategies are increasingly being implemented in a number of New Zealand hospitals.

## Improving accessibility to Fresh Frozen Plasma

In many ways fresh whole blood might be considered to be the ideal replacement product in massive transfusion settings. Indeed there is a point of view that the current problems associated with dilutional coagulopathy in this setting are a direct consequence of the removal of whole blood as a standard product. Unfortunately fresh whole blood is not easily available. This is largely due to the fact that testing for blood borne viruses, such as HIV and hepatitis B and C, is needed to improve the safety of the product. This takes time to perform.

Published reports arising from Iraq and Afghanistan indicate that the ratio of blood components transfused during massive transfusion in trauma settings influences overall survival. In particular survival improves as the ratio of units of red cells to plasma transfused gets closer and is likely optimal when this ratio is 1:1. This approach will result in plasma being used earlier and in larger volumes than was the case some years ago. The impact on patient survival of this approach is significant as shown in the graph below (sourced from Borgman et al in the Journal of Trauma Injury, Infection and Critical Care 2007; 63:805-813).

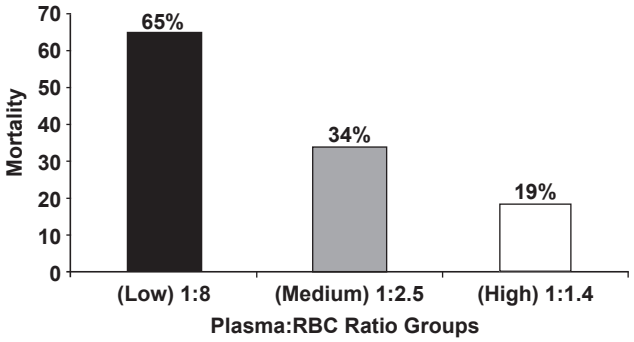


**Fig. 1.** *Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.*

The 1:1 ratio approach brings a number of logistical challenges for the Blood Bank. The key challenge is how to ensure that plasma is available for transfusion as quickly as possible. FFP is stored at or below -25 degrees Celsius. The component is thawed in a water bath prior to being issued for transfusion. This process takes up to 20 minutes – a significant time delay when a patient is bleeding at a rate of 150mL/minute. There are two possible ways to overcome this. Firstly the use of whole blood in the initial response period whilst FFP is being thawed. Other than Factors V and VIII, coagulation factor levels are generally well maintained in stored whole blood. Factor VIII is an acute phase protein and hence unlikely to be a problem when the patient is clinically stressed. Unfortunately at this stage whole blood is not readily available in New Zealand and most other developed countries. It is also worth noting that pre-storage leucodepletion of whole blood, introduced in New Zealand in 2001 and fast becoming an international standard, removes platelets as well as white cells.

The second way is to maintain a stock of thawed FFP so that it is readily available when needed. This works well clinically but is likely to result in significant expiry of unused plasma because the shelf life of the thawed component is currently only 24 hours.

In addition, the need for FFP can dramatically change in the intervening 20 minutes required to thaw the component. Once plasma has thawed and is ready for issue the clinical status of the patient may have altered significantly, either haemostasis has been achieved (bleeding has stopped) or they may have died from the injuries. This leads to an increase in expiry rates of the thawed component. There is an inevitable financial cost to this.

## Can we avoid expiry of thawed FFP?

The relatively short shelf life of thawed FFP means that there will likely be an ongoing expiry of thawed FFP. This will particularly be the case when an individual hospital uses low volumes of the component. There are however a number of ways in which the level of expiry might be reduced.

## Extending the shelf life of thawed FFP

One possible approach to reducing the size of the problem would be to extend the shelf life of the thawed component. However the shelf life is part of the component specification agreed with Medsafe and any change to this will require approval by the regulator. To make this change evidence must be submitted to the regulator to show that an extension of the shelf life will not impact the safety or efficacy of the component. This issue is currently being considered in a number of countries.

The 24 hour shelf life currently used by NZBS is also used in most European countries including the United Kingdom. It is also the standard agreed in Australia between the Australian Red Cross Blood Service and the Therapeutics Goods Administration (TGA). During the last two years the Australasian and New Zealand Society for Blood Transfusion (ANZSBT) has worked closely with key stakeholders in Australia to develop a framework for extending the shelf life of thawed FFP to 5 days. Guidance arising from this process is available on the society website (anzsbt.org.au). The review process recommended the development of a new component called 'Extended Life Plasma'. This recognised that extension of the shelf life does change some of the characteristics and risk profile of the component. The process and recommendations however remain contentious and formal regulatory approval has not been achieved.

The concept of 'Extended Life Plasma' is similar to the 'Thawed Plasma' component available in the United States. NZBS is currently collecting data to support a submission on an extended shelf life for FFP to Medsafe. This process will however take some time. The likelihood of a successful submission will be increased if regulatory authorities in Europe approve the change.

Two main factors will need to be considered when developing a submission to extend the shelf life of the component. The first involves demonstration that prolonged storage of the thawed component does not result in clinically significant reduction in coagulation factor levels. There is considerable international data on this. Nonetheless NZBS will need to provide local data to support any change. The second factor involves demonstration that prolonged storage does not increase the risk of bacterial contamination of the component. Freezing and thawing of the FFP can lead to damage of the plastic container. This can result in pinhole type defects which allow entry of bacteria into the pack. Careful packaging and handling of both the frozen and thawed component are therefore very important.

NZBS is currently undertaking studies to support a submission to Medsafe on this issue. It will however likely be some time before approval is obtained and any agreed changes implemented.

## Group Compatible but not Identical FFP

An alternative method to reduce the level of expiry will be to revisit the rules around blood groups for issue of FFP. Currently most Blood Banks in New Zealand utilise a 'group for group' approach when issuing clinical FFP. Essentially this involves the patient receiving FFP with the same ABO group.

An alternative approach will be to use 'group compatible FFP'. In this scenario the FFP that is provided will be compatible with the patient's blood group but not necessarily of the same ABO group. Compatibility rules for plasma are shown in the table below:

| Recipient blood group | Compatible donor group |
|---|---|
| **O** | **O, A, B, AB** |
| **A** | **A, AB** |
| **B** | **B, AB** |
| **AB** | **AB** |
| ***Either RhD positive or RhD negative can be given safely to all recipients.*** | |

**Table. ABO and RhD Compatible Plasma**

Ideally all clinical FFP would be group AB. This is the universal donor group for FFP since AB FFP contains no ABO antibodies. However only 3-4% of the population is group AB and so this approach will not work well. Group A FFP will however be compatible with around 85% of recipients. Hence a move to an FFP inventory comprising mainly A and AB FFP will increase the likelihood of thawed plasma being reusable in a subsequent patient.

NZBS plans to move to the '*group compatible approach*' when issuing thawed FFP progressively during 2010. Changes are currently being made to donor panels to support the change.

A small stock of group B FFP will continue to be manufactured. This can be used for group B recipients where there is a high likelihood of the FFP being used. This will reduce pressure on the available supplies of group AB FFP. Group O FFP will no longer be produced.

The use of 'group compatible' FFP should reduce expiry of thawed FFP in those hospitals with a moderate to high use of clinical FFP. NZBS is working closely with hospital transfusion committees to ensure that the change does not impact adversely on clinical care.

## Massive Transfusion Protocols

A Massive Transfusion Protocol (MTP) essentially involves a rules based approach to the provision of transfusion support in massive transfusion settings. MTPs are currently in place in Auckland, Counties Manukau and Waikato hospitals. More hospitals are actively considering implementation.

The MTP serves two main functions:

Firstly it overcomes the communication problems between the clinical team managing the patient and the blood bank responsible for providing the components. Responsibility for activating the MTP lies with the clinical team.

Once activated the Blood Bank is informed and a series of actions then follow. This should streamline supply of components in a timely manner. The clinical team request release of components by MTP box number and are responsible for 'standing down' the Blood Bank when the clinical situation is under control. Early results suggest that the system works well and is effective in achieving the goal of improved communication.

Secondly MTPs allow a structured approach to the mix of components used in massive transfusion settings and allow the implementation of a higher ratio of FFP and platelet components.

MTPs currently in use in New Zealand are based on the principle of a 1:1:1 component mix involving red cells, plasma and platelet components. The protocol includes rules for laboratory investigation and allows the content of individual boxes to be changed based on the results of such tests.

A couple of points warrant mention:

- Introduction of MTPs require close co-operation between the clinical teams and the Blood Bank. This is best managed by the Hospital Transfusion Committee (HTC).
- The 1:1:1 ratio is based on components derived from a single whole blood donation. Platelet components available in New Zealand are provided as 'adult therapeutic doses' and are equivalent to platelets obtained from 4-6 whole blood donations. Hence the number of platelet components required will be significantly less than the number of red cell and plasma components.
- MTPs do not remove the requirement to undertake laboratory testing and to modify the transfusion requirements based on results. This is particularly important in post partum haemorrhage settings where close monitoring of fibrinogen levels and early introduction of cryoprecipitate might be needed.

NZBS is highly supportive of the use of MTPs and will be happy to provide appropriate advice and support for their implementation. Considerable benefit will be achieved if a consistent approach to the contents of the MTP boxes can be achieved across DHBs. This will be particularly beneficial when clinical advice is sought from an NZBS Transfusion Medicine Specialist – if we know the contents of the boxes then it will be much easier to provide good clinical advice.

## The Role of the Transfusion Service in the Management of ABO Incompatible Renal Transplantation

In 2008 New Zealand performed its first ABO incompatible renal transplantation. Since then two more cases have been undertaken. The ABO blood group barrier in organ transplantation is now being crossed more often than ever before. Severe donor shortages, as also experienced in other countries, has necessitated this decision. The largest waiting list comprises of blood group O patients. All three ABO incompatible transplants performed to date have been blood group O patients.

The first ABO incompatible renal transplant was reported in 1955. The allograft never showed significant function and the recipient died within 25 days of the transplant. The potential for successful ABO incompatible renal transplantation became a reality when in 1970 Bier and colleagues began to show the potential for therapeutic plasma exchange (TPE) in reducing ABO antibody levels thus prolonging graft survival of porcine kidneys in dogs. Since then further evaluation allowed clinicians to consider TPE as an important component in the management of ABO incompatible renal transplants.

The TPE treatment plan is based on ABO titres with the goal of achieving anti-A and anti-B titres to an acceptable level prior to transplantation. While there are several protocols for TPE to reduce antibody titres, there is a lack of clinical trials to provide a standardized procedure. There is also incomplete understanding of the immunological mechanisms for a temporary reduction of ABO titre to permit organ survival. In the Auckland District Health Board Renal Transplantation protocol a titre of 8 or less is considered acceptable prior to transplantation. The standard is to perform four procedures prior to transplantation. The patients also receive multidrug immunosuppressive therapy. The number of TPE procedures will be influenced by the initial titre and there may be a need to carry out more than the standard four procedures.

The New Zealand Blood Service is responsible for managing the TPE procedure as well as ensuring that pre and post TPE anti-A and anti-B ABO titres are measured to assess the response to the procedure. Transplantation could be postponed or cancelled dependent on the effectiveness of the TPE. Antibody titres are closely monitored post transplant and further procedures may be warranted based on an assessment of the risk of antibody mediated rejection. Although the presence of ABO antibodies leads to hyper acute rejection after ABO incompatible transplantation, a rebound of these antibodies after transplantation still allows the graft to survive and function well. This is called accommodation and the mechanism for this is still uncertain. The titres may also rebound between procedures. Some of this may be from extracellular to intravascular movement of IgG immunoglobulins.

## NZBS Plans Upgrade of the Blood Management System

NZBS is planning an upgrade to Progesa, its 10 year old national blood management system. NZBS is currently preparing a business case for approval to proceed. This will require sign off by both the NZBS Board and the Ministry of Health before it can proceed.

Progesa provides a continuum of information from the donor through to the recipient of the blood product. The system is installed nationally throughout NZBS and in almost every DHB Blood Bank, it manages national and local blood and blood product stocks, and controls the accreditation and selection of blood products for patients.

The initial phase of the project will involve implementation of 'eProgesa', the latest version of the software in a 'like for like' replacement of current functionality. Based on a modern technology platform the new version will address increasing concerns with the resilience and supportability of our current system.

eProgesa will provide a platform for future functional enhancements and increased connectivity with DHB based systems. It also offers a range of new features that will be considered for future implementation to increase the quality of care and patient safety, including:

- Electronic on line ordering of blood and blood products from and by DHB Blood Banks.
- The use of Personal Digital Assistants (PDAs) at the patient's location leading to better control and audit over the process of requesting, supplying and transfusing blood and blood products to patients.
- Electronic donor identification using digital photos, fingerprints and signatures to simplify and improve confidence in donor identification.
- Improved donor queue management to improve the donor experience and reduce waiting times. This should improve donor retention.

NZBS is very aware of the importance of ensuring that any upgrade results in minimal impact on the services provided to hospitals and clinicians. This is reflected in the broad scope of the project.

Implementation of eProgesa is expected to take 18 months to 2 years to complete, reflecting the level of validation required and the number of stakeholders involved.