New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

Internationally two main themes dominate the world of transfusion, these are safety and cost. It is increasingly recognised that the goal of 'zero risk' is not achievable. New technologies and strategies to improve the safety of the blood supply however continue to emerge.

Regulatory authorities in a number of countries continue to promote a pharmaceutical model for Transfusion Services with an emphasis on the implementation of quality systems based on Good Manufacturing Practice (GMP) principles. This undoubtedly contributes to increased safety and effectiveness of blood components. NZBS manufacturing sites are inspected each year by Medsafe GMP auditors. A Licence to Manufacture is issued based on the outcome of such audits.

Numerous studies have demonstrated that potential recipients of blood components expect absolute safety. The process of informed consent should alert potential recipients to the risk associated with transfusion. Ongoing litigation both in New Zealand and other countries with respect to Hepatitis C transmission suggest however that informed consent alone will not necessarily protect against future legal risks.

In this environment the question arises as to how, and by whom, decisions on new safety strategies should be made. NZBS is undoubtedly responsible for ensuring that potential safety initiatives are identified and reviewed. In this context NZBS acts as a 'champion for blood'. Clearly decision making must however take into account other demands on the available health budget. Within New Zealand this is the role of the Ministry of Health.

In this edition of Blood Issues the recommendations arising from the recent stakeholder workshop on vCJD and European Donor Deferral are identified. A group of experts and stakeholders were brought together to consider the issues involved in extending current precautionary measures relating to vCJD and transfusion. The workshop was successful with a series of unanimous recommendations being developed. The process may serve as a template for addressing other potential developments in the future. NZBS is committed to a process of open consultation on issues such as this and will be keen to hear of any suggestions as to how its decision making process might be improved.

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Jehovah's Witness and Refusal of Transfusion

Blood transfusion is unacceptable to most Jehovah's Witness patients and it is a fundamental belief which they are not willing to negotiate. Based on the ethical principal of respect for autonomy, the preference of competent adults to refuse any medical treatment is usually honoured. It is important not to make assumptions about preferences for medical care based on religious belief alone because Jehovah's Witnesses have a range of beliefs regarding the use of blood for transfusion. It is important to respect the wishes of each individual.

Watchtower Bible and Tract Society Council have previously permitted its members to accept products fractionated from blood plasma only but a Spring 2000 ruling permits acceptance of all "primary" components of blood. At present some Jehovah's Witness patients will accept fractionated blood products such as immunoglobulin and coagulation factors but not red cells, FFP or platelets. The Spring 2000 ruling may open doors for products like haemoglobin based oxygen carriers. Pre-deposit of autologous blood is not acceptable to Jehovah's Witness patients but intra-operative red cell salvage and intra-operative haemodilution may be acceptable to some.

In most occasions the decision making process is clear, but there are some situations where it may be extremely difficult. An example is when there are concerns about the validity of an expression of refusal. Only a competent and informed adult can make a legitimate refusal. A similar situation arises when parents refuse medical treatment, including blood transfusions, for their children based on their personal beliefs. Society has the power to safeguard the rights and interests of children by overriding parental preference, however any decision to do this is a serious matter.

A few years back, Great Britain's Association of Anaesthetists issued a guideline to its members that the wishes of patients who are Jehovah's Witness and who do not want to receive blood transfusion must be respected. According to the guideline, administering blood to a patient who has refused it is "unlawful, ethically unacceptable and may lead to a criminal and/or civil proceeding". A properly executed living will should be honoured and each Jehovah's Witness patient should be consulted about what treatment he or she will accept. The guidelines however, do not extend to children who are unable to give competent consent in life-threatening situations, regardless of their parent's directives and in these cases, the guidelines call for the administration of "all life saving treatment".

What We Have Learned From The Management Of Jehovah's Witness Patients

It is of utmost importance that time should not be wasted in convincing Jehovah Witness patients to accept transfusion when an alternative approach could be adopted. It is important to understand that most other forms of medical and surgical interventions are acceptable. A large number of major surgical procedures including heart transplant and cardiopulmonary by-pass have been carried out on Jehovah's Witness patients without the requirement for blood transfusion.

These procedures demonstrated the tolerance of extremely low haemoglobin levels in different situations and that blood loss can be significantly reduced with the appropriate approach. There is no effective alternative to haemoglobin for the carriage of oxygen to the tissues. Synthetic alternatives like Flusol have not been very effective in these situations but haemoglobin solutions that have recently become available in some countries may be acceptable to some Jehovah's Witness patients.

Platelet Transfusion Therapy

Introduction

Platelet transfusion is a well established clinical intervention but despite universal agreement that platelet transfusion is an effective treatment for thrombocytopenic patients, there are controversies about the optimal dose of platelets to use, and the platelet count level at which to transfuse a non-bleeding patient. There are insufficient well designed, randomised, controlled trials which answer these questions properly and enable practice guidelines to be developed which are acceptable to everyone.

In recent years, the increased demand for platelets for transfusion and the recognition of risks associated with platelet transfusion (which include allo-immunisation and disease transmission) has focused our attention on developing an approach for the appropriate use of platelets.

Platelet Transfusion In Bleeding Patients

In 1962, the relationship between platelet count and haemorrhage was documented for the first time in patients with leukaemia. Haemorrhage was not noted until the platelet count fell to less than 50 x 10^9/L and 90% of patients with a platelet count less than 5 x 10^9/L had some form of bleeding. In 1974 a study by Slichter (Clin Hematol 1978;7:5:523) showed that in stable patients blood loss only accelerates when the platelet count falls below 10 x 10^9/L. From this and other published information it can be said that severe life threatening bleeding is common when the count is below 5 x 10^9/L. When the platelet count is between 5-10 x 10^9/L there is an increased risk of spontaneous bleeding and in patients with a platelet count between 10-50 x 10^9/L there is an increased risk of bleeding during haemostatic challenge e.g. surgery or trauma. Most of the current guidelines are based on this information.

A Platelet Dose

A "standard" platelet dose varies from country to country. In USA the figure is usually more than 3 x 10^{11} and in Europe it may be as low as 2.4 x 10^{11}. In New Zealand an average adult dose contains about 3 x 10^{11} platelets. This should increase the platelet count by 20-40 x 10^9/L in a 70kg recipient. Although there is evidence that a higher platelet dose results in greater post-transfusion increments and lengthens the transfusion interval, it does not significantly reduce haemorrhagic events. A dose of 0.6-0.7 x 10^{11}/10kg of body weight has been recommended for stable thrombocytopenic patients but there is no evidence that it is better than smaller, more frequent doses to prevent bleeding.

Pooled vs Single Donor Platelets

A single donor platelet is a platelet dose collected from a single donor using an apheresis machine. It reduces the risk of donor exposure and also has reduced risk of bacterial contamination. A current study has shown that pooled leucodepleted platelets are comparable to leucodepleted apheresis platelets in reducing the rate of HLA-allo-immunisation. When patients are already allo-immunised to HLA, an adult dose of HLA-matched platelets can be collected from a single donor using apheresis procedure.

NHMRC/ASBT Guideline for Platelet Transfusion

In 2001 the National Health and Medical Research Council (NHMRC) and the Australasian Society of Blood Transfusion (ASBT) in co-operation with Royal Colleges and other relevant groups have produced a Clinical Practice Guideline for the use of platelets. A summary of the guideline is given below and a full version of the document is available from NHMRC at: http://www.nhmrc.gov.au.

Transfusion of platelets is appropriate to prevent or control bleeding in patients with a deficient platelet count or deficient platelet function. The platelet count is the primary trigger for use of platelets, with clinical risk factors for bleeding and extent of bleeding.

Use of platelets is likely to be appropriate as prophylaxis in the following situations:

- Bone marrow failure: At a platelet count of <10 x 10^9/L in the absence of risk factors and <20 x 10^9/L in presence of risk factors l(e.g. fever, antibiotics, evidence of systemic haemostatic failure).
- Surgery/Invasive procedure: To maintain platelet count at >50 x 10^9/L. For surgical procedures with high risk of bleeding e.g. neurosurgery, it may be appropriate to maintain at 100 x 10^9/L.
- Platelet function disorders: May be appropriate in acquired or inherited disorders, depending on the clinical features and setting. In this situation the platelet count is not a reliable indicator.

Use of platelets is likely to be appropriate as therapy in following situations:

- Bleeding: May be appropriate in any patient in whom thrombocytopenia is considered a major contributory factor.
- Massive haemorrhage/transfusion: Use should be confined to patients with thrombocytopoenia and/or functional abnormalities who have significant bleeding from this cause. May be appropriate when the platelet count is $<50 \times 10^9$/L ($<100 \times 10^9$/L) in the presence of diffuse microvascular bleeding.

Antenatal and Perinatal Transfusion Medicine 1

Detection of Foetomaternal Haemorrhage (FMH)

It is well known that leakage of foetal blood into the maternal circulation can occur in significant volume throughout pregnancy. In particular, the delivery period represents a time of increased risk of this event. Detection of this haemorrhage and the estimation of its volume, coupled with appropriate treatment have contributed to the dramatic reduction in frequency of occurrence of haemolytic disease of the newborn (HDN) due to RhD antibodies.

In western societies during the 1940s, one in two hundred women developed anti-D and 32 of 100,000 experienced intra-uterine or neonatal deaths due to HDN. There was a 20% foetal death rate in the first affected pregnancy and 40% in subsequent ones. By the 1990s the death rate had dropped to 1.3 in 100,000 with 90% of non-hydropic and 70% of hydropic infants surviving.

The detection of FMH and the accurate estimation of its volume coupled with the judicious use of anti-D for prophylaxis, the advent of smaller families and improved antenatal care have all contributed to the dramatic improvement in outcome for this disease.

Detection of FMH has been shown to be an appropriate investigation in a number of situations:

- The determination of the volume of Rh(D) positive foetal cells transferred to an Rh(D) negative mother.
- The evaluation of foetal well being after maternal trauma.
- The investigation of an unexplained increase in maternal alpha-foetoprotein level.
- The investigation of foetal distress associated with abnormal heart tracings.
- The investigation of intra-uterine foetal death.
- The investigation of unexplained neonatal anaemia.

However, it also has been used inappropriately at times to assist in the diagnosis of placental abruption. In this situation, it has been shown that there is a significant level of false negative results rendering it an unreliable and hence unsafe investigation on which to base clinical decisions.

Like all laboratory tests there are factors surrounding the measurement of FMH that the clinician must bear in mind when interpreting laboratory results. A number of methods can be used to detect and to estimate FMH and its reported incidence varies according to the method used. The skill and expertise required to perform these tests also varies as does the sensitivity and specificity of each method. A clear understanding of the limitations of the available tests is important for clinicians so that results may be interpreted with confidence.

It has been estimated that some degree of FMH occurs at a frequency of 7% in the first trimester, 16% in the second, 29% in the third and 50% at delivery. Indeed the use of highly sensitive fluorescence-activated cell sorting has demonstrated the presence of foetal cells (in very low numbers - mean volume, 0.156ml) in 100% of postpartum women. Increased risk of significant FMH occurs with abortion, ectopic pregnancy, medical interventions (e.g. amniocentesis, external cephalic versions etc), antepartum haemorrhage and maternal trauma. It has been shown that 1 in 1000 women will experience a FMH of >25ml. Also, 50% of FMHs that occur with volumes >15mls do so without known risk factors.

The rationale behind testing for FMH is the detection of cells or products of foetal origin within the maternal circulation. The markers used vary from Haemoglobin-F (foetal haemoglobin), Rh(D) positive red cells, alpha-fetoprotein, and cell nucleus characteristics.

Some are quantitative in character and some qualitative.

Various methods described are as follows:

- Qualitative
  - Micro Du
  - Rosette test
  - Gel agglutination test
- Quantitative
  - Kleihauer-Betke test
  - Flow cytometry
  - FISH (Fluorescence in situ hybridisation) and DNA amplification techniques

All quantitative tests have an unavoidable CV (coefficient of variation) of at least 10% and reporting systems can vary also.

As New Zealand relies heavily on the Kleihauer-Betke test as its basis for clinical practice, the remaining discussion in this article will focus on the strengths and weaknesses of this methodology.

Kleihauer first published his method in 1957. The test employs acid elution of maternal haemoglobin from the maternal red cells resulting in pale 'ghost' cells. The use of counting grids in a microscope allows for a quantitative value for FMH to be derived after a series of mathematical calculations. Because it does not rely upon the Rh phenotype of the mother or infant, it is suitable for assessing antenatal trauma in all pregnant women, not just Rh(D) negative ones.

There is however a fundamental inaccuracy in the use of a test for HbF to assess the volume of FMH.

Maternal HbF-containing cells are known to increase during pregnancy. In approximately 25% of pregnant women, HbF starts to increase after 8 weeks gestation and may reach 7% by 32 weeks. The presence of these maternal HbF-containing cells may give a falsely high assessment of any calculated FMH. Skilled technologists are required to distinguish this situation.

Problems are also encountered in the presence of other conditions associated with high HbF levels, such as hereditary persistence of HbF, sickle cell anaemia, aplastic anaemia and thalassaemia.

Global problems with Kleihauer-Betke method include:

- Marked variation in methods employed - failure of standardisation.
- Operator dependent - requires skilled staff to perform and interpret consistently.
- There is wide CV - up to 150-500% has been reported.
- The method tends to over-estimate FMH.
- Cannot be automated therefore is labour and time intensive.

Sources of error in the method are:

- Test is time, pH, and temperature dependent.
- Variation in thickness of the film can affect results.
- Variation in the number of cells/low power field can affect results.
- Non-staining of some foetal red cells can occur.
- Increased adult F cells can confound the result.

Enrolment by laboratories in External Quality Assurance Programs together with standardisation of methods, internal QC and the training of staff correctly can improve the accuracy and precision of this intrinsically sensitive method. (Sensitive to FMH 0.05%).

WinRho SDF ™

Anti-D (Rho) Immunoglobulin (Human) for Injection

WinRho SDF ™ is a freeze-dried gammaglobulin (IgG) fraction containing antibodies to Rh_o(D). WinRho SDF ™ is prepared from human plasma by an anion-exchange column chromatography method and is used to suppress the immune response of non-sensitised Rh(D) negative individuals who receive Rh(D) positive blood either by foetomaternal haemorrhage during delivery of an Rh(D) positive infant, abortion, following amniocentesis, abdominal trauma or transfusion.

WinRho SDF ™ is manufactured by CangeneCorporation, is distributed by CSL Bioplasma and issued by NZBS in response to requests for Anti-D immunoglobulin.

CSL Bioplasma have notified NZBS that Medsafe has approved a Changed Medicine Notification for this product and the changes relate to an increased volume of 0.9% Sodium Chloride Injection USP in the diluent vial from 2.5 to 8.5ml, as well as changes to the packaging and the labelling of the product. The purpose of the change is to provide a Sodium Chloride product with improved ph stability.

Reconstitution instructions remain the same and the unused portion is discarded. These changes will come into effect as the current product inventory is replaced.

vCJD, Europe and Transfusion

In May this year NZBS held a consultation involving key stakeholders to review recent developments in the US and Canada regarding the extension of precautionary measures to reduce the risk that vCJD might be transmitted by transfusion. The background to the consultation was discussed in the last edition of *Blood Issues* (March 2002).

The consultation process involved a full day workshop. This included presentations by experts from New Zealand and Australia. Stakeholders included the Ministry of Health, Medsafe, the Blood Banking community within New Zealand and Donor Representatives. The two major consumer groups, KIDS Foundation and the Haemophilia Foundation were actively involved with both lay and clinical representatives.

A series of recommendations were developed at the workshop. These are shown below. The recommendations have since been endorsed by the NZBS Board and forwarded to the Minister of Health for approval.

Experts and stakeholders unanimously agreed the following recommendations:

1. NZBS should consider the introduction of additional precautionary measures aimed at further reducing the risk of transmission of vCJD by transfusion of blood and blood products when it is confident that introduction of such measures will not adversely impact on its ability to supply blood components and products in a timely manner. The current analysis indicates that this requirement is not yet in place.

2. The position should continue to be actively monitored and formally reviewed in twelve months, or in the event of significant developments reviewed again as soon as possible.

3. Reinforcement of current precautionary measures should only be considered when effective risk management systems are in place to assure the continued supply of fractionated plasma products. NZBS should take active steps to develop and implement effective risk treatment plans in this area.

4. NZBS should, as a high priority, develop and implement systems to improve plasma collection levels with the aim of establishing a strategic plasma reserve at CSL Bioplasma. This should focus on source plasma collection.

5. NZBS should exclude prospective donors who give a history of transfusion of blood or blood components in the United Kingdom between 1980 and the present so that consistency between geographic exclusion and a history of transfusion is evident.