New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

At the end of January NZBS issued a Medical Alert. This related to a cluster of severe hypotensive reactions in cardiothoracic patients who had received pooled platelet transfusions. The cluster was identified following a routine review of reports of adverse reactions to blood and blood products. The new reporting form introduced during last year is now available at all DHBs in New Zealand. More work will be required to develop a system for national collation of the data emerging from the system. It is however the beginnings of a system for Haemovigilance in New Zealand and as the recent Medical Alert demonstrates it is already producing results. Information on the contents of the Medical alert is available in this edition of Blood Issues, the full alert can be seen on the NZBS Clinical website (www.nzblood.co.nz)

Introduction of the new national transfusion request form is also progressing well. The form is already in use in Waikato, Wellington and Christchurch. A number of other DHBs are planning to implement it. The form contains guidelines on the use of blood components based on those developed by the Australian and New Zealand Society for Blood Transfusion and the Australian NH&MRC. A copy of the form and a link to the Guideline site is also available on the NZBS website.

Production of a New Zealand Handbook of Transfusion Medicine is nearing completion. A final draft will be distributed to Chairs of Hospital Transfusion Committees later this month for comment. It is hoped that a pocket size handbook will be available by the middle of the year. This will provide useful information on blood products and their uses along with information of the services that NZBS provides to hospitals and clinicians.

NZBS is committed to support clinicians in providing high quality products and services for patients. In the near future we will aim to appoint a series of Transfusion Nurse Specialists at key sites to assist with education and audit initiatives. An initial attempt to establish similar positions in 2002 faltered. It was however clear that the role is important and considerable support for progressing the initiative has been apparent. This time round we are better prepared and I believe that we have addressed the problems which were seen last year. These Transfusion Nurse Specialist positions will play a vital role in improving the overall practice of transfusion in New Zealand.

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Transfusion-associated Sepsis

From the early days concern about the sterility of blood was a major issue. In fact, transfusion-associated sepsis (TAS) or reactions that occur during transfusion of blood components contaminated with bacteria are one of the earliest recognized complications of blood transfusion. Inadequate sterilization of reusable glass bottles and giving sets was the main reason for bacterial contamination of blood components.

Introduction of closed systems for blood collection and processing, together with the development of plastic containers and the careful refrigerated storage of blood has dramatically decreased the incidence of TAS. However severe, often fatal reactions due to the transfusion of blood components contaminated with bacteria still do occur and this occurrence may be the most important infective complication of blood transfusion today.

Bacterial contamination can occur with any fresh blood component, including plasma, but the risk of TAS is higher with platelet components. This is probably due to the combined factors of the high storage temperature of platelets which promotes bacterial growth and that the patients who receive platelets are often neutropenic. Platelet transfusion related sepsis is estimated to occur in approximately 1 in 6000 to 1 in 12,000 transfusions. The incidence is much lower for red cell transfusion.

Reported cases of TAS have increased in recent years. This may be partly due to increased awareness of the condition and to the increased usage of platelets. Severe reactions caused by the endotoxins present in components contaminated with gram-negative bacteria are easy to recognise but the much less severe TAS associated with gram-positive cocci which commonly occurs in platelet concentrates may be far more difficult to identify. Numerous studies have indicated that the magnitude of the problem may be far greater than the number of cases reported.

The bacterial contamination rate of cellular blood components varies between 0.05% and 0.5%. The signs and symptoms of TAS overlap with those of non-haemolytic febrile transfusion reactions and haemolytic transfusion reactions. TAS must be considered if any of the following signs and symptoms develop during or soon after transfusion.

- Fever or >1°C increase of recipients temperature from the pre-transfusion value.
- Chill and rigor.
- Tachycardia. Heart rate >120/min or an increase in heart rate by >30/min from pretransfusion value.
- Drop in systolic BP by 30mm Hg or more.
- Vomiting, diarrhoea, nausea, bleeding, shock.

If a Transfusion – associated Sepsis is suspected:

Follow the standard hospital protocol for TAS reactions.

- Suspend the transfusion immediately.
- Collect a blood sample from the recipient and the suspected unit for bacteriological investigation.
- Initiate treatment immediately if the reaction is severe. It may be important to start antibiotic treatment prior to bacteriological confirmation with a broad-spectrum antibiotic coverage eg beta-lactum antibiotic together with an aminoglycoside.
- Provide aggressive supportive care if septic shock occurs.
- Document the incident.
- Inform the Blood Bank who will recall and quarantine all remaining components associated with the implicated unit.

What can Blood Transfusion Services do to reduce this risk?

There are two circumstances that may lead to bacterial contamination of collected blood. Bacteria may be present in the donor's blood in the form of a low level bacteremia or may come from outside the blood stream (from the donor's skin or from another part of the environment.)

Mild transient bacteremia may occur without any apparent reason but more pronounced bacteremia is associated with procedures like dental work and infections like gastroenteritis. For this reason donors are deferred following dental surgery or after an episode of diarrhoea.

Thorough skin preparation procedure before venepuncture prevents contamination by skin flora and leucocyte depletion of all components can significantly reduce the number of bacteria that may be present in the collected blood.

Strict monitoring of the storage temperatures for blood and blood components is essential to reduce the opportunity for organisms to multiply to a high level.

All these measures reduce the risk of TAS but do not eliminate the risk completely. A number of additional measures have been proposed to reduce the risk even further

- Removal of the first aliquot of blood during collection from the donor. This will remove any contaminating bacteria that may come from the skin.
- Pretransfusion testing for the detection of bacteria in blood components. The aim is to identify a contaminated unit before transfusion.
- Decontamination using a variety of anti-bacterial agents.

The New Zealand Blood Service is actively looking at all the options that can be used, but it is unlikely that Transfusion Associated Sepsis will ever be eliminated totally and continuous surveillance of the situation will be necessary.

Medical Alert - Severe hypotensive reactions following Platelet Transfusions

On 24th January 2003 NZBS was informed of a patient who had a severe hypotensive reaction to platelet transfusion following cardiac surgery. The patient subsequently died. A review of adverse reaction reports during this week was undertaken and three further cases with a similar clinical picture were identified. All three of these patients survived.

All four cases involved adult patients who had undergone surgery involving cardiopulmonary bypass. In all cases the transfusion involved pooled platelet preparations and none involved apheresis derived platelets. This is an unusual and worrying cluster of reactions. The reactions appear to be anaphylactic in type. In two of the four patients an elevated Tryptase level was documented and results are awaited in a third case.

NZBS has commenced a review of the clinical and manufacturing details of the cases and to date no clear explanation for the reactions has been identified. Investigations are continuing but may take some weeks to complete. As a precautionary measure, whilst these investigations are being undertaken NZBS has issued an instruction to Blood Banks that apheresis platelet preparations should be provided for perioperative transfusion support of cardiac surgery patients.

NZBS is closely monitoring the situation and Medsafe, the regulator has been informed. Adverse reactions should continue to be reported to your local Blood Bank using the established reporting system.

Zoster Immunoglobulin

NZBS was unable to collect enough plasma from our donors in time to enable CSL to manufacture Zoster Immunoglobulin for replacement of the current stock which expires on 28 February 2003. This necessitated the purchase of supplementary stock from the Australian Red Cross Blood Service. (ARCBS)

The Australian Red Cross Blood Service Zoster Immunoglobulin is manufactured by CSL Ltd from human plasma collected in Australia. It is identical to the NZ product in all respects other than the source plasma.

There are a number of variations from the NZBS product in the packaging, labelling and product information. The salient differences are:

- The ARCBS logo is on the package and product labels.
- The product information states that the product is distributed by ARCBS.
- The barcode on the package is larger than that on the NZBS product and also contains eye readable information.

Please consult your Transfusion Medicine Specialist if you have any queries about this product.

Fibrin Glue – Tissue Sealant

Surgeons have often expressed the need for an adhesive tissue glue. Although normal platelet function and clotting will readily seal most surgical wounds, special problems have demanded special solutions to stop bleeding or to hold tissues together. General, vascular and cardiothoracic surgeons have occasionally needed a product to deal with large areas of traumatised bleeding tissue that cannot easily be dealt with by standard surgical techniques. Others have sought a product to deal with bleeding from arterial suture lines where the tissue is weak, friable and unable to hold sutures well. In these patients, relatively fast blood loss from the tissue persistently washes away activated platelets and the developing blood clot, preventing good haemostasis from being achieved.

Neurosurgeons have requested a product to help with sealing leaks in dura mater. Leakage of cerebrospinal fluid through a surgical or traumatic wound in the dura can be difficult to stop and fibrin glue has been very useful for this purpose. Fibrin glue has also found a special niche in the field of ear surgery. Use of a tiny amount of fibrin glue can sometimes be a simple and useful approach for stabilising a bone in the middle ear without using foreign agents that may lead to scarring.

Blood Services and other manufacturers around the world have often produced a locally devised product to assist surgeons who needed a tissue glue. In New Zealand, the fibrinogen-rich product Cryoprecipitate has been available in some centres so that surgical teams can prepare fibrin glue. NZBS is in the process of producing a standardised guideline for clinicians on the use of Cryoprecipitate for the preparation Fibrin Glue.

Fibrin Glue is prepared by mixing the blood product Cryoprecipitate with an equal volume of Thrombin, a fibrinolytic inhibitor and calcium. The mixture will form a tough clot within seconds. The guideline provides instructions for either a quick-setting Fibrin Glue; clotting within 5 to 10 seconds, or a slow-setting product taking approximately 20-40 seconds to set. These two types of glue are similar in physical strength and other properties. They are designed to meet the different needs of individual surgical situations.

Cryoprecipitate was described in detail in Blood Issues, September 2001, Issue 2. It contains the cold-insoluble proteins present in plasma and is particularly rich in fibrinogen, von Willebrand factor, fibronectin and factor X111. The product supplied in New Zealand is now prepared in individual doses from a single 600ml plasma donation collected with an apheresis machine. As cryoprecipitate is a blood product a small risk exists for transmission of viruses as well as other adverse effects.

The second solution used to prepare Fibrin Glue is prepared from standard pharmaceutical agents licensed as medicines in New Zealand. The main constituent is the blood coagulation enzyme Thrombin. As a human form of thrombin is not available in this country, topical bovine thrombin manufactured from North American (not European) cattle Thrombostat, Parke Davis is used. The concentration of thrombin is adjusted to 20u/ml for the rapid setting fibrin glue or 3 u/ml for the slow-setting formulation.
Calcium is added to the solution to achieve a physiological concentration which will optimise the action of thrombin. A fibrinolytic inhibitor is also added to ensure activity of fibrinolytic activators and plasmin that might cause breakdown of the fibrin glue is minimised and the product remains as a tough tissue sealant until removed by wound healing.

A critical step in using Fibrin Glue is the process for dispensing the product into the wound. The two separate solutions - Cryoprecipitate and Thrombin solution, are drawn up in separate syringes and equal volumes are dispensed and mixed at the site of application. This requires a special applicator to ensure that the volumes delivered are equal and that they are evenly mixed during delivery. A suitable range of dispensers as well as a spray applicator are manufactured by Micromedix (NZ agent: Medtel).

Fibrin Glue must never be injected into blood vessels as it will cause thrombosis. It should also be noted that as the source of thrombin is bovine, many patients will produce an anti - (bovine) thrombin subsequent to application of the glue. This antibody will permanently interfere with the thrombin clotting time test. It will not interfere with the action of human thrombin.

No tissue sealant has proved entirely satisfactory for achieving haemostasis on rapidly bleeding surfaces unless the surgeon can temporarily halt the blood flow for a few seconds and obtain a dry surface on which the Fibrin Glue can gain adhesion. If blood continues to well up from the surface the fibrin will not gain adhesion. Fibrin consists of a meshwork of protein fibres and it depends for its effectiveness on anchoring to adjacent tissues and trapping red cells to prevent further blood leakage.

Warfarin – Managing bleeding and excessive anticoagulation

During Warfarin therapy, loss of anticoagulant control can occur for a variety of reasons. These include accidental overdose, use of one of the drugs known to potentiate its coagulant effect, or as a result of intercurrent illness. In most cases it can be managed by adjusting the Warfarin dose, but if the patient is bleeding or in need of urgent surgery, more active management is necessary. In all such cases, repeat measurement of the patient's International Normalised Ratio (INR) is indicated to measure the effectiveness of the action taken. A doctor trained in haemostasis should be consulted as necessary.

Bleeding while on Warfarin treatment increases significantly if the INR is >5.0. The therapeutic approach will depend on the INR and whether there is major or minor bleeding.

The Consensus Guidelines of the Australian and New Zealand Society of Thrombosis and Haemostasis are:

High INR (>5.0 but less than 9), with no bleeding or minor bleeding

If there is no other risk factor for haemorrhage, withdraw Warfarin for a few days. A prolonged INR may persist for

a few days after Warfarin has been discontinued and it is wise to monitor INR regularly. Restart Warfarin only when INR is <5.0. If there is any risk factor for bleeding (history of bleeding, duodenal ulcer, intracranial bleed, over 70 years of age, epistaxis) give 1.0 - 2.5 mg oral vitamin K. If the INR is still too high after 24 hours a repeat dose of Vitamin K should be given.

High INR (<9.0), with no bleeding

Stop Warfarin and give 5mg Vitamin K, Repeat the INR in 6-12 hrs. Give coagulation factor replacement if there is a high risk of bleeding. Restart Warfarin only when the INR is <5.0.

Major bleeding at any level of INR

Reversal of the Warfarin effect with Vitamin K, prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) is often necessary. The anticoagulant effect can be reversed with PCC in a dose of 50IU Factor 1X/kg.

The PCC product which is available in New Zealand, Prothrombinex, contains Factor 11, 1X and X but not factor V11 and it is necessary to use FFP to provide the missing Factor V11. It should be administered as a slow infusion of 3ml/minute. Alternatively FFP may be used alone at a dose of 12 -15ml or more/kg. Vitamin K in a dose of 5mg by slow intravenous injection should be given with PCC and/or FFP.

PCC may precipitate thrombosis and should be used with caution in patients with underlying Hypercoagulable State. Patients with prosthetic heart valve are at risk of thrombo-embolic problem with full reversal of anticoagulant effect. The degree of reversal must therefore be decided on an individual basis. Whenever possible the cause of bleeding should be identified and treated.

Surgery on Warfarinised patients

For minor surgical procedures, Warfarin should be stopped or the dose adjusted to achieve a target INR of 2.0 on the day of surgery. INR should be checked preoperatively and if the value is less than 2.5, the patient can proceed to surgery.

For major surgery, Warfarin should be stopped at least 3 days before surgery. It usually takes 4 days for the INR to drop to 1.5. For patients with a high risk of thromboembolic event (patient with a metal heart valve, for example), it may be necessary to start heparin when the INR drops below the target range. The timing for restarting Warfarin therapy will depend on the risk of postoperative bleeding.

In an emergency situation administration of Vitamin K (1-2 mg IV) will reduce the INR in about 6 to 8 hours. FFP administered at a dose of 12 - 15 ml/kg will bring a high INR down immediately.

Duration of therapy

The effect of PPC or FFP will last only a few hours. Vitamin K causes more prolonged correction. It is important to monitor the INR regularly to adjust and continue therapy.

Implementation of Progesa

During 1999 NZBS published its plans to establish an integrated national blood service. Central to these plans was the implementation of a national information system. After a rigorous selection process, Progesa, developed by MAK Systems, was chosen as the platform to support the national service. Progesa is used in many countries around the world, and is the most frequently used modular blood management system internationally.

Progesa has been implemented in two main phases by NZBS. The first part involved support for the collection, manufacturing and accreditation processes. The second related to introduction of the patient module, which includes blood banking.

NZBS completed the introduction of the manufacturing processes in November 1999, with all collection sites operational on Progesa by October 2000. Today all blood that is collected, tested and processed in New Zealand is managed through Progesa. The availability of a national BMS has facilitated introduction of Universal Leucodepletion and was beneficial when Nucleic Acid Testing for HIV and HCV was introduced in 2001.

Implementation of Phase Two of Progesa commenced in March 2000. The Progesa patient module is now in use in all NZBS operated blood banks (Christchurch, Otago, Wellington, Palmerston North, Hamilton and Auckland) and a number of DHB operated blood banks (North Shore, Invercargill, New Plymouth, Timaru, Greymouth, Tauranga, Gisborne, Whangarei, Masterton, Hutt, Thames, Whakatane.)

NZBS has been working closely with Mak Systems to ensure that information held in Progesa can be transferred into external laboratory and patient management systems. This was a pre-requisite for implementation of Phase Two Progesa in Waikato and Auckland. NZBS has a working HL7 interface to the Delphic Éclair system that was implemented in May 2002. A number of technical difficulties have been experienced with this solution, however a viable solution is expected shortly.

The intention is to have Progesa completely rolled out to the remaining primary DHB blood banks by June 2003.

Clinical Practice Guidelines

There are a number of websites which contain valuable resources for clinical staff who prescribe and order blood for patients.

www.nhmrc.gov.au - National Health and Medical Research Council of Australia (NHMRC)

www.asbt.org.au - Australasian Society of Blood Transfusion (ASBT)

www.transfusionguidelines.org.uk - UK Blood Transfusion and Tissue Transplantation Guidelines.

www.bcshguidelines.com - British Committee for Standards in Haematology