Blood and transfusion medicine update

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1. National Massive Transfusion Protocol (MTP) design

A group of blood and transfusion representatives from both regional and tertiary hospitals around NZ have been working on standardizing and improving the national MTP algorithm. The aim of this project is to simplify and standardize all MTPs for all health care workers, regardless of location, and to provide a sensible, nationwide MTP. Ultimately, we want to improve communication between blood banks and clinicians, and reduce wastage of blood products.

A one page MTP (for a tertiary hospital) incorporates a standard MTP, a code crimson/red (trauma) MTP and an obstetric MTP.

The changes within this project include –

1. The introduction of a "Stat Pack". This is an initial 2 RBC (normal MTP) or 2 RBC + 2 FFP (code crimson/red MTP), in order to transfuse the patient and provide an opportunity to reassess the situation.
   This is useful because >40% of MTP activations do not go past box 2, and nearly all of these activations at Auckland City Hospital have not had an initial RBC transfusion with a pause and reassess. These statistics are similar amongst other DHBs, and that is why we have instituted these changes.

2. Following the initial transfuse and reassess stage, you will move onto activating the MTP. This will be simplified to Packs 1/2/3:

   Pack 1 2 RBC, 2 FFP
   Pack 2 4 RBC, 4 FFP, 3 cryoprecipitate
   Pack 3 4 RBC, 4 FFP, 1 platelets

   The Obstetrics MTP will receive 3 cryoprecipitate instead of FFP in Pack 1

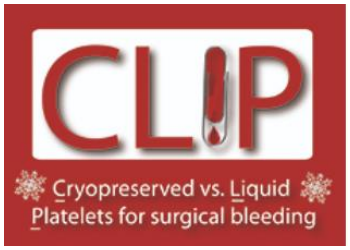
   The code crimson/red MTP will follow the stat pack with alternating Packs 2 and 3 (not Pack 1)

   An example will be included once final professional design is completed

3. There will now be a mandatory "MTP coordinator" when an MTP is activated, who will be a senior clinician, and the point of contact for blood bank. Hospitals will identify this person either by a high visibility vest or a front-of-scrubs sticker (similar to those used in ED during a trauma resuscitation to identify roles).

Successful trauma management is obviously not just about the fine details of blood product ratios and an MTP, but it is rather a coordinated approach to rapid assessment and definitive damage control surgery. While this is occurring, there should be resuscitation with blood products that represent the reconstitution of whole blood with minimal crystalloid administration.

2. Cryopreserved platelets



Platelet transfusion is a life-saving component in the treatment of major bleeding in such scenarios as trauma, major surgery, obstetric emergencies, and acute medical conditions. The main issue with our current formulation of platelets is their short shelf-life of only 7 days. This limits the ability to keep an adequate supply at medium-sized and small hospitals. In addition, almost 30% of platelets are wasted each year because they expire before administration. This not only results in significant financial loss in excess of $5million/year (each bag costs $900), but it is also a discourtesy to platelet donors.

Unlike red blood cells, platelets cannot be refrigerated as this significantly impairs their function, and room temperature storage (RTS) for >7days is limited by the risk of infection.

Unlike refrigeration, and somewhat surprisingly, cryopreservation of platelets at -80°C increases the shelf life to 2 years. If cryopreserved platelets are as safe and effective as liquid-stored platelets, it would allow smaller hospitals to easily provide platelet transfusions, would reduce platelet wastage, and possibly produce better patient outcomes through more effective haemostasis.

There are two clinical trials which are relevant obligatory steps requiring completion before Cryopreserved platelets will be ready for use in NZ.

CLIP-I (NZ) was a pilot study conducted by Auckland City Hospital Cardiovascular ICU Research and the NZ Blood Service (NZBS). This pilot assessed production and distribution logistics, feasibility and safety aspects of cryopreserved platelets (CPS). In addition, the results of the trial were used by NZBS to support the successful product registration of CPS with MEDSAFE.
Over 12 months, 91 patients were enrolled, with 23 receiving platelets (25% of enrolled patients) and they were randomized to either RTS platelets or CPS. There were no differences in outcomes between the groups. CLIP-1 NZ also demonstrated that NZBS was able to manufacture and distribute CPS, and that these platelets were safe for patients. We have submitted CLIP-I (NZ) for publication.

CLIP-II (NZ) will be a multi-centre, blinded, randomized controlled, non-inferiority trial of CPS vs. conventional RTS platelets for the management of post-operative bleeding in patients undergoing cardiac surgery. CLIP-II will be conducted in all 5 cardiac surgery centres in New Zealand. We will need to recruit ~800-900 patients in order to enroll 230 patients (recruitment rate around 25%) in this study.

If this research demonstrates that CPS are not inferior to traditional platelets for the control of major bleeding occurring during cardiac surgery, then their use will be extended to other situations where urgent platelet transfusion is indicated, and they will be made available in hospitals that do not currently keep them on-site.

The research impact includes -

1. Reduction in inequity - patients presenting to smaller or more remote hospitals will have access to platelets in a more-timely manner, so that the latest MTP advice can be followed. This has been shown to improve outcomes in diverse clinical scenarios including trauma, major surgery and obstetric emergencies
2. Significant cost savings
3. Less wastage of donated platelets

3. 4-Factor prothrombin complex concentrates (PCCs) for New Zealand & Australia, & the use of

PCCs in non-warfarin contexts

Australia and New Zealand are the only countries to exclusively have the 3-Factor prothrombin complex concentrate (PCC) *Prothrombinex*. Prothrombinex contains factors II, IX, X, with variable smaller amounts of factor VII, and Heparin 192 iu/vial.

4-Factor PCCs contains factors II, VII, IX, X, and protein S & C. This product will be introduced into NZ towards the end of 2022, replacing our current Prothrombinex.

PCCs are routinely used for reversal of warfarin, however, there is growing evidence for PCCs use in trauma and cardiac surgery.

A recent systematic review of the use of PCCs for the treatment of bleeding in trauma patients, showed that PCCs could be a beneficial adjunct during an MTP, in addition to FFP. In trauma, PCCs combined with FFP have shown reduced mortality when compared to FFP alone. Use of PCCs also lead to a reduction in RBC transfusions, when compared to transfusions with no PCC use. There was no difference in thromboembolic events between the two groups (van den Brink, 2020).

A Cochrane review will be published this year on PCC use in cardiac surgery. Again, this shows a reduction in amount of RBCs transfused, reduction in the incidence of RBC transfusion, and no increased incidence of thrombotic events. At Auckland City Hospital, we now routinely use PCCs in high risk cardiac surgery patients who cannot tolerate the volume associated with FFP transfusion (Hayes, 2020).

4. Cytosorb – for the emergency removal of Ticagrelor and Rivaroxaban

With no available reversal agent for Ticagrelor or Rivaroxaban, there is a significant challenge treating patients taking these drugs who also have life-threatening bleeding (such as upper GI bleeding, intracranial haemorrhage, ruptured abdominal aortic aneurysm, or those requiring emergency cardiac surgery).

Rivaroxaban is not dialysable as it is highly protein-bound (~95%). It will take 4 half-lives (~28 hours, range: 20-36 hours) for Rivaroxaban effect to have decreased by more than 90%, in patients with normal renal function. Clearly, this is too long to wait in a life-threatening bleeding context.

Andexanet Alpha (available in USA) is a specific reversal agent for Rivaroxaban, but it is not available in Australasia, costs over $60,000 for a bolus and small infusion dose, and there are safety concerns regarding its prothrombotic effect. Prothrombinex will only partially reverse the effects of Rivaroxaban.

Ticagrelor is a reversible inhibitor of ADP on platelets, and has no reversal agent available. If any platelets are transfused to a patient on this drug in a bleeding context, these platelets will in turn become inhibited.
A novel way of removing these drugs is using *Cytosorb*. This 300 ml cartridge is filled with porous polymer beads which absorb drugs with a molecule size <60kD. This technique requires placement of a vascath, a dialysing circuit allowing a blood flow of around 150-250 ml/min, and a pump to re-circulate blood.

So far Cytosorb has been successfully used in cardiac surgery (used while on cardiopulmonary bypass)

both in Auckland and Wellington, with approximately 20 patients at each site. This technique provides an option for those extreme cases of life-threatening bleeding caused by these two drugs, where haemorrhage cannot be controlled by other drug, blood, interventional, or surgical means.

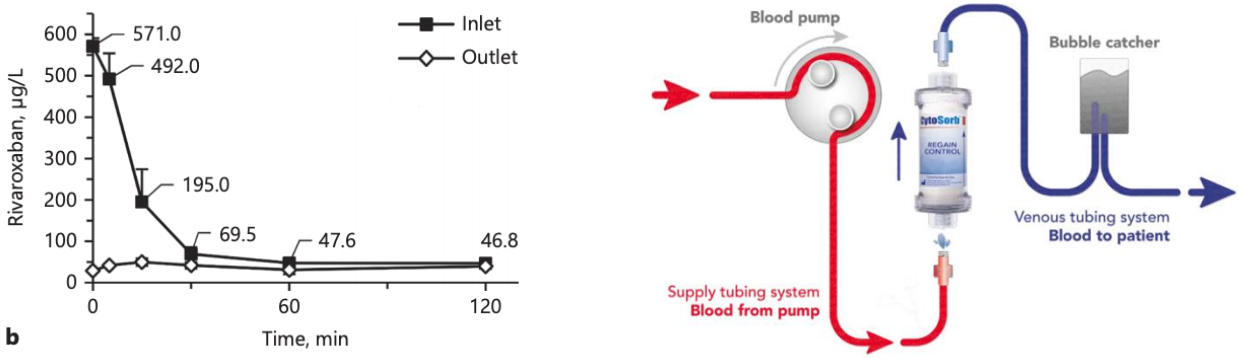


Figure 1 In vitro recirculation model showing inlet/outlet Rivaroxaban plasma concentrations

References:

1. Hayes, K. F. (2020). Prothrombin complex concentrate in cardiac surgery for the treatment of non surgical bleeding. *Cochrane Library*.
2. van den Brink, D. W. (2020;18). Effectiveness of prothrombin complex concentrate for the treatment of bleeding: A systematic review and meta-analysis. *Journal Throbmosis and Haemostasis*, 2457-2467.