Transfusion Update: Bleeding is out, your own blood is in

Emma Patrick

Base Hospital, New Plymouth

The last 4 years have seen a paradigm shift in our approach to managing bleeding and transfusion practice. This brief presentation will aim to look at some of the changes in blood product management and our challenges for the future.

Australasia is at the forefront of a worldwide move towards blood conservation strategies that has seen a steady decline in the use of packed red cells by 8.9% between 2010 and 2012. There appears to be no slowing of this trend in 2014. Research continues to demonstrate that conservative red cell transfusion strategies in the majority of anaemic post-operative patients does not appear to affect outcome in terms of morbidity, recovery or quality of life (So-Osman et al 2012 Blood Transfusion 11:289-95). There are always exceptions to the rule and those with critical and acute ischaemic cardiac states should perhaps be considered for a higher transfusion threshold. Recent publications have looked at transfusion thresholds and outcomes in GI bleeding and again support a conservative policy (2)

Massive transfusion protocols

Massive transfusion protocols (MTP's) have become widespread in their clinical application in the last 4 years. The initial studies by Holcomb examining outcomes from US trauma centres supported early initiation of red cells and coagulation products in severe trauma. Military studies from Iraq and Afghanistan further supported the concept that a 1:1:1 "balanced" transfusion practice in major haemorrhaging trauma appeared to confer a survival benefit.

New evidence suggests there is potential for harm from over transfusion. We need to avoid missing early cues to tailor product selection to target specific coagulation defects. MTPs must be used in association with clinical judgment for the best outcome. The rise of point of care coagulation testing is of great value in this process however it remains in the domain of mostly tertiary centre's so we cannot discard the standard coagulation testing available to the majority of hospitals.

WE still await a true RCT indicating the benefits of 1:1:1 therapy, but the PROMMTT study (13) did show patients with a better than 1:2 ratio of products had a 3-4 times less likelihood of dying than if the ratio less dominated with plasma compared to red cells. The forthcoming publication of the PROPPR study looked prospectively at the different outcomes in fixed ratio options for MTPs. The results could define better what we put in the boxes in future hospital MT protocols.

Fibrinogen appears to have a critical role in the management of massive haemorrhage with the target fibrinogen higher than previously suggested. It appears especially important in the context of massive obstetric haemorrhage.

If fibrinogen is the most important clotting product to support in exsanguination, and we can provide a ready source of it in cryoprecipitate, or fibrinogen concentrate, the question then becomes why not just use that initially to manage the patient until surgical control can be obtained. As fibrinogen concentrate is stable at room temperature, and does not require ABO typing, it offers a different management pathway for massive bleeding. Its' dosing can be controlled by traditional coagulation testing (the Von Clauss fibrinogen level) or integrated into TEG or ROTEM (the functional fibrinogen, FF TEG, or FIBTEM). There is the potential for goal directed therapy using POC devices as a real alternative to the empirical treatment with a MTP providing fixed ratios. Initial studies are encouraging (14), but currently fibrinogen concentrate is not manufactured in Australasia, and the cost of the products is high. Cryoprecipitate in New Zealand is obtained for plasmapheresis from high fibrinogen level donors and provides a high quality source of fibrinogen to use in massive bleeding. One single donor plasmapheresis unit contains up to 1.6G of fibrinogen.

Acute trauma coagulopathy

This appears to have a role in the evolution of acute hypofibrinolysis, leading to early death in severe trauma. A combination of tissue injury and shock appears to drive an endogenous process involving activation of Protein C that promotes early coagulopathy (7). Fewer than 25% of trauma patients will present with ATC and of those, the expected mortality is in the order of 50%. Therefore early detection of coagulopathy, targeted treatment with blood products, early tranexamic acid and careful yet aggressive management of acidosis, thermoregulation and continuing blood loss should be targeted at this cohort of patients.

Tranexamic Acid

Crash 2, MATTERs and MATTERs II study and the forthcoming WOMAN Trial and CRASH 3 provide new information on the role of TXA. Initially designed over 50 years ago for the treatment of post-partum haemorrhage, we have come full circle with tranexamic acid. It has become integrated into routine joint replacement surgery, to reduce intra-operative and post-operative bleeding and is currently being examined for its role in managing post-partum haemorrhage and traumatic intracranial bleeding. Despite ongoing concerns regarding thrombotic events these have not born out in the literature. There is evidence that lower doses at 10mg/kg bolus are sufficient to decrease acute fibrinolysis, and at higher doses it is associated with seizure activity. It should be used at a lower dose and with caution in patients with significant renal failure.

Novel Oral Anti-Coagulants (NOACs)

These agents pose a significant challenge for the acute anaesthetist. Dabigatran is a direct thrombin inhibitor licensed for prevention of thrombotic events due to non-valvular atrial fibrillation. Rivaroxaban and apixaban are factor Xa inhibitors. They are licensed for use in the prevention and treatment of VTE after orthopaedic surgery. Currently neither of these drug classes require ongoing coagulation or therapeutic drug level monitoring according to the guidelines of use. In a small group of patients with AF and acute coronary syndromes we may see patients presenting on triple anti-thrombin therapy: aspirin, clopridrogel and dabigatran or warfarin.

The problems arise in that the group of patients most likely to be prescribed NOACs are precisely those more at risk of renal impairment, advancing age >75, intercurrent illness and polypharmacy leading to drug interactions (i.e aspirin). The benefit of reducing stroke must be weighed up against the risk of bleeding, without anti-dote or reversal available.

With the advent of prothrombinase complexes such as Prothrombinex and Beriplex and clear guidelines on warfarin reversal we have seen a marked drop in the consumption of FFP for acute bleeding in warfarinsed patients and an improvement in their management.

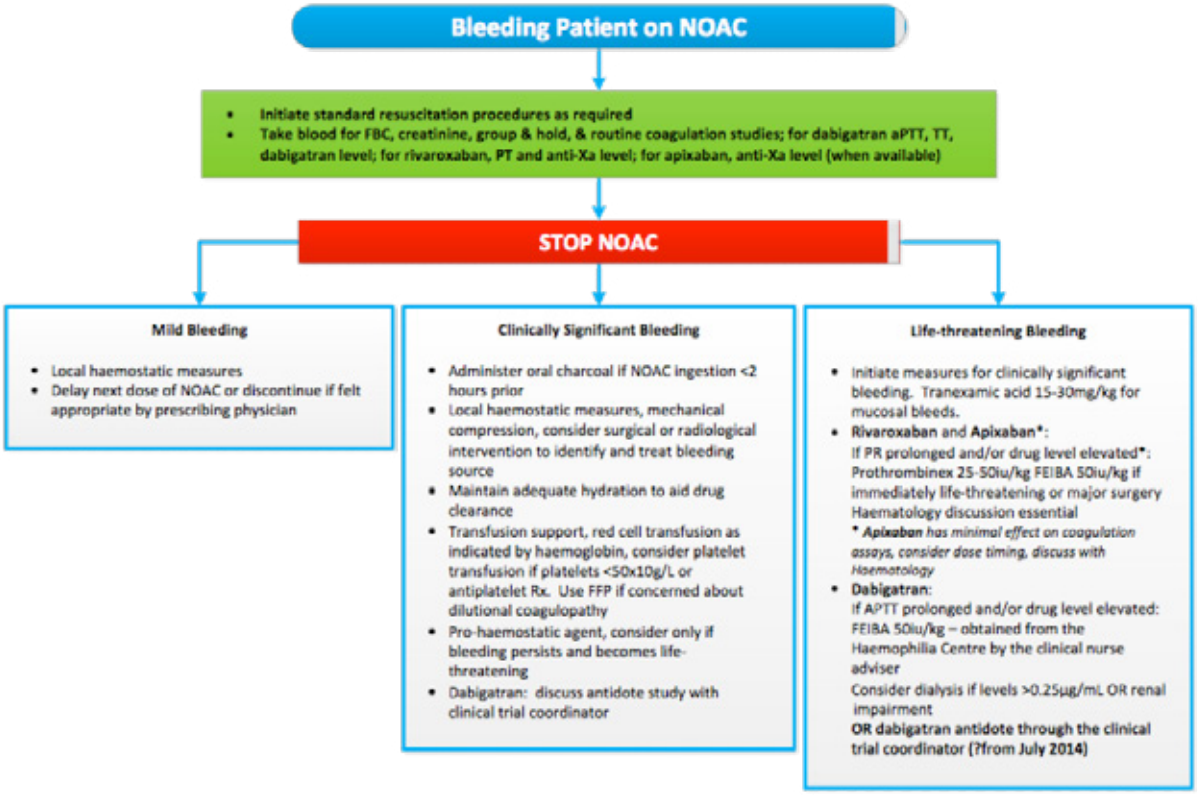
The challenge of managing bleeding patients, or patients requiring emergent surgery on NOACs remain. Monitoring of the residual effects of Dabigatran should include APPT, PR, and thrombin clotting time (TCT or TT). Some labs have the ability to provide a dabigatran level, and anaesthetists should use the APPT, TCT and dabigatran levels in assessing the bleeding potential of invasive procedures. The effect on coagulation factor correlated directly with dabigatran levels. An elevated APPT indicates dabigatran effect, with a linear relationship with dabigatran levels up to 200 ng/ml, and then a flattening of the curve occurs. However a normal APPT cannot assure an absence of dabigatran effect.

The thrombin time (TT) is an assay that assesses the activity of thrombin in plasma. The TT is sensitive to the effects of direct thrombin inhibitors, including dabigatran, and can be used to assess the presence of dabigatran in plasma. A linear relationship between the TT and serum dabigatran concentration has been observed. It is very much more sensitive to the presence of dabigatran and a normal TT (or TCT) indicates a lack of dabigatran effect.

A specific reversal agent is being developed. It is an Fab fraction that selectively competitively binds Dabigatran with a binding affinity many times greater then Thrombin. Reversal of the effects are near immediate. Phase 3 studies are currently ongoing with this agent, including in Australasian centres. The hope is a specific antidote for the reversal of Dabigatran may be available in the next five years. Orphan status has been obtained by the FDA for the accelerated regulatory approval of the drug.

Rivaroxaban has a shorter half-life than dabigatran, is less reliant on renal clearance and it can be monitored using a PT (INR) test, as it increases in a dose dependent manners. It appears that rivaroxaban may be more readily reversed using prothrombinex. A reversal agent is in development, a cyclodextran similar to suggamadex that should reverse the current market anti-Xa drugs.

It appears that transfusion of plasma and platelets is not effective unless for the management of haemorrhage, thrombocytopaenia or dilutional coagulopathy. While we wait for the magic bullet of a reversal agent, there may be some benefit in using 4 Factor prothrombinase complex (Prothrombinex -VF) , activated 4 factor prothrombinase (FEIBA) and activated FVIIa under haematology guidance as these would all be off label use. Activated charcoal can be given if the NOAC has been administered in the last 2 hours. Dialysis is effective at removing dabigatran (65% at 4 hours) . Maintaining a good diuresis is important for the renal excretion of these drugs. These complex cases must engage a multidisciplinary approach between anaesthetist, surgeon, haematologist and cardiologist to ensure the best possible patient outcome.



Resources:

NZ Blood Service Annual Haemovigilance Report 2012. Acknowledgement for graphical data for NZ blood product usage in presentation.

National Blood Authority: www.nba.gov.au

Excellent patient blood management guidelines available for critical care, critical bleeding , perioperative care and medical . Available as a free online resource for ipad and hard copies. Learning CME modules available. Obstetric and paediatric modules on their way.

Blood Safe elearning Australia: www.bloodsafelearning.org.au – useful app for management of Iron deficiency anaemia

HealthObs Ltd. Apps for current NZ guidelines for reversing warfarin and managing patients on dabigatran and Rivaroxiban

Transfusion evidence library. www.transfusionevidencelibrary.com. Comprehensive online database of systemic reviews and RCTs updated monthly. Membership required.

www.nataonline.com Review of recent research with synopsis and critiques of papers.
All aspects of transfusion discussed. Membership required for full access to resources.
Annual conference.

www.canadianthrombosis.org For guidelines on NOAC reversal and summary of current evidence

http://www.escardio.org/communities/ehra/publications/novel-oral-anticoagulants-for-atrial-fibrillation/documents/ehra-noac-practical-execsumm-ehj-2013.pdf European guidelines on NOAC use in AF. Useful charts and management in renal failure.

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