AN INTEGRATED APPROACH TO DAMAGE CONTROL RESUSCITATION

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In the last few years, a new approach has been developed for the massively bleeding trauma patient, called Damage Control resuscitation. This approach involves the use of permissive hypotension, the prevention and aggressive treatment of hypothermia, the reversal of acidosis with bicarbonate or THAM, and early aggressive empirical treatment with blood products in a 1:1:1 ratio. This is all aimed at increasing clotting substrate. With the availability of recombinant factor VIIa, fibrinogen, and recombinant fXIII, the ability to provide adequate substrate for clot in the altered milieu may be possible. In the meantime we rely on plasma, platelets and cryoprecipitate.

Permissive Hypotension in the Bleeding Patient

Fluid resuscitation while definitive surgical treatment is being initiated should preserve vital organ function without increasing bleeding. The questions of how much volume to give, what systolic blood pressure to accept, and which surrogate biochemical endpoints to use, are currently being evaluated.

Following the landmark paper by Bickell et el (1), low volume resuscitation and permissive hypotension became routine in many institutions. It is now believed that increased BP, certainly in pre-theatre pentetrating trauma reverses vasoconstriction, dislodges early thrombus, increases blood loss and causes dilutional coagulopathy and metabolic acidosis. Recommendations (2) now suggest resuscitating to a palpable radial pulse (around 80 mmHg systolic) in soldiers with blunt trauma, and a palpable central pulse (a systolic about 60 mmHg systolic) in penetrating military trauma. If there is no brain injury, clear mentation may be a reliable indicator of adequate perfusion. In the presence of head injury, European guidelines suggest a systolic of 110mmHg , but there are no actual guidelines for optimal blood pressure in the head injured, exsanguinating patient.

An optimal perfusion pressure may be found by sequential measurement of lactate or even sublinguinal capnography, (3) but firm guidelines are not yet available. Certainly lactate should be frequently measured in these patients. Elevated levels predict poor outcome, but minimising the elevation through change in cardiac output has not been shown to improve outcome.

Management of Hypothermia

Although there is interest in the place of therapeutic perioperative hypothermia in brain protection, most people agree that hypothermia in exsanguinating trauma is bad. Multiple studies have shown that hypothermia is a predictor of poor outcome. Management is aimed at increasing ambient temperature, warming fluids and using forced air warmers. A further problem with these patients is that their endogenous thermal heat production is reduced in the state of shock. Although the best way to increase their temperature is to increase cardiac output, this contradicts the above thesis of reducing blood loss.

Importantly, while hypothermia reduces the function of many organ systems, it has a profound effect on coagulation. Experimental models in pigs using cold baths, and in-vivo models, have shown that thrombin production is thermally generated. Hypothermia (by 4 degrees C) impairs the initiation of coagulation (formation of the fVIIa/ tissue factor complex), whereas acidosis affects both this and the propagation of clot. In addition, fibrinogen production is reduced in the presence of hypothermia, and fibrinogen synthesis is reduced and degradation in increased in the presence of acidosis. The effects of acidosis are NOT reversed immediately by bicarbonate or THAM. (4)

The bottom line is that substrate is not available or does not function adequately in the presence of hypothermia and is markedly worsened by acidosis. In such circumstances substrates for clot formation (plasma, platelets and

cryo) need to be supplied, probably at levels above what allows clot to form in non acidotic, normothermic levels. Recombinant factors VII and XIII or fibrinogen concentrate may aid in re-establishing competent clotting systems. Alkaline buffers in in-vitro studies were ineffective.

The Massive Transfusion Protocol

There is a romantic memory of many in trauma management of the days where whole blood was the default resuscitation fluid. While most practitioners seem to find it a logical fluid to use, it was given to selectively to otherwise near dead patients where any fluid would have provided improved results. In World War II and the Korean conflict, due to the misconception over haemoconcentration, colloid was administered and eventually banked blood resuscitation became standard care. Early survival improved, but many casualties subsequently died of acute renal failure.(1) Recognition of the need to resuscitate the intravascular space led to more aggressive crystalloid resuscitation. The use of whole blood resuscitation was lost due to the needs of other areas clinical areas, principally immuno-oncology.

Recently, the focus on mortality associated with bleeding in trauma, has led to a re-evaluation of the place of whole blood. Some transfusion services are unable to rapidly provide sufficient clotting factors for the exsanguinating trauma patient, leading to the development of a refractory factor deficiency and death from uncontrolled haemorrhage. There are several reasons why transfusion services may be overwhelmed by blood product demand and these include the following:

1. Lack of availability of fresh whole blood
2. Delays in the ordering of plasma by clinicians
3. The requirement for coagulation test results to trigger release of plasma and platelets
4. Delayed release of products due to the need to thaw plasma and cryoprecipitate.

A hypothesis has been developed that states that trauma care in patients with massive trauma, and coagulopathy can be improved by using reconstituted whole blood, thus bypassing many of the issues listed above, and allowing rapid transfusion of previously thawed blood and blood products. This is the 1:1:1 concept of resuscitation in massive transfusion.

It is important to recognise that reconstituting packed red cells, with a unit of fresh frozen plasma (250 ml) and a unit of platelets, provides blood with fewer factors and platelets than a unit of whole blood. But it does provide significantly higher platelets and factor levels than most traditional transfusion protocols.

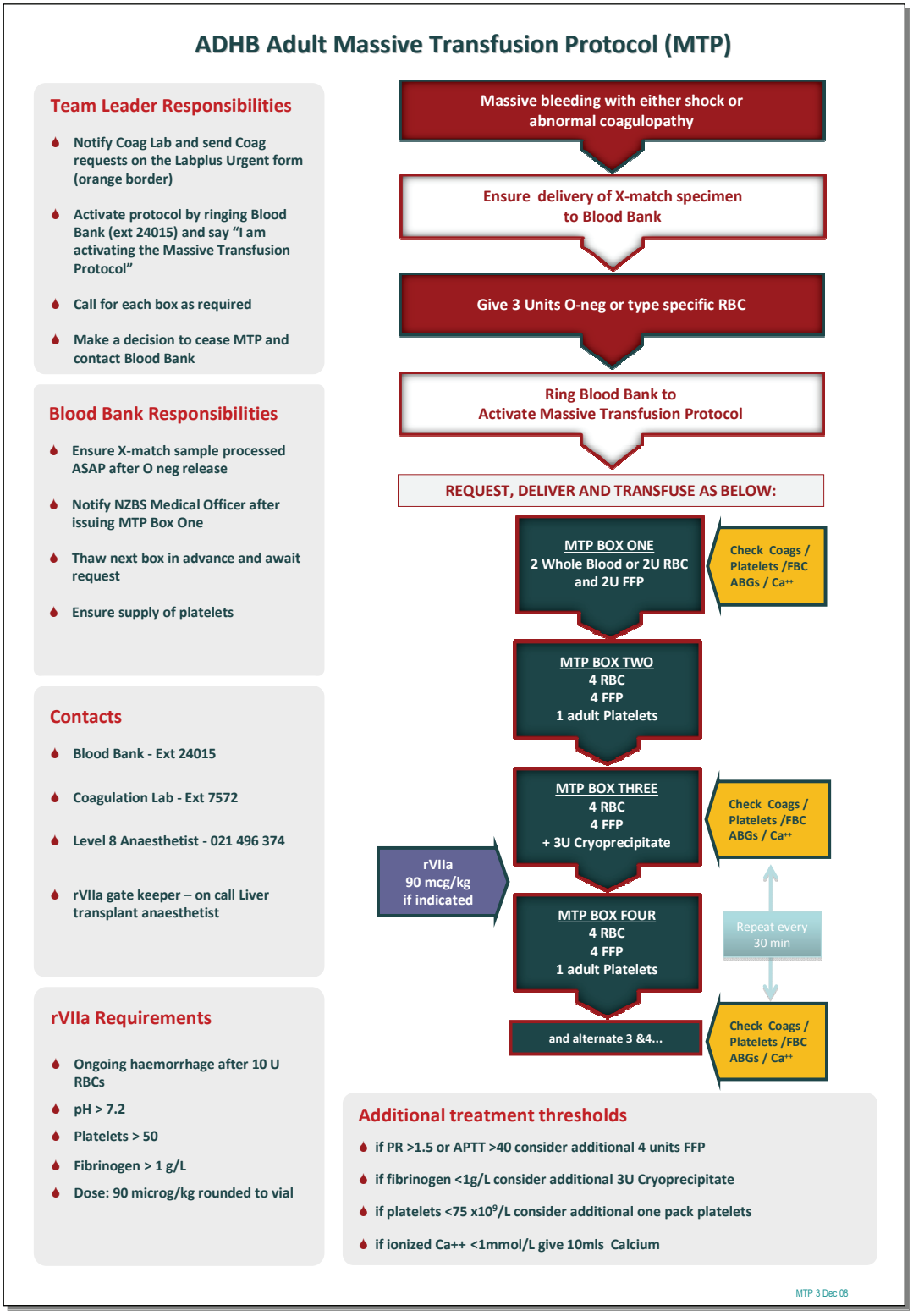
Several other developments have occurred that may improve utilisation of 1:1:1 blood component therapy. Damage control resuscitation accepts a degree of hypovolaemia and hypotension which reduces the volume of fluids given to a patient before surgical intervention. Blood banks are better able to deliver the products required, where in the past such large volumes were needed to resuscitate the patient that crystalloids were often used. Management of hypothermia, acidosis and low cardiac states has improved markedly in the last decade, so now the fluid use can work more effectively. Trauma systems have improved markedly; meaning patients requiring rapid resuscitation arrive in hospital earlier, and receive surgical treatment faster.

The paradigm shift occurred in civilian hospitals in the 1990s with greater availability of plasma for resuscitation of trauma patients. In a retrospective review of trauma patients undergoing emergent surgery at an urban Level I trauma centre, Duchesne and colleagues found a significant mortality difference in patients who were transfused with >10 units of RBCs when plasma accompanied the RBCs in a 1:1, as opposed to 1:4 ratio (26% vs. 87.5%, p=0.0001) (2) A retrospective cohort study of combat casualties in Iraq by Borgman and colleagues (3) studies 246 patients that received either a low (1:8), medium (1:2.5) or high (1:1.4) ratio RBC to FFP. Patient characteristics were similar except that severe thoracic trauma was more prevalent in the low plasma ratio group. In univariate analysis, as the ratio of plasma to RBCs received increased, hospital mortality decreased in an apparent dose-response fashion (65% vs. 34% vs. 19%, p<0.001).

This lead to similar protocols being implemented for civilian trauma hospitals, and more recent studies suggest survival benefits exist when utilising the 1:1:1 protocol. Gunter et al (4) studied survival from civilian trauma before and after the introduction of a Trauma Exsanguination Protocol (TEP). Those receiving FFP;RBC at a ration of 2:3 or greater had a significant reduction in 30 day mortality compared with those that received less than that. (41% vs 62%,p=0.008). The same group (5) analysed a subset of patients and showed reduced total multiorgan failure in the TEP group(16% vs 37%, p=0.001). This group received more intraoperative FFP and platelets, but less

factors were required in the first 24 hrs of in hospital care ($p < 0.01$) They suggest that giving 1:1:1 blood products more aggressively in early trauma bleeding paradoxically reduces the amount needed, by more effectively managing the coagulopathy, and therefore reduces the total immuno-modulatory effect of blood products on the patient. In these studies the volume of crystalloid given reduced from 7L to 4.8L ($p < 0.001$) and the amount of colloid increased (11.0 L to 14.7L, $p= 0.001$).

Included below is the current massive transfusion protocol designed to facilitate timely release of blood products in patients with major bleeding at ADHB. It follows many of the tenants of the policy discussed above. Also included is the current protocol for off label use of fVIIa in trauma. Recent studies have questioned the place of



FVIIa in early trauma related bleeding (4-6 unit RBC loss). At present, there is no indication for early use of FVIIa in trauma. Using it as part of a cocktail to tidy up ongoing non surgical bleeding in trauma patients may have logic but is unsupported by studies. Some authors have suggested placing an embargo on the use of FVIIa in trauma until further studies confirm its place.

So are we seeing the next iteration of the colloid vs crystalloid debate unfolding before us, or are we seeing something special with fresh frozen plasma used early in traumatic coagulopathy? Current studies do not have the power to answer these questions, but newer protocols at least seem to reduce the delay in getting products to the patients that desperately need them.

References

1. Bickell WH, Wall Jr MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:1105–9.
2. Revell M, Greaves I, Porter K. Endpoints for fluid resuscitation in haemorrhagic shock. *J Trauma* 2003;54:S63–7.
3. Søreide E, Deakin CD. Pre-hospital fluid therapy in the critically injured patient— a clinical update. *Injury* 2005;36(9):1001–10.
4. Martini WZ Coagulopathy by Hypothermia and Acidosis: Mechanisms of Thrombin Generation and Fibrinogen Availability. *J Trauma*. 2009;67: 202–209.
5. The next generation in shock resuscitation Moore et al The Lancet 2004 Vol 363 (9425) pp1988-1996.
6. Duchesne JC, Holloway VL, Weintraub SE, *et al*: Review of current blood transfusions strateties in a mature level I trauma center. Were we wrong for the last 60 years? *J Trauma* 2007, 63:481.
7. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB: The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 2007, 63:805-813.
8. Gunter OL, Au BK, Isbell JM, Mowery NT, Young PP, Cotton BA. Optimizing outcomes in damage control resuscitation: Identifying blood product ratios associated with improved survival. J Trauma. 2008;65:526–33.