Transfusion strategies in acute haemorrhage

By Rote or by Rote-m?

Nepean WTET summary 3/11/20

Background and Rationale

- Coagulopathy of trauma is its own pathology; it may be further exacerbated by dilutional (unbalanced transfusion/resus) or consumptive coagulopathies, or by hypothermia / acidosis. Specific features include impaired platelet function, dysfibinogenaemia and hyperfibrinolysis etc
- Many studies have tried to identify optimal methods of resuscitation in these patients from fixed ratio strategies of blood products (1:1:1 vs 1:1:2) vs whole blood vs coags/viscoelastic guided

Advantages and Disadvantages

- Advantages of viscoelastic testing in haemorhage;
    - Bedside test, with continuous access to real time data (do not need to wait for test completion to analyse information being produced)
    - Can inform on clot lysis pathologies – tranexamic acid (TXA) repeated doses
- Disadvantages of viscoelastic testing in haemorrhage
    - Only as good as the interpretation and associated action (flow sheets / local algorrhythm)
    - Requires training (both performing and interpreting)
    - Machine, maintenance and cartridges overall more expensive
    - Formal tests still needed for iCa^{2+}, diagnosis of inhibitors (mixing studies), drugs (levels)

Key studies

- Villanueva 2013 NEJM
    - SS (>6y) RCT; haematemesis, bloody nasogastric (NG) aspirate and/or malaeana; excluded exsanguinating bleeding, acute coronary syndrome (ACS), stroke, transfusion <90d or Rockall score 0 with Hb>12g/dL. Randomised to restrictive (threshold 7g/dL target 7-9/dL) vs liberal (threshold 9g/dL, target 9-11g/dL) transfusion. Stratified by presence/absence of cirrhosis. Gastroscopy <6h. Protocol applied til discharge from hospital or death. N=889
    - Primary outcome rate of death from any cause within 45d; 5% vs 9% (P=0.02) still significant after adjustment for baseline risk factors. Restrictive better in Child-Pugh A/B
    - Death due to unsuccesfully controlled bleeding however was 0.7% vs 3.1% (P=0.001)
    - Re-bleeding lower in restrictive group; 10% vs 16% (P=0.001). Median transfused U 0 vs 3
- Cotton 2013 Ann Surg
    - SS (US level 1 trauma center) RCT; Adults with highest-level trauma activation criteria with evidence of active bleeding requiring uncross-matched blood. Excluded if >4U pre-hospital, moribund (CPR, ED thoracotomy pre randomisation). Due to lack of resources blood group A and A/B excluded. Late addition of excluding severe TBI. Randomsied to modified whole blood (WB) vs standard component therapy (PRBC, FFP, plts). Remained on protocol til declaration of haemostasis, death or withdrawl, up to 24h. All blood leucoreduced; as this renders platelets nonfunctional, for every 6U WB (as per PRBC) 1 pool apheresis plts. N=107
    - Primary outcome; 24h blood product use; no difference between RBC, FFP, plt use
    - Excluding TBI patients (N=67); significantly less total products with WB (11 vs 16U, P=0.02)

- PROMMTT 2013 JAMA surg
    - Prospective cohort (10 US level 1 trauma); highest level trauma activation and transfused =/>1U RBC <6h. Looked to establish relationship between early and higher ratio FFP/plt:RBC and outcome. N=1245 (and N=905 for 3U of RBC/FFP/plt)
    - Higher ratios of FFP:RBC and Plt:RBC were independently associated with reduced 6h mortality (mostly haemorrhagic death). Ratios <1:2 were 3-4x more likely to die that those with ratios =/>1:1. This is not upheld beyond 24h
- PROPPR 2015 JAMA
    - MC (12 level 1 trauma centers) RCT; Patients meeting highest level trauma activation randomised to FFP:plt:RBC ratio of 1:1:1 vs 1:1:2 (NB 6U of platelets in 1 pool, therefore 1:1:1 boxes contained 6 FFP, 1 'pool' of platelets and 6 RBC and 1:1:2 boxes contained 3U FFP, no platelets in first box and 6 RBC – platelets would be given first from second box). Order of delivery specified (alternate). N=669
    - Primary outcome; absolute % group differences for 24h and 30d mortality; no significant mortality difference at 24h (12.7% vs 17.0%, -4.2%, 95% CI -9.6% to 1.1%, P=0.12) or at 30d (22.4% vs 26.1%, -3.7%, 95% CI -10.2% to 2.7%, P=0.26)
    - Similar amounts of RBC given. More patients in 1:1:1 group achieved haemostasis (86.1% vs 78.1%, P=0.006)
- Gonzalez 2016 Ann Surg
    - SS (level 1 US trauma center) RCT; Injury requiring massive transfusion protocol (MTP) activation on arrival to hospital based on Resus Outcome Consortium criteria (BPs<70mmHg or BPs 70-90mmHg with HR=/>108/min). Excluded if penetrating torso, unstable pelvic fracture or multisite bleeding. Randomised (based on weekly rotation of transfusion strategy) to viscoelastic (TEG) vs conventional coagulation tests, CCT (INR, PTT, fibrinogen, d-dimer) guided transfusion. Platelet count was available to both groups as part of CBC (FBC) and coagulation tests though checked in TEG group, clinicians were blinded to results. MTP included on activation 4U O-ve RBC, 2 FFP). Transfusion response to results was protocolised for both arms. D-dimer or LY30 would determine tranexamic acid (TXA). N=111
    - Primary outcome; 28d survival; significantly higher in TEG group (P=0.032). Death 19.6% vs 36.4%, P=0.049)
- ITACTIC 2020 Intensive Care Med
    - MC RCT; Trauma requiring MTP activation (as per local protocol). Randomisation window <3h of injury and <1h arrival to ED. Randomised 1:1 into viscoelastic haemostatic assays, VHA (rTEG or RoTEM) vs CCT. TXA to all. Blood drawn for testing at baseline and after 4U RBC; haemostatic therapy delivered based on results as per study algorithm. N=396
    - Primary outcome; proportion of patients at 24h alive and free of massive transfusion; 67% vs 64%, OR 1.15, 95% CI 0.76-1.73
    - Cause of death uncontrolled bleeding 25% vs 30%. Thromboembolic events 15% vs 24%

Summary (my practice)

- As with many things in medicine, an investigation will only be associated with a benefit if tied to an appropriate intervention. It is still unclear exactly what values we should target irrespective of test (conventional laboratory vs viscoelastic) and this is reflected in local protocols;
    - In both conventional and viscoelastic arms, interventions were more aggressive in ITACTIC than Gondalez study (as an example ITACTIC would treat INR >1.2 whereas Gondalez =/>1.5)
    - More aggressive administration of clotting products might have meant the prolonged time to results of conventional clotting tests were better tolerated (trend to over-treating?)
- If there is ongoing uncontrolled haemorrhage, medical 'optimisation' is failing and the need for surgical or radiological interventions should be re-reviewed; haemostatic resuscitation is not a substitute for damage control (+/- definitive) surgery. It is important to not forget the role of iCa2+, avoiding hypothermia and giving 2nd dose TXA (unless contraindicated) in major trauma also
- There seems to be no advantage of giving whole blood in a hospital setting. I use a 1:1:1 ratio