Blood Matters

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"The most valuable blood for your patient is their own blood" [1]

Blood management starts pre-operatively with consideration of optimising red cell mass, intra-operatively by applying processes to minimise blood loss and post-operatively optimising the ability to tolerate anaemia.
Each individual patient should be evaluated to identify opportunities at every stage to support blood management and ensure they are fully optimised. Blood is a valuable commodity, and we should value the sacrifice made by donors that support the availability of products to ensure patients have a safe surgical journey.
The decision to transfuse should not be taken lightly. In addition to blood being a valuable product it does come with risks to our patients. Having processes in place to modify this risk is very important.
The main predictor for perioperative transfusion is preoperative anaemia, volume of surgical blood loss and failure to adopt a more restrictive threshold for transfusion.

The concept of *patient blood management* (PBM) introduced by the World Health Organisation (WHO) in 2011 is a systematic, evidence-based approach focused on patient requirements such as achieving the highest patient care, weighing the benefits of transfusion against the risk, with minimal transfusion-related adverse events.
Strategies to address these risks are referred to as the three pillars of PBM.
Reducing perioperative blood loss requires a multimodal and multidisciplinary approach. Although high-quality evidence exists in certain areas, the overall evidence base for reducing intraoperative blood loss remains limited.

Limiting transfusion in cancer surgery may matter too....
Perioperative factors and updates for specific situations:
Optimising iron

- pre-operative use of iron has now been well established therefore moving the spotlight or focus to post-operative anaemia for this discussion.

Post-operative IV iron to treat anaemia.
Diagnosis of postoperative iron deficiency can be even more difficult than that of preoperative deficiency since ferritin levels may be elevated as part of the acute phase response after surgery [2]

Post operative anaemia [2 & 3]
Evidence is scant, though as reference a consensus statement from workgroup of experts was published to help guide some decision making [2]:

Recommendations for best clinical practice:
All patients who have undergone major surgery (defined as blood loss > 500 ml or lasting > 2 h) and who had pre-operative anaemia or moderate-to-severe blood loss during surgery must be screened for anaemia after surgery.
Postoperative anaemia may be present in up to 80–90% of patients undergoing major surgery, although this prevalence varies widely according to different definitions.

Perioperative anaemia in non-pregnant women should be defined, as for men, as a haemoglobin concentration < 130 g.l.
During recovery from uncomplicated major surgery, haemoglobin concentrations should be monitored, either by standard laboratory or point-of-care testing, on a regular daily basis, at least until the third postoperative day, to detect anaemia.
Postoperatively, iron deficiency should be defined by ferritin concentration < 100 μg.l−1, ferritin < 100–300 μg.l−1 and transferrin saturation < 20%, or reticulocyte haemoglobin (ret-he) content < 28 pg. Though the value of ret-he is more useful in monitoring EPO use in setting of renal failure (the STfR takes longer), neither is perfect, but it is a good place to start. Its use is encouraged for review of pre-operative intravenous iron and in the post-operative setting where ferritin may be less useful. High blood loss during surgery may also indicate the need for iron replacement in anaemic patients. In the postoperative period, when the administration of iron is necessary, early intravenous (i.v.) iron therapy is recommended, after considering contraindications. Where possible, it should be administered using a single high-dose preparation for the repletion of iron stores.

For non-cancer patients with severe postoperative anaemia and inflammation-induced blunted erythropoiesis, or those declining blood transfusion, consider additional treatment with an erythropoiesis-stimulating agent.
If patient blood management measures did not prevent the development of severe postoperative anaemia, the adoption of a restrictive transfusion threshold (haemoglobin level: 70–80 g.l−1, depending on patient comorbidities) is recommended in most adult, clinically stable hospitalised patients.

Recommendation to establish a patient blood management expert group in every hospital [4]

Consideration of post-operative Iron. Intravenous (IV) iron treatment is recommended in postoperative patients because oral iron is limited by its poor absorption and frequent intolerance.

Most benefit is seen in patients with pre-existing iron deficiency anaemia not treated pre-operatively. Although multifactorial in origin, pre-operative anaemia, peri-operative blood loss (surgical bleeding, coagulopathy, phlebotomies, etc) and postoperative blunted erythropoiesis are the main contributing factors to postoperative anaemia after major surgery. Haemodilution due to excessive fluid administration, which may cause ‘dilutional’ anaemia or aggravate pre-existing anaemia, and other nutritional deficiencies (e.g. vitamin B12, folic acid) and pharmacological interactions are also contributing factors.
Iron therapy: oral vs. i.v. iron?

The National Institute for Health and Care Excellence in the UK (NICE) recommends offering oral iron after surgery to patients with iron deficiency anaemia. However, in the postoperative period, oral iron is often not tolerated or absorbed and has several limitations including frequent gastro-intestinal side-effects and, consequently, poor treatment adherence. Additionally, the inflammatory response induced by surgery stimulates hepcidin synthesis and release, which in turn inhibits intestinal iron absorption, making oral iron therapy largely ineffective. Various randomised placebo-controlled trials (RCT) in orthopaedic and cardiac surgery patients have demonstrated that oral iron therapy was not better than placebo in correcting postoperative anaemia and reducing transfusion requirements [3].

The ability of hepcidin to down-regulate ferroportin from the cell surface not only provides a

molecular explanation for the regulation of iron homeostasis but also helps to explain the coordinated response producing the hypoferremia of inflammation and infection [6].

Manage anaemia or threshold for tolerating anaemia to avoid blood transfusion. Lessons learned from Jehovah's Witness management has helped in this domain. Cross over in this section with treatment of anaemia with optimising Iron, treatment of other nutritional deficiencies e.g Vit B12 and folate, supporting erythropoiesis and EPO treatment when indicated [3].

Iatrogenic loss: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8470754/

During a hospital stay, 25% of patients develop relevant anaemia. This is called Hospital-Acquired Anaemia (HAA). It is very common that patients having normal haemoglobin values upon admission develop anemia over the course of hospitalisation. The incidence ranges from approximately 25–75% prior to discharge using the nadir haemoglobin values during hospitalisation. Potential aetiologies for HAA are iatrogenic blood loss from phlebotomy or "anaemia of chronic disease" induced by acute phase reactions stimulated by interleukins activating hepcidin synthesis. HAA has been postulated to be a hazard of hospitalisation that is potentially preventable. Early diagnostic of anaemia in critical care units is needed, to differentiate between HAA and other causes of anaemia.

Consideration of side effects for all treatments needs to be considered. Ferrinject does potentially cause hypophosphatamia though the clinical significance of this is likely low [7].

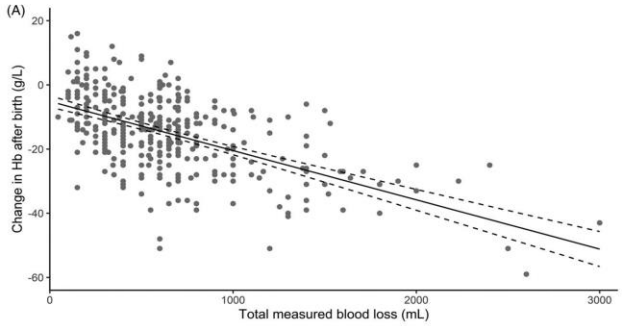
Tranexamic acid [8]:
Interest in tranexamic acid ballooned in recent years after publications of specifically CRASH-2, WOMAN and POISE-3 trials. Development of interest was slow considering that it's use was first recognised by two Japanese doctors Drs Utako and Shosuke Okamoto shortly after World War 2 ended. The initial drive for development was to help prevent women bleeding to death due to post-partum haemorrhage which was a major killer of women in Japan at the time. They invented a new chemical entity called Epsilon-aminocaproic acid (EACA) that inhibited the enzymatic breakdown of fibrin by plasmin in 1962. Tranexamic (more potent) was developed later by them though its full potential was not recognized for decades. Initially adopted mostly by dentist in the first instance it's use slowly crept into current practice. Poise-3 reported that tranexamic acid reduces major bleeding by 25% and reduces the need for blood transfusion, without the risk of thromboembolic events. Wider TXA acid use will improve surgical safety, avoid unnecessary blood use, reduce the risk of transfusion and save funds for other health care purposes. Recommend TXA should be considered in all adults having in-patient surgery.

ATACAS trial found TXA also reduces the risk of reoperation because of major bleeding and reduced receipt of a blood transfusion.

Elective TXA (most benefit urological procedures i.e prostatectomies and orthopaedic surgery i.e. hip and knee surgery) is now commonly used.

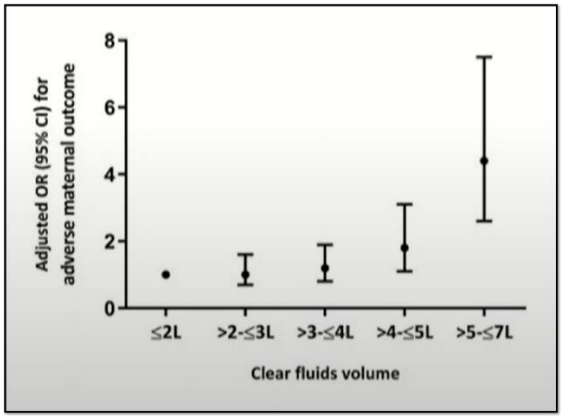
The only trial that was adequately powered for primary safety outcomes is POISE-3 though not achieved non-inferiority to placebo but stated that there is 96% probability it is safe to use as indicated [9].
New in obstetric bleeding?
Quantitative blood loss (QBL) is moderately correlated with adjusted change in Hb for all volumes of

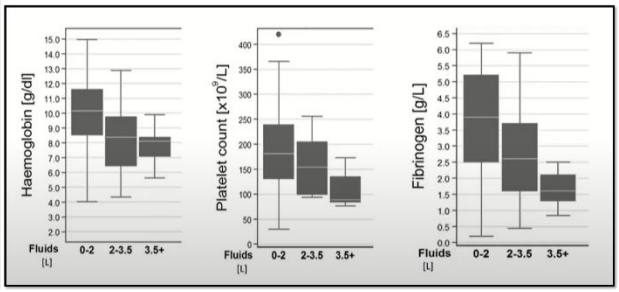
bleeding and gives clinicians more accurate knowledge of blood loss than visual estimation. This low-cost, low-fidelity intervention can influence the timely escalation of clinical care and therefore patient outcome [10].



15 g/L drop in Hb per 1000mls of blood loss.

Dilutional factors … excessive crystalloid fluid therapy?
Clear fluids volume >4 L was independently associated with adverse maternal outcome in women with persistent postpartum haemorrhage [11 & 12].





Calcium as a factor [13]?

Among high-risk patients with PPH low Ca^{2+} at PPH diagnosis was associated with a higher risk for severe bleeding independently of other laboratory and clinical indicators. Thus, Ca^{2+}, as a standalone parameter or when combined with fibrinogen level, can aid in identifying women with high-risk PPH.

Furthermore calcium may play a role in uterine contraction…[14]
Trauma bleeding (Credit to Dr Nadia Forbes for summaries)
MHP, what is new?
ITACTIC[15]

Summary: Study to inform whether using point-of-care coagulation testing, referred to in the paper as viscoelastic haemostatic assays (VHA) to direct massive haemorrhage protocol use, as opposed

to standard practice (conventional coagulation tests, CCT) would improve mortality and reduce the need for massive transfusion (10+ units of blood in the first 24h after injury).

Outcomes • Primary: No difference in mortality at 24hrs: 67% vs 64% (95% CI 0.76-1.73) • Secondary outcomes: No significant difference in 28day mortality or median time to haemostasis • Subgroup Analysis: Significant reduction in 28-day mortality in severe TBI group (44% vs 74%) p=0.016
And Coagulopathic (by PTr) patients: CCT 55%; VHA 41% OR: 0.56 (0.26-1.24) (note not powered to detect these differences though)

CRYOSTAT 2 [16]
Does transfusion of early and empirical high-dose cryoprecipitate in addition to standard care improve survival in bleeding patients with trauma who require activation of a major haemorrhage protocol?

RCT at 26 UK and USA trauma centres of adult traumas who triggered MHP • Standard care (MHP) vs MHP plus 3 pools cryo (6g fib) within 90 min Outcomes • Primary: No difference in 28 day mortality (26.1% vs 25.3%) • Secondary: No difference in mortality at 6 hrs (7.1% vs 8.6%) or 24hrs (11.2 vs 12.2%) • Secondary: No difference in proportion of deaths from bleeding at 6 or 24hrs • Prespecified subgroup analysis of pt. penetrating trauma, 28 day mortality was significantly HIGHER for the cryo group (16.2% vs 10%; OR 1.74 (95% CI 1.2-2.51) P=0.006

The results from this trial do not support empiric cryoprecipitate therapy in trauma patients with major haemorrhage

PATCH [17]
In adult patients with major trauma, who are at risk for trauma-induced coagulopathy does early administration of 1g of tranexamic acid (TXA) followed by an infusion of 1g over 8 hours, compared with placebo, increase survival with a favourable functional outcome at 6 months?

Pragmatic, double blinded, placebo-controlled trial .36 trauma centres in Australia, NZ and Germany. Adult pt. assessed as high risk of coagulopathy (COAST score >3)
• 1g TXA at scene and 1g over next 8hrs vs placebo Outcomes
• Primary: No significant difference in survival with a favourable functional outcome at 6 months (GOS-E>5) • Secondary:

Significant reduction in mortality at 24hrs (9.7% vs 14.1%) and 28 days (17.3 vs 21.8%) but no difference in mortality at 6-months

Among adults with major trauma and suspected trauma-induced coagulopathy who were being treated in advanced trauma systems, prehospital administration of tranexamic acid followed by an infusion over 8 hours did not result in a greater number of patients surviving with a favourable functional outcome at 6 months than placebo, though mortality was significantly reduced at 24 hours and at 28 days in the TXA group.

PROCOAG
Double blinded, randomised, placebo-controlled superiority trial in 12 French level 1 trauma centres
• Adult trauma pt. at risk of massive haemorrhage • 1ml/kg of 4F PCC vs 1ml/kg saline Outcomes •

Primary: No significant difference 24hour blood product consumption (12u vs 11u) P=0.72
• Secondary: Significant increase in thromboembolic events (Arterial and Venous) 35% vs 24%: RR 1.48 (95% CI 1.04-2.1) P=0.03
RePHILL[18]

THE BACKGROUND • Early transfusion in traumatic haemorrhage increasingly moving to the pre-hospital space
• Two RCT's of pre- hospital plasma in traumatic haemorrhagic shock with discordant results:
• PAMPER (2018) 2u FFP vs crystalloid. Lower 30day mortality (23% vs 30%) p<0.05 and lower admission INR. (largely blunt with long transport times)
• COMBAT (2018) 2u FFP vs crystalloid. No difference 28day mortality (15% vs 10%) p>0.05 (v short transport times: mean 16 min)

Multicenter RCT: 4 prehospital services in UK in adult trauma pt. with systolic < 90mmHg • Prehospital administration of 2u RBC's and 2u Lyoplas (Lyophilised (Freeze dried) plasma vs 4 250ml bags NaCl • No significant difference in mortality (43% vs 45%) • No difference in failure to clear lactate (50% vs 55%) vital signs, or INR on arrival to ED • Did however have higher Hb on arrival (133g/L vs 118g/L) p< 0.0001 • Did receive higher total of blood products at 24hrs - RBC 6.34 vs 4.42 (p=00.4) - Plasma 5.04 vs 3.37 (p=0.002)

TORRES ET AL: 2023 [19]
• Retrospective Cohort of 2785pt with severe haemorrhagic shock from American College of Surgeons T-QIP database • Looked at whole blood adjunct MHP (WB-MHP) vs standard component based (CT-MHP) Outcomes • Lower 24hr mortality (HR 0.63; CI 0.41-0.96; P=0.03) • Lower 30day mortality (HR 0.53; 95% CI 0.31-0.93; P=0.02)
Cancer and blood [20]

Impact of transfusion worth considering perioperatively.
Other interesting blood related titbits
Waste of blood[21]
Making every drop count: reducing wastage of a novel blood component for transfusion of trauma patients.

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