

Perioperative blood management

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ABSTRACT

Perioperative anaemia and allogenic blood transfusion (ABT) are known to increase the risk of adverse clinical outcomes. The quality, cost and availability of blood components are also major limitations with regard to ABT. Perioperative patient blood management (PBM) strategies should be aimed at minimizing and improving utilization of blood components. The goals of PBM are adequate preoperative evaluation and optimization of haemoglobin and bleeding parameters, techniques to minimize blood loss, blood conservation technologies and use of transfusion guidelines with targeted therapy. Attention to these details can help in cost reduction and improved patient outcome.

Key words: Anaemia, blood conservation, cell salvage, patient blood management, perioperative

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INTRODUCTION

Traditionally, blood transfusion (BT) has been the common therapeutic intervention and mainstay for treating perioperative anaemia and surgical blood loss. Anaemia in acute and chronic condition is associated with increased risk of morbidity and mortality.^[1] Pathophysiology of anaemia and transfusion in the perioperative period is complex and incompletely understood.^[2] The existing therapies for the same have not produced any demonstrable improvement in outcome.^[3] The morbidity and mortality associated with BT are attributed to increased susceptibility and transmission of infections, transfusion reactions, altered immune response, circulatory overload, transfusion-related acute lung injury, with resultant longer hospital stay and increased costs.^[1,4] Also there is over utilization of components of blood leading to growing gap between supply and demand.^[5] Both anaemia and BT have been identified as predictors of adverse outcome and may be effectively addressed by utilization of multimodal perioperative patient blood management (PBM) strategies.^[6]

Patient blood management is currently defined by the Society for the Advancement of Blood Management

(available at <http://www.sabm.org>) as “the timely application of evidence based medical and surgical concepts designed to maintain haemoglobin (Hb), optimize haemostasis and minimise blood loss in an effort to improve patient outcome.”^[7] Reduction in allogenic BT (ABT) for each individual patient to the level of as low as reasonably achievable risk by providing alternatives to transfusion as outlined in the matrix of PBM [Figure 1] goals are as follows.^[8,9]

- Detection, diagnosis and proper treatment of anaemia
- The prevention of present or potential coagulopathy
- Applying all appropriate modalities of blood conservation
- Multimodal team approach including shared patient decision.

Patient blood management has been recognised by the World Health Organisation (WHO) as the new standard of care (World Health Alliance resolution A 63.12) and has urged all 193 member countries of WHO to implement this concept.^[10] There is a pressing need for this new ‘standard of care’ so as to reduce BT and

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improve the quality of care. Hence, this article focuses on achieving goals of PBM in the perioperative period.

PREOPERATIVE APPROACH

Perioperative anaemia is not uncommon in patients presenting for major surgery. It is presently evident that correction of anaemia with BT may not improve patient outcome^[11,12] Patients undergoing elective surgery with potential for large blood volume loss need early screening for anaemia. Even though no clear universal Hb threshold has been identified, algorithm based management recommended by PBM strategy can reduce the transfusion requirement in the perioperative period.^[13]

A preoperative visit should also have an adequate assessment to detect and correct abnormalities in haematological homeostasis.^[14] History of abnormal bleeding tendencies in the past (e.g. following bruises, trivial injuries and previous surgeries), prior BTs, congenital coagulopathy, thrombotic events (e.g. deep vein thrombosis, pulmonary embolism), and family history should be elicited. Drugs such as antiplatelet and/or anticoagulant agents (e.g. aspirin, clopidogrel, warfarin), vitamin supplements, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitor antidepressants (e.g. fluoxetine, paroxetine), herbal medicines (e.g. ginko, ginseng, garlic) can adversely affect bleeding.^[15] Signs of increased bleeding tendency (e.g. ecchymoses, petechiae, pallor) and diseases associated with abnormal bleeding have to be evaluated in physical examination. Risk factors for organ (e.g. heart, brain) ischaemia which may ultimately influence transfusion trigger for BT should also be evaluated.^[12]

Stepwise standard laboratory testing (SLT) is based on clinical evaluation (e.g. Hb, haematocrit [Hct],

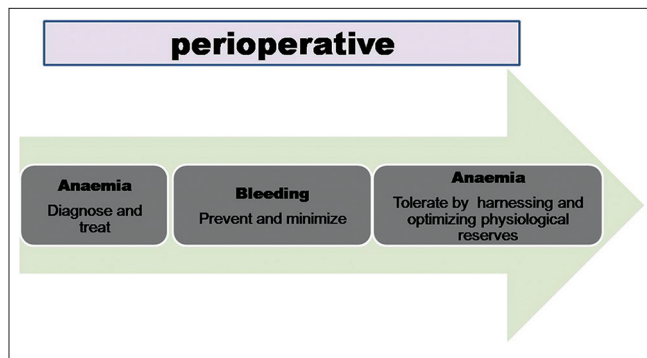


Figure 1: The three pillar matrix in perioperative patient blood management

coagulation profile, prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalised ratio [INR], bleeding time, clotting time [CT], platelets, fibrinogen, D-dimer).^[14] Evaluation and optimization of other parameters like nutrition, blood pressure and ventilation will also help in reducing transfusion requirement.

Preoperative patient optimisation improves not only blood loss and transfusion requirements, but also morbidity and mortality in the perioperative period. Anaemia should be treated with iron supplementation [Figure 2] preoperatively.^[16] Additional erythropoietin/erythropoiesis stimulating agents (ESA) is helpful in selected patients (e.g. chronic kidney disease, anaemia of chronic disease).^[17] Discontinuation of anticoagulant therapy (e.g. warfarin, anti Xa drugs, antithrombin agents) should be considered before elective surgery with appropriate specialist consultation. Whenever possible antiplatelet agents (e.g. clopidogrel, ticagralor, prasugrel) except aspirin should be discontinued for a sufficient time prior to surgery. Patients with *in situ* vascular stents may require continuation of drugs. Selected patients may require shorter acting drugs (heparin, low-molecular-weight

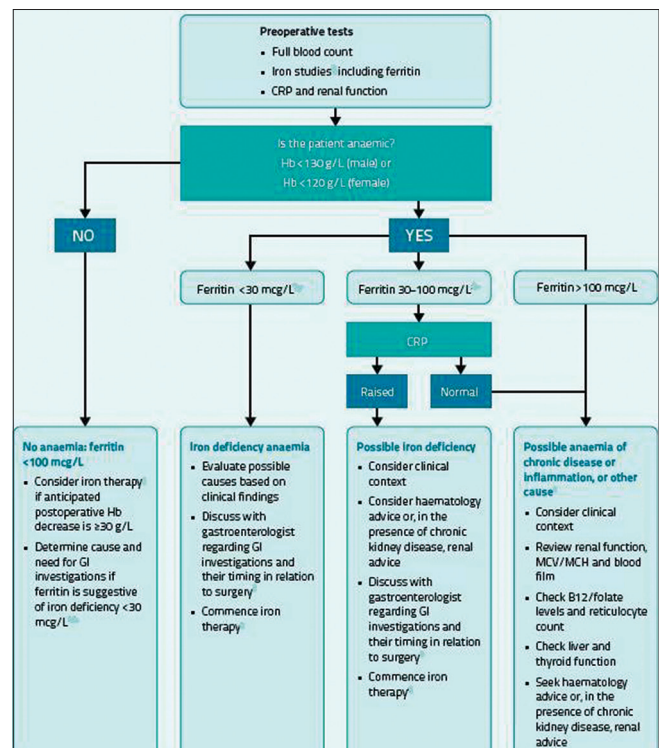


Figure 2: Preoperative haemoglobin assessment and optimisation template (edited, electronic copy freely available at website <http://www.nba.gov.au>). Hb – Hemoglobin; CRP – C-reactive protein; GI – Gastrointestinal; MCV – Mean cell corpuscular volume; MCH – Mean cell corpuscular hemoglobin

heparin) for transition. In emergency surgeries, reversal of anticoagulants (prothrombin complex concentrates [PCC], Vitamin K, Fresh frozen plasma [FFP]) and antifibrinolytics to minimize blood loss maybe instituted.^[14]

In patients at high risk of bleeding, preoperative multidisciplinary team meetings (anaesthetist, surgeon, haematologist, and radiologist) may help to discuss the correct surgical approach. This should include feasibility of less invasive (laparoscopic or radiological interventions), staging procedures (performed in two stages as in corrective spinal surgery) or a decision to use larger operating team thus reducing duration of surgery.^[11,15]

Preoperative autologous blood donation^[14,18]

Patients can be considered for preoperative autologous blood donation (PAD) when they are scheduled for elective procedures in which they are likely to receive transfusion. Patients donate a unit of blood per week from a month prior to their operation and donations can be more than once a week but the last one should be 72 h prior to surgery. Such a system is labour intensive and depends on good organization, both of collection and storage of blood and coordination of operating lists with guaranteed operating dates. It is expected that patient will generate additional red cells between the time of donation and time of surgery. Iron supplementation and erythropoietin/ESA therapy to enhance erythropoiesis with PAD has been considered. Cost effectiveness is low mainly because of a high proportion of discarded units. The predonated units are stored, in the same way, as allogenic blood and have depletion of 2,3-diphosphoglycerate (2,3DPG) and impaired ability for erythrocytes to unload oxygen to tissues.

INTRAOPERATIVE STRATEGIES^[15,19]

Patient blood management measures during surgery generally focus on reducing blood loss and/or on collecting and reinfusing the patient's own shed blood.

Maintenance of intravascular volume^[20-23]

In general, intravenous fluids (IVF) are administered according to protocols based on tradition, expert opinion and often with limited evidence. Individualised goal-directed therapy is necessary to optimise intravascular volume and microcirculation, thereby maintaining adequate tissue perfusion. Fluid administration is aimed at providing basal metabolic requirements, compensate for preoperative deficits

and replacing losses including surgical site losses. Choice of fluid (crystalloids, colloids and blood components) and quantity administered is based on monitored haemodynamic parameters.

Use of regional anaesthesia

Central neuraxial blocks such as spinal/epidural anaesthesia are associated with a reduction in blood loss during surgery (approximately 25-30%), the benefit extending to the postoperative period too (e.g. pelvic, orthopaedic, vascular procedures).^[24,25] Systemic hypotension induced by sympathetic blockade and decreased venous tone is responsible for blood saving effect by neuraxial anaesthesia.

Positioning^[15,19]

The surgical position of the patient can significantly influence intraoperative bleeding (if patient is incorrectly positioned, obstruction of venous return produces venous engorgement). Elevating the operative site above level of the right atrium facilitates venous drainage and decreases local venous pressure. Twisting the neck interferes with jugular venous drainage (e.g. head and neck surgery) causing pooling of blood at surgical site and should be avoided. In the prone position, pressure on the abdominal wall should be avoided (so as to minimise the compression on inferior vena cava) to reduce blood flow through collateral vertebral venous plexus. In the supine position left side tilt avoids compression on inferior vena cava in selected patients.

Ventilation^[15,19]

Positive pressure ventilation under general anaesthesia can hamper venous return. Minimizing mean intrathoracic pressure during controlled ventilation with minimal use of positive end expiratory pressure and low tidal volume increases venous return, helps in reducing blood loss.

Controlled hypotensive techniques^[15,19]

Reducing mean arterial pressure to 50-75 mmHg is achieved by various drugs such as inhalational agents, propofol, beta blockers, alpha blockers, calcium channel blockers, direct arterial/venous vasodilators, ganglion blockers, adenosine and prostaglandins E₁. This method mandates continuous haemodynamic monitoring and has been employed in hip, spinal and open prostate surgeries. Coronary artery disease, uncontrolled hypertension, cerebrovascular disease and anaemia are contraindication to controlled hypotensive techniques.

Maintenance of normothermia^[14,19]

Hypothermia renders the patient hypocoagulable by altering the platelet function and the coagulation cascade due to temperature dependent enzymatic reaction. Even mild hypothermia (<1°C) increases blood loss approximately by 16% and increases the relative risk of transfusion approximately by 22%.^[26] Use of temperature monitoring as a guide and employing warming devices (warm fluids, blankets etc.,) prevents intraoperative hypothermia.

Acute normovolemic haemodilution^[15]

This technique is used in major surgical procedures where high to moderate blood loss is anticipated (e.g. major cardiac, orthopaedic, thoracic or liver surgery) and is performed before the surgical bleeding phase. Normovolemia is maintained by simultaneous replacement by crystalloid and/or colloids to reach Hct values of 20-30%. The fundamental principle of acute normovolemic haemodilution (ANH) is the production of well-tolerated intra-operative anaemia. The preoperative dilution of circulating blood volume reduces the number of red blood cells and plasma constituents lost during surgical bleeding. Finally, the fresh whole blood is returned at wound closure, providing red cells, fresh clotting factors and platelets when they are most needed. As compared to PAD, the advantages of ANH are its use in nonelective surgery, avoidance of blood storage lesions and clerical errors.^[13] The evidence suggests that the efficacy of ANH (reduces the risk of transfusion by < 10%) has modest haemostatic benefit when compared to usual care.^[15]

Surgical technique^[15,19]

The development and implementation of surgical techniques that reduce bleeding contribute to the multimodal approach on reduction of blood loss. Less invasive surgery such as laparoscopy (e.g. nephrectomy, Splenectomy and computer assisted surgery (e.g. knee arthroplasty) have shown greater reduction in bleeding. Staged approaches, extended surgical team (reduced duration of surgery), use of electrocautery/harmonic scalpel, surgical adhesives and tissue sealants (topical hemostatic agents), use of a tourniquet with proper exsanguination and use of vasoconstrictors reduce the allogenic transfusion requirements.

Cell salvage^[13,15,19,27]

Intraoperative cell salvage (CS) is utilized in surgeries involving large anticipated blood loss. This technique involves the collection of shed blood, processing it and reinfusion of autologous red cells lost during surgery. The end product of the process is packed red cells with

a Hct of 50-60%.^[19] Salvaged red cells are superior to or at least equal to banked homologous blood in terms of red cell survival, pH, 2,3-DPG, and potassium levels. The technique has shown to reduce exposure to allogenic transfusion and is applicable to open heart surgery, vascular surgery, total joint replacements, spinal surgery, liver transplantation, neurosurgical procedures and some Jehovah's Witnesses (provided the equipment is set up in continuity with the circulation and specific consent is obtained).^[28] The use of CS in cancer, obstetric and bowel (contaminated) surgeries with introduction of unwanted material has been considered a relative contraindication^[13,14] The high cost of the machinery and the need for trained operators are the drawbacks of CS.

Coagulation factors^[15,19,29]

In patients with congenital or acquired haemostatic disorders, certain types of isolated (fibrinogen, factor XIII and factor VIIa) or combined PCC coagulation factors are clearly indicated to avoid excessive bleeding. Evidence recommends use of fibrinogen concentrate/cryoprecipitate in hypofibrinogenemia; factor XIII concentrate (30 IU/kg) in factor XIII deficiency (<60% activity); Vitamin K and PCC (20-30 IU/kg) in patients on oral anticoagulant therapy/elevated bleeding tendency and prolonged clotting time CT; recombinant factor VIIa in bleeding which cannot be stopped by conventional, surgical or interventional radiological methods and/or when comprehensive coagulation therapy fails.^[14] Role of desmopressin in minimizing perioperative bleeding or perioperative allogenic blood transfusion in patients without a congenital bleeding disorder is not convincing.^[14]

Antifibrinolytic agents^[15,19,29]

Use of antifibrinolytic drugs is one of the main strategies for decreasing blood loss and lowering the risk of transfusion during surgical (e.g. cardiovascular, trauma, orthopaedics) procedures.^[30] The synthetic derivatives of lysine, tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) have been the most commonly used antifibrinolytics since the withdrawal of aprotinin. TXA and EACA reversibly bind to both plasmin and plasminogen inhibiting clot degradation at sites of bleeding. TXA is 6-10 times more potent than EACA and has a longer elimination half-life.

Transfusion of blood components

Though transfusion trigger typically ranges from Hb of 6-10 g/dL, the indications for BT depends on a specific situation and patient.^[12] Restrictive transfusion threshold (Hb 7-8 g/dL) of red blood cells is safe

compared to liberal transfusion threshold (Hb > 9 g/dL) and therefore recommended to target Hb concentration of 7-9 g/dL during active bleeding.^[14] Transfusion of platelets, FFP, cryoprecipitate, fibrinogen, factor XIII, factor VIIa and PCC for prophylaxis and treatment of excessive bleeding is based appropriately on abnormalities in monitored parameters.^[31]

POSTOPERATIVE STRATEGIES

Bleeding can continue after surgery into the postoperative period. Strategies used in the intraoperative period such as maintenance of normothermia, antifibrinolytics and red CS can continue during this period.

Drain management^[15]

Use of postoperative drains is to diminish hematoma and compression of vital structures. Closed suction drainage after lower limb arthroplasty increases the blood transfusion rate by >40% when compared to the control group without drains.^[32] Reinfusion of blood from wound drain, with or without processing is used in cardiac and orthopaedic surgery. This is safe only if volume <1 litre, and the process is completed within 6 h.^[19]

Cell salvage^[14,19,27]

Postoperative CS and reinfusion, with or without washing, has been shown to be effective in decreasing perioperative blood loss after total knee arthroplasty, total hip arthroplasty and instrumented spine surgery. This is restricted to elective procedures with significant anticipated postoperative blood loss through drains in the first 6 h.

Lower transfusion threshold

Laboratory investigation are based on clinical evaluation of estimated blood loss, and blood components are transfused accordingly.^[14]

INTRAOPERATIVE AND POSTOPERATIVE PATIENT MONITORING

Intraoperative and postoperative patient monitoring for PBM consists of monitoring for perfusion of vital organs, blood loss, anaemia, coagulopathy and adverse effects of transfusion.

Perfusion of vital organs monitoring^[19,33,34]

The goal of continuous haemodynamic monitoring is to ensure adequate tissue perfusion and oxygen delivery, to predict instability and to institute therapy. Level of monitoring is based on the extensiveness of surgery

and expected blood loss. Monitoring for perfusion of vital organs using standard American Society of Anesthesiologists recommendations includes heart rate, blood pressure, oxygen saturation, capnography and urine output in addition to clinical evaluation. Visual assessment of the surgical field for the presence of any excessive bleeding has to be noted. Quantitative measurement includes estimation of blood loss including checking suction canisters, surgical sponges and surgical drains. Hb/Hct monitoring, arterial blood gas analysis is based on clinical signs and estimated blood loss. More extensive continuous haemodynamic monitoring is based on blood loss, haemodynamic instability and comorbidities. Invasive arterial blood pressure, central venous pressure and pulmonary artery catheter based parameters monitoring have to be individualised. Additional monitoring may include mixed venous oxygen saturation, echocardiography and cerebral monitoring (cerebral oximetry and near infrared spectroscopy).

Monitoring is becoming less invasive with advances in technology. Devices using pulse contour analysis (pulse-induced contour cardiac output, lithium dilution cardiac output and volume view) to determine cardiac output (CO), stroke volume variation (SVV) and pulse pressure variation (PPV) are commercially available.^[34] CO and SVV can also be measured using Flotrac and esophageal Doppler. Predicting preload responsiveness and optimizing strategies driven by SVV/PPV/CO help in optimising transfusion requirement and tissue perfusion.

Coagulation monitoring^[19,35]

The aim of intra-operative coagulation monitoring is to prevent and treat the pathological mechanisms of increased perioperative bleeding.

Clinical monitoring includes periodic visual assessment of the surgical field and communication with the surgical team as standard practice to detect impending or established coagulopathy. This entails an assessment of the amount of blood lost and the presence of microvascular bleeding from mucosal lesions, serosal surfaces, catheter insertion sites and wounds. Further, temperature is monitored to maintain normothermia.

In susceptible patients, blood gas analysis will aid the detection of acidosis, anaemia and hypocalcaemia. Routine coagulation parameters like INR, aPTT, PT, platelet count and fibrinogen levels are to be individualised. Activated clotting time (ACT)

monitoring is recommended when high dose of heparin is used intraoperatively. Patients with inherited coagulation defects may exsanguinate with trauma or major surgery necessitating second level coagulation tests for specific factor replacement (such as factor VIII, IX and von Willebrand factor concentrate).

Thromboelastography and rotational thromboelastometry measurements should be performed at the beginning of surgery as the baseline, when clinically abnormal bleeding occurs and after therapeutic interventions.

Point of care coagulation testing^[19,36]

Point of care (POC) techniques are bed side tests and interpret various aspects of haemostasis more comprehensively and rapidly. They enable economical and effective treatment when compared to SLTs. Their implementation in haemostatic treatment algorithms may reduce both the rate of transfusion of allogeneic blood products and the total cost of treatment for blood loss and coagulopathies. POC techniques can be used to screen coagulopathies and to monitor their treatment, in the preoperative period, resuscitation room, operating room and intensive care unit.

Platelet function

The number of platelets does not reflect the quality of platelet function.

Bedside aggregometry can be used to study the platelet function. The platelet function analyser (PFA)-100 (Dade Behring) provides a measure of platelet function in citrated whole blood. This method can be used prior to surgery, to rapidly identify aspirin effects and platelet disorders. Intraoperatively, limitations of the PFA-100 include its strong dependence on platelet count (>100 G/l) and Hct (>30%). Optical and impedance platelet aggregometry can be used to assess platelet reactivity by measuring changes in luminescence or impedance upon platelet agonist stimulation. PFA-100 and impedance aggregometry (Multiplate) can be performed at bed side with short sample reading times of <6 min.

Potential complications following surgery include thromboembolic events and recurrent or excessive bleeding. SLTs and/or POC coagulation monitoring are used to guide transfusion intervention in the postoperative period. Current evidence suggests that POC measurements of the speed of clot initiation, formation and strength/elasticity/rigidity, can identify patients at risk of thromboembolic events.^[36]

Monitoring adverse effects of transfusion^[37]

During and after transfusion, patient should be periodically monitored for hypoxaemia, respiratory distress, elevated peak airway pressure, urticaria, hypotension and signs of hypocalcemia, hyperthermia, haemoglobinuria and microvascular bleeding.

BLOOD SUBSTITUTES

The paucity and complications associated with blood and blood products have resulted in the search for a better substitute. Yet, an ideal substitute is not available. The emphasis is presently shifted from blood replacement fluid to oxygen carrying blood substitutes to treat pathologies initiated by anaemia and hypoxia. Emulsions of perfluorocarbons (PFC) and the solution of Hb maintain functionality of microcirculation that is significantly dependent on adequate levels of oxygen (O₂), nitric oxide (NO) and hemodynamic interactions with vascular endothelium.

Perfluorocarbon based oxygen carriers^[38-40]

Perfluorocarbons are chemically inert molecules containing primarily as the name suggests, fluorine and carbon atoms. They are capable of dissolving large amounts of many gases, including oxygen. These molecules are hydrophobic in nature, and hence have to be emulsified prior to intravenous administration. After intravenous administration, the droplets of this emulsion are taken up by the reticuloendothelial system and then slowly broken down. They are then transported to the blood, where they are bound to lipids and move to the lungs. In the absence of significant *in vivo* metabolism, PFC are removed from the body by exhalation.

Perfluorocarbon based oxygen carriers (PFCOCs) are convenient, largely available, economic, pathogen-free and storable O₂ carriers. PFC emulsions have linear O₂ carrying capacity but are inefficient to sustain human cellular function. The basic difference between O₂ transport by PFCs and Hb is that PFCs dissolve, whereas the Hb bind O₂. In the case of Hb, a strong bond is established between O₂ and the haem. In the case of PFCs, there is only a physical weak equilibrium between concentration and solubility. With PFCOCs, there is no saturation and no possibility for chemical binding, and as O₂ is released, carbon dioxide (CO₂) is absorbed. It can also carry nitrogen (air), volatile anaesthetics, NO and may find a place for decompression sickness, protection for neurological damage caused by air microemboli during cardiopulmonary bypass.

In normal conditions with central arterial pO_2 of 100 mmHg and venous pO_2 of 35 mmHg, PFCOC emulsions can release 65% of O_2 , compared to about 30% for Hb in the RBCs. O_2 releases from PFCOCs is effective at any physiologically relevant partial pressure. O_2 uptake and release by PFCOCs is not affected by pH and temperature. Since PFCOCs undergo no oxidation or other modification over time, their O_2 uptake and release characteristics are not affected by storage or in circulation. Introducing a PFCOC emulsion into the circulation is akin to increasing the O_2 solubility of blood's plasma compartment. When Hb and PFCOC are present in the circulation simultaneously, the PFCOC will always release its O_2 first, thus conserving the Hb bound O_2 until it is released to the hypoxic tissues.

Because of their small particle size, PFC emulsions penetrate collateral capillaries of an ischaemic microcirculation, supplying oxygen and restoring aerobic metabolism. With an increased inspired oxygen concentration (FiO_2), PFCOCs increase systemic O_2 delivery and extraction when compared to a plasma expander.

Perfluorocarbon based oxygen carriers microbubbles have been developed and reported to dissolve clinically relevant amounts of O_2 when administered in dosages that are about 1/500 of usual quantities.

Haemoglobin based oxygen carriers^[39-41]

Haemoglobin solutions are produced from either outdated human blood or bovine blood by lysing the red cells and purifying the Hb. These Hb products are modified to increase the P_{50} into the range of 28-32 mmHg so that it should deliver O_2 to tissues. The initial attempts at transfusing stroma free Hb produced renal dysfunction, coagulopathy, and hypertension (arteriolar vasoconstriction from NO scavenged by infused Hb). Also, existing Hb based substitutes have been proven to be unsafe, causing myocardial infarction and increasing mortality. Hence, strategies have been adopted to increase Hb stability and reduce toxicity. These include cross linking dimers of haemoglobin tetramers (intramolecular/intermolecular), polymerised Hb, surface modified (conjugation) Hb, liposomal encapsulated Hb and recombinant Hb.

Platelet substitutes have been developed but have not been shown to be clinically effective.

It may be possible to grow RBC, platelets and neutrophils *in vitro* from stem cells for therapeutic use.^[40]

CONCLUSION

This article focuses on PBM in the perioperative period, a multidisciplinary, multimodal, individualised approach of standard of care to minimise ABT and the risks associated with it. The strategies include improved blood utilization by timely and adequate preoperative evaluation for detection and treatment of anaemia. Perioperatively blood conservation technologies and techniques to prevent/minimize blood loss are used. Employing strict evidence based transfusion thresholds for blood component administration by POC testing and targeted therapy using transfusion guidelines will help in attaining the ultimate goal of patient safety.

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Announcement

INDIAN COLLEGE OF ANAESTHESIOLOGISTS

The Indian College of Anaesthesiologists is an academic body of the Indian Society of Anaesthesiologists. The ICA is registered as a Trust in New Delhi and functions under ISA through a MOU. Membership of the college is limited to ISA Members only. Membership fee Rs. 5,000/- I request all members of ISA to become part of ICA.

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