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Review Article

Alternatives to Blood Transfusion in Resource Limited Settings

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Abstract
The ability to transfuse blood and its components is one of the major achievements of modern medicine which has made possible the development of many surgical procedures and medical therapies including stem cell transplantation. However the supply of blood is limited and blood transfusion is associated with various hazards including the transmission of pathogens. This review is focused on proven strategies to reduce homologous blood transfusion and how these can be employed in resource limited settings to maximize the use of this scarce human resource.
Key words: *blood transfusion, autologous blood transfusion, blood conservation strategies, bloodless medicine and surgical procedures.*

Introduction

The key elements for a national transfusion policy are a nationally coordinated blood transfusion service, collection of blood only from voluntary nonremunerated blood donors from low-risk populations, testing of all donated blood, including screening for transfusion-transmissible infections (TTI), blood grouping and compatibility testing and reduction in unnecessary transfusions through the effective clinical use of blood, including the use of simple alternatives to transfusion (crystalloids and colloids) wherever possible.

Although this recommendation has been promoted since the World Health Assembly of 1975, the majority of the poorest countries have been unable or unwilling to implement such a policy. This is largely due to problems with cost and inventory levels as majority of blood donated in our blood banks are from family replacement or commercial donors with voluntary blood donation accounting for less than 5% of blood donated annually [1-3]. Infection rates for HIV in transfused children range from 1.4% to 4.5%. Hepatitis B and C infections are also involved and there is positive correlation between number of transfusions and HCV positivity while exposure to malaria parasite is as high as 40.9% [4-8]. Blood typing for additional antigens such as C, E, Kell Kidd, (JK), S and Duffy (Fy) for prevention of alloimmunization in poly transfused patients are not available. The reported incidence of blood transfusion reaction is 8.7% and is mostly due to febrile non haemolytic transfusion reactions. Adverse effects of blood transfusion are correlated with a positive history of multiple transfusions ($p < 0.01$) [9].

Blood safety considers the entire process from the type of person who donates blood, to how blood is collected, stored, tested, and transported to the patient for transfusion, which patient receives what component and the effect on the patient after the transfusion. This process should be carefully controlled according to strict protocols. More attention should be given to blood safety in the curriculum of medical schools in order to produce physicians who are skilled in appropriate use of blood and of transfusion alternatives in order to reduce exposure to homologous blood with its associated deleterious effects.

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The rationale for reduction in the use of homologous blood.

The rationale for advocating the minimization of red cell transfusions are due to the known hazards of blood transfusion, concerns about blood inventory, evidence for the physiological adaptation to anaemia, evidence for the excessive use of elective red cell transfusion, evidence for the human tolerance of anaemia and the presence of alternatives to homologous blood.

The body responds to anaemia through a number of physiological mechanisms which include increased levels of 2, 3 D PG, shift of oxyhaemoglobin dissociation curve with decreased oxygen affinity, increased oxygen extraction, increased oxygen release, increased contractility, tachycardia, decreased after load, increased cardiac output, vasodilatation and diminished blood viscosity. These physiological changes enable the body to deliver oxygen maximally to the tissues even at low haemoglobin levels in individuals without cardiovascular disease.

The Network for the Advancement of Transfusion Alternatives (NATA) was created by cooperation amongst anaesthetists, surgeons and blood bankers to use pharmaceuticals, technology, medical and surgical techniques to reduce the transfusion of homologous blood. The strategies being considered in this review have thus been in practice and are readily implementable in low resource settings.

Blood conservation program

In every hospital where blood is transfused, a blood conservation program should be put in place to save lives and scarce resources. This includes the correction of anaemia through the use of haematinics such as iron, vitamin B12, folic acid, recombinant human erythropoietin, restrictive transfusion protocol, reduction of blood loss with tranexamic acid, sealants and fibrin glues, recombinant FVIIa and autologous blood which can be in the form of preoperative autologous donation, normovalaemic-haemodilution and peri-operative cell salvage.

Why do we believe that these strategies of reduced transfusion and transfusion alternatives will be safe for our patients?

Over time, a number of randomized controlled clinical trials have provided the evidence to support a restrictive transfusion strategy in groups of patients in different clinical settings.

Blood conservation strategies had worked well in adults but Lacroix and co workers studied transfusion strategies for children in paediatric intensive care units. This study involving stable, critically ill children showed that a restricted strategy with transfusion threshold of 7 g of haemoglobin (Hb) per decilitre was as safe as a liberal strategy with transfusion threshold, 9.5 g per decilitre. Rates of multiple-organ dysfunction were similar in the two study groups. They concluded that in stable critically ill children, a haemoglobin threshold of 7 g per decilitre for red-cell transfusion can decrease transfusion requirements without increasing adverse outcomes[10].

For patients with upper gastrointestinal bleeding, a randomized controlled clinical trial showed that withholding transfusion until the haemoglobin level fell below 7 g per decilitre resulted in better outcomes than using 9 g per decilitre as the trigger for transfusion. When compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding and was associated with a significant 45% relative-risk reduction in 45-day mortality[11].

In another setting, Hebert et al of the Canadian Critical Care Trials Group reported a multicentre randomized controlled trial of

transfusion requirements in critically ill patients conducted to determine whether a restrictive strategy of red cell transfusion and a liberal strategy produced equivalent results by comparing the death rate from all causes at 30 days and the severity of organ dysfunction. 838 critically ill patients were enrolled with euvolaemia with haemoglobin levels of greater than 9g/dl; 418 were assigned to a restrictive transfusion strategy in which red cells were given if the haemoglobin level fell below 7g/dl and haemoglobin concentrations were maintained at 7-9g/dl while 420 patients were assigned to a liberal transfusion strategy in which transfusions were given when the haemoglobin concentration fell below 10g/dl. Haemoglobin concentrations were maintained between 10-12g/dl. There was similar overall 30 day mortality in both groups 18.7 % versus 23.3%, (p = 0.11). In patients who were less acutely ill, the rates were significantly lower in the restrictive strategy group, the mortality was 8.7% versus 16.15% (p= 0.03) and in patients less than 55 years old, mortality was 5.7% vs. 13%, (p=0.02) in the restrictive transfusion versus the liberal transfusion group. However this lower mortality rate was not among patients with clinically significant cardiac disease which had 20.5% mortality vs. 22.9% in the liberal group (P= 0.69). The result of this randomized controlled trial showed that a restrictive strategy of red cell transfusion is at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina[12].

In support of a more liberal transfusion policy for anaemic patients with cardiac ischaemia, Wu et al also found in a large retrospective review of data from the Cooperative Cardiovascular Project that substantial number of lives may be saved when transfusions are administered to patients who present with acute myocardial infarction and a (haematocrit) HCT of 33% or lower [13].

Could we therefore say that severely ill patients will benefit from a more liberal transfusion policy?

To examine this question, the CRIT study (Anaemia and Blood Transfusion in the Critically Ill) examined 4892 patients. 44.1% of these patients were transfused with one or more units with a mean Hb of 8.6g/dl (SD 1.7). The number of units transfused was an independent risk factor for mortality and length of hospital stay. Transfused patients had more complications and were more likely to experience complications[14]. A similar study, (Anaemia and Blood Transfusion in the Critically Ill), (ABC study) was performed in European intensive care units. Mortality was higher for transfused patients than non transfused patients with similar organ dysfunction as assessed by the Sequential Organ Failure Assessment Score. The weight of evidence indicates that transfusion at Hb levels less than 8g/dl may not improve survival in elderly patients with high illness burden[15-17].

In a trial funded by the National Heart Lung and Blood Institute which examined functional outcomes in cardiovascular patients undergoing surgical repair of hip fractures, a liberal transfusion strategy, compared with a restrictive strategy, did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk [17].

If blood transfusion does not confer the expected benefits in critically ill anaemic patients what should we do?

This brings us back to the first point in a blood conservation program which is to correct the anaemia with haematinics such as iron, vitamin B12, folic acid and recombinant

erythropoietin where indicated. Both intravenous and oral iron administration result in increased haemoglobin and serum ferritin levels. Oral iron is suitable for use in outpatients but may be associated with gastrointestinal disturbances while intravenous iron may cause anaphylactic reaction, arthralgia, is more expensive and has to be administered under supervision. Bearing in mind that in our environment, anaemia is associated with such co-morbidities as hookworm infestation, schistosomiasis, HIV, haemoglobinopathies and malaria, these have to be screened for and also treated [18-20].

Correction of anaemia in cancer patients and those undergoing long term haemodialysis can also be achieved by the administration of recombinant human erythropoietin. This is usually given in thrice weekly doses subcutaneously which may be a problem for patient compliance. Peginesatide, a synthetic peptide based erythropoeisis-stimulating agent administered once monthly has been shown to be as effective as erythropoietin given three times per week in maintaining haemoglobin levels in patients undergoing haemodialysis[21].

The next important aspect of a blood conservation program is the use of the patient's own blood. This is not a new procedure but was first reported by John Blundell in 1818[22]. Auto transfusion was limited due to clotting of blood. With the introduction of sodium citrate as anticoagulant, it became possible to predeposit the blood for use by patients for elective surgery. This became accepted such that by the end of the first quarter of the last century, autologous transfusion was widely practiced. However with the organisation of blood banks, homologous blood transfusion gained ascendancy until the new era ushered in by concerns about infectious complications of blood transfusion and the AIDS pandemic.

Components of an autologous blood program include preoperative donation, acute isovolaemic-haemodilution, intra-operative blood salvage and post operative blood salvage.

Before commencement of such a program, it is important to draw up clear guidelines followed by extensive education of all the health workers who will be involved in it. Patient information leaflets should be written so that any patient who undergoes the procedure will be well informed, consented and able to explain the procedure to others. Once a program is in place, continuous vigilance, periodic assessment is necessary to ensure adherence to the protocol and any incidents used as an opportunity to raise standards [23].

Pre-deposit autologous blood transfusion

This is blood donated by a patient undergoing elective surgery likely to require blood transfusion which is stored and when needed re-infused to the patient. When blood is taken from the patient through predonation, the red cell mass is decreased at the time of surgery resulting in stimulation of erythropoeisis. In resource limited settings, autologous predonation typically takes place within the hospital where the transfusion will be carried out and does not attract shipping costs. However autologous predonation is not for patients about to undergo emergency surgical procedures as postponement of surgery can cause outdating. The following guidelines have been used successfully at the National Orthopaedic Hospital, Lagos since 1992[23]. Use of autologous blood decreases the demand for homologous blood and helps the patient to avoid all the major hazards associated with homologous transfusion. Where patients and their relatives bear the burden of providing blood for transfusion

under the family replacement donor system, it is less burdensome and more cost-effective. [24]

Eligibility for Pre donation of Autologous Blood: Male and female patients for major and intermediate surgery elective likely to require blood transfusion.

Age 8 to 70 years but not more than 9ml/kg of blood should be collected in those less than 50kg body weight. PCV should not be less than 30%.

It is important that the actual collection is performed after the patient has paid the assessment fees for surgery rather than the initial period of being informed about the surgical procedure to prevent out dating. The time required for donation is 72 hours for oneunit, 10 days for two units and seventeen days for three units. Up to four units of blood can be collected keeping in mind the expiry date of each unit.

Contraindications: Patients with Sickle cell disease, cardiovascular disease**,** cardiac dysrrythmia**,** congestive cardiac failure**,** myocardial infarction in the previous six months**,** labile hypertension**,** insulin dependent diabetes mellitus**,** bacteraemia, cerebrovascular disease and **o**bstructive airway disease should not autologous blood as it is not safe for them to do.

Procedure/Technique for Predonation: The actual donation should be performed after all payments for surgery have been made.

Not more than 9ml/kg body wt or 450ml of blood should be collected into a CPDA blood bag. For children not more than 7ml/kg body weight of blood should be collected into a paediatric blood bag at a time.

All collections should be 7 days apart and stored in a separate blood bank. Where this is not possible, it can be stored in a separate compartment of the blood bank refrigerator labeled

For Autologous Blood Only: Each unit of autologous blood should have a self adhesive label with the following details: Full name, Date of birth, Sex, Hospital Number, Autologous number, Date and time of collection, Expiry date, Patients signature.

The final collection of autologous blood should be not less than 72 hours before surgery. The blood group should be determined and the donated unit appropriately labelled.

An immediate spin with a sample from the patient should be carried out less than 24 hours before surgery.

How do we manage blood transfusion in the perioperative period when someone has donated autologous blood?

In general, an automatic transfusion threshold should be avoided and a plan made to use autologous blood if there is reasonable likelihood of acute blood loss. In practical terms, this means transferring the autologous blood from the blood bank in a blood transport box to the blood bank refridgerator in the operating theatre.

Blood should be given on a unit-by-unit basis when necessary bearing in mind that one unit of blood may be sufficient.

When autologous blood is available, this should be transfused first.

A variety of automated and semi automated devises exist to harvest blood intra operatively which is washed, rinsed in saline and re- infused into the patient intra - operatively. Collection can also be made from drains post-operatively. The use of recombinant erythropoietin alfa in patients with low haemoglobin levels has helped the collection of more units of blood before surgery[25-28]. When acute isovolaemic-

haemodilution is employed with predonation, a large number of eligible patients are able to avoid the use of homologous blood altogether in total hip replacements, prostatectomy and coronary bypass surgery.
Reports in literature show wide variation in the criteria used by anaesthetists for pre-operative and intra-operative transfusion as well as reluctance to accept autologous transfusion. [28]

Acute IsovolaemicHaemodilution (AIHD)
This is another form of autologous donation and transfusion which can be carried out in the non -elective setting usually after the induction of anesthesia. It involves removing a predetermined volume of the patient's own blood immediately prior to the commencement of surgery and its simultaneous replacement with crystalloids or colloids to maintain blood volume. The advantages of AIHD include the production of autologous blood, the availability of fresh blood containing coagulation factors and platelets, reduction in red cell loss due to lower HCT, better haemodynamics and increased oxygen availability. Additional beneficial physiological haemodynamic changes include an increased cardiac output, decreased blood viscosity and decreased peripheral resistance. The best setting for AIHD is orthopaedic surgery, major general surgery, liver resection, cardiovascular surgery and in young, otherwise healthy patients undergoing elective surgery.

Eligibility for Acute Isovolaemic-Haemodilution (AIHD): The eligibility for AIHD are somewhat similar to autologous predonation and are mainly Haematocrit of 30% or more or haemoglobin concentration of 10g/dl or more.
Surgery with anticipated blood loss likely to be greater than 15ml/kg body weight or greater than one litre or 20% of blood volume.
Age from 2 to 65 years and in children with anticipated blood loss greater than 10ml 1kg.

Contraindications for Acute Isovolaemic-Haemodilution (AIHD): Sickle cell disease, severe cardio-vascular disease, patients with bleeding disorders, bacteraemia. liver disease. severe renal disease.

Procedure: A predetermined volume of blood is removed according to the formula
Volume to be removed =Expected blood volume (EBV) X $\frac{\text{Initial} - \text{Desired PCV}}{\text{Mean of initial and desired PCV}}$
The expected blood volume is calculated using the formula (EBV= weight in kg x 70 for adults and weight (kg) X 80.

For adults and children, the total blood volume removed should not exceed 40%. Blood collection should be carried out from one intravenous line with simultaneous replacement of crystalloid 3 ml: 1 ml of blood, colloid 1 ml: 1 ml of blood in another line. The collected blood should be appropriately mixed and the autologous label should be affixed unto the blood bag. The blood should be stored in a temperature controlled refrigerator if more than six ours will elapse before use. The central venous pressure, pulse, blood pressure and urine output should be monitored and the blood volume and oxygen delivery maintained at all times.

Intra-operative Blood Salvage: This involves the collection of shed blood from a wound, body cavity or joint space and its subsequent re-infusion into the same patient.

Eligibility for Intra-operative Blood Salvage: Intra-operative blood salvage is useful in patients undergoing ***elective*** cardio-

thoracic surgery, selected orthopaedic surgery, and emergency/trauma surgery such as: ruptured spleen/liver, vascular injuries, urologic surgery. [29]

Contraindications for Intra-operative Blood Salvage: Cancer patients. Bacteraemia or contaminated surgical fields (bacteria, fat, amniotic fluid, urine, penetrating abdominal wounds). Osteomyelitis. Intra-peritoneal infection. Blood which has been shed for more than 6 hrs should not be re-infused.

Devices for blood salvage include gauze filtration, simple suction collecting system and automated suction collection system. Gauze filtration is inexpensive, suitable for collecting blood from body cavities but an aseptic technique has to be applied. A ladle or small bowl is used to scoop the blood which is then mixed with anti -coagulant such as heparin or citrate (60mls of 3.8% Na citrate), filtered through the gauze and re-infused into the patient.

For the manual suction collection system, suction tubing is connected to a specially designed storage bottle containing anti coagulant. Blood is sucked directly from the cavity or wound into the bottle. Automated Suction Collection Systems (Cell Savers) have the capacity to collect, anti-coagulate, wash, filter, re-suspend red cells in crystalloid prior to re-infusion but they require a dedicated operator and are expensive. Intra-operative blood salvage and reinfusion can be complicated by coagulopathy, air embolism, infection, fat embolism and micro aggregate effects.

Post operative blood salvage may be carried out in cardiovascular surgery and joint replacement surgery where large volumes of blood are shed in the postoperative period. A tube drainage device can be connected to an integral blood bag and filter. Post-operative blood salvage is fraught with problems- the wound drain is dilute and only small volume of cells are recovered, the red cells are partially haemolysed, the coagulation system is activated during surgery therefore the wound drain contains activated coagulation proteins. Additionally drainage over a long period damages the red cells. Post operative blood salvage may thus not be practical in an environment with high ambient temperatures [29].

Transfusion Alternatives

Another key strategy in reducing homologous blood usage in clinical settings is the effective clinical use of blood, including the use of simple alternatives to transfusion (crystalloids and colloids) wherever possible. For patients under anaesthesia, if the vital signs are stable and the patient is **not** at risk for myocardial ischaemia, (ie patients with coronary artery disease, valvular heart disease such as significant aortic stenosis), congestive heart failure or cerebral ischaemia presenting as history of transient ischaemic attacks, (TIAs) or as previous thrombotic stroke, blood transfusion should not be given, rather the blood volume should be restored with adequate colloids or crystalloids. Patients at risk for the above conditions who have unstable vital signs should receive autologous blood and if this is not available, then homologous may be given. Transfusion should be given on a unit-by-unit basis. In the post-operative period, the patient should be treated as for chronic anaemia. Haematinics should be restarted a soon as possible (oral iron, ferrous sulphate/gluconate 200mg tds, folic acid 5mg). Blood should not be given merely to reduce hospital stay as evidence points to increased length of stay due to higher infection morbidity in patients who received homologous blood in contrast to autologous blood. [30-32]

Blood Substitutes

Crystalloids such as 0.9% saline solution, Ringer's lactate, Darrow's solution, 5% Dextrose in 0.4% saline, 5% Dextrose and colloids such as gelatins, hydroxyethyl starch may be used in the treatment of mild and moderate as well as in AIHD. Three volumes of crystalloids is used to replace one volume of blood and one volume of colloid replaces an equal volume of blood. Colloids and crystalloids should therefore be stocked in adequate quantities in theatre, casualty and labour ward. Isoplasma, Ringers' lactate and Darrow's at reasonable prices should be stored in the pharmacy.

Pharmacological agents

Pharmacological agents are useful in a blood conservation program and consist of agents that stimulate erythropoeisis such as erythropoietin or agents that enhance haemostasis e.g. Desmopressin. Desmopressin is an analogue of vasopressin which increases serum levels of factors VIII and VWF. Aprotinin is an anti fibrinolytic agent. Aprotinin has resulted in decreased transfusion requirements in open heart surgery, urology and liver transplantation. Fibrin glue is made from fibrinogen and thrombin and is used increasingly to decrease post-operative bleeding surrounding suture lines. All of these factors can be integrated to offer comprehensive care in bloodless management.

These strategies can be used to limit blood transfusion in the pre operative setting. The patient should be worked up carefully and assessed to know the appropriate blood conservation techniques to be applied. Blood counts should be improved with erythropoeitin, iron, folic acid, vitamin B_{12}, adequate nutrition and phlebotomy minimized to necessary tests especially in children. To improve haemostasis, non steriodal antiinflammatory agents should be stopped as well as anticoagulants. Coagulopathies should be identified and addressed. Vitamin K should be given when necessary.

Intraoperatively ,meticulous attention to surgical haemostasis with surgery along avascular anatomical planes, AIVHD, intra-operative blood cell salvage, hypotensive anaesthesia, hypothermia all help to reduce blood loss. Use of electrocautery electrosurgical coagulator, endoscopy, laser, non-invasive monitoring haemostatic agents; aprotinin, desmopressin, epsilon amino-caproic acid, (fibrinolytic inhibitor) tissue adhesives and volume expanders all help to minimize blood transfusion.

In the post operative setting, careful vigilance and prompt control of bleeding, optimum support of cardiac and respiratory function and appropriate resuscitation with colloids and crystalloids are essential. Haemostasis is enhanced by aprotinin, Vitamin K and fibrinogen. Blood pressure is controlled to avoid disrupting spontaneous haemostasis and blood count is improved as in the preoperative setting with the use of erythropoietin, iron, folic acid, Vitamin B_{12}, nutrition, while restricting phlebotomy to necessary tests.

Conclusion

The WHO recommends that blood and blood products should be prescribed only if less hazardous therapy has proved or is likely to be ineffective and if the benefits of transfusion outweighs the risk. Overall concern about the safety and adverse effect of blood transfusion has prompted the search for transfusion alternatives to decrease or avoid the use of homologous blood. These strategies include the correction of perioperative anaemia, pharmacological and non pharmacological measures to reduce

blood loss, pre-operative autologous blood donation and perioperative blood cell salvage. Anaemia should be regarded as a treatable medical condition and not a laboratory value. Transfusion medicine needs to be incorporated into the curriculum of both under graduate and post graduate medical education and extended to other health care personnel to enable more health workers increase use the of transfusion alternatives in clinical practice.

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