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CONTRIBUTED REPORTS

Bloodless Medicine and Surgery

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1 Introduction

Bloodless Medicine and Surgery (BMS) is the provision of quality health care to patients without the use of allogeneic blood with the aim of improving outcome and protecting patients' rights [1,2]. It involves the use of Blood Conservation techniques in combinations that are specific to the individual patient, ideally following a protocol and a multidisciplinary approach, and is synonymous with Transfusion-free Medicine and Surgery [3,4].

The term Patient Blood Management has crept into popular use in some circles, and has been recently defined by the Society for the Advancement of Blood Management as "the application of evidence-based medical and surgical concepts aimed at relying on a patient's own blood rather than on donor blood and achieving better patient outcomes" [5]. The basic principles or 'pillars' of Patient Blood Management were ratified by the 63rd World Health Assembly, and are identical to those of BMS as discussed herein.[6]

BMS has traditionally been considered in clinical situations where patients refuse blood, and when 'safe' blood is unavailable or in short supply.1 Many clinicians are surprised to learn that blood transfusion is based on tradition and associated with a poorer outcome (unrelated to infectious hazards) in a wide variety of patients [7]. Today, BMS has emerged as the standard of care appropriate for all patients because it is evidence-based and associated with a better outcome [1].

2 A brief history of bloodless medicine & surgery

For about 2000 years up until the 19th century bloodletting rather than blood transfusion was the standard practice in medicine [8]. Virtually all surgeries prior to the 20th century were essentially 'bloodless', and some were remarkably successful. Theodore Kocher, for instance, did his first thyroidectomy in 1872, and by the end of his career he had done 5000 thyroidectomies with only 1% mortality. Kocher never transfused any patient and he won a Nobel Prize [9].

Karl Landsteiner's discovery of the ABO blood groups in 1900 started off the modern era of transfusion medicine. In 1915 Richard Lewisohn introduced anticoagulation with sodium citrate. Blood transfusion was used for World War I and II military casualties. Bernard Fantus set up the first hospital based blood bank in Chicago, USA about 1937.10 From then on blood transfusion became a universal practice in medicine, so that the popular dictum seemed to be "When in doubt transfuse!" [3].

BMS started as an attempt by some dedicated surgeons in the 1960s to accommodate patients who declined blood transfusion, notably Jehovah's Witnesses [11, 12]. Their religious belief is based on a distinctive interpretation of specific passages from the Bible, such as: "You are to abstain from … blood" – Acts Ch. 15 v. 29 (New English Bible) [13, 14]

Denton Cooley, widely regarded as the founding father of modern bloodless surgery, performed the first bloodless open-heart surgery on one of Jehovah's Witnesses in May 1962 [2, 12]. In 1977 Ott and Cooley published a pioneer report of 542 open-heart surgeries

without allogeneic blood transfusion in patients ranging in age from one day to 89 years,15 demonstrating that the "impossible" was possible – and safer. Other surgeons joined, but their ingenious techniques did not gain wide acceptance then [2].

The advent of HIV/AIDS in 1981 forced a reconsideration of blood transfusion practices and a desire for BMS on account of the epidemic proportions of HIV, and the fact that the surest (though not the commonest) route of transmission is through blood transfusion. Many other pathogens old and new that are transmitted by blood (Table 1) [16], and many non-infectious hazards (Table 2) [17] received renewed attention and prominence. The cost of making blood "safe" rose astronomically while the supply of "safe" blood shrank. This added further impetus to the search for transfusion alternatives and the promotion of blood conservation techniques [1, 2].

Recently however, the focus has shifted from the hazards of allogeneic blood to its efficacy – or lack of it. The Canadian Critical Care Trials Group study on Transfusion Requirements in Critical Care (TRICC) by Hérbert and co-workers in 1999 was a landmark prospective randomized study of 838 ICU patients comparing a liberal transfusion versus restricted transfusion policy. It revealed better results with the restricted transfusion group: lower ICU mortality, lower hospital mortality, lower 30-day mortality, and a trend towards decreased organ failure.18 Several other studies have confirmed adverse outcome in transfused patients not related to infectious hazards [19-24]. Allogeneic blood has been found to increase hemorrhage, impair perfusion of the microcirculation, impair oxygen release from hemoglobin, and worsen rather than improve tissue oxygenation [25-29]. Some of these effects are thought to be due to storage lesions. On the other hand, it has not been possible to demonstrate the benefits of RBC transfusion [7, 19, 29, 30].

Thus, while BMS started as an advocacy and then became widespread because of the infectious hazards and high cost/scarcity of allogeneic blood, Evidence-Based Medicine has recently emerged as the driving force behind its current practice, with improvement of outcome as the major aim.

3 Blood conservation techniques

Blood conservation techniques form the basis of the practice of BMS, and may be grouped under of four basic categories or "pillars": [3]

1. Optimizing the Hematocrit
2. Minimizing blood loss
3. Optimizing tissue oxygenation
4. Lowering the 'Transfusion Trigger' (tolerance of anemia)

Virtually all techniques of blood conservation are meant to buttress one or other of these pillars, and when used in combination they effectively reduce or eliminate the use of allogeneic blood with its costs and hazards, and improve clinical outcome (Table 3).

3.1 Optimizing the hematocrit

Optimizing the hematocrit increases the tolerable blood loss or the margin of safety in the event of blood loss in surgery, and reduces morbidity and mortality in non-surgical patients. Iron therapy is at the center of current efforts in this regard with or without Erythropoiesis Stimulating Agents (ESAs), even in the absence of absolute iron deficiency [1,2, 31].

1. **Oral Iron Therapy** is the modality of choice for eligible patients. Ferrous sulfate, gluconate or fumarate may be used to administer ideally 200-220mg of elemental iron per day. Adjuncts to be given daily include Vitamin C 500mg, Vitamin B12 150µg, Folic Acid 5mg, Multivitamins, and nutritional support [4, 31]. The author avoids folic acid in malignant disease [32].

2. **Parenteral Iron Therapy** corrects anemia more rapidly, and may be used alone or in conjunction with ESAs. Intravenous iron is also preferred in anemia of chronic disease Iron dextran is the classical preparation and a low molecular weight iron dextran is available. However, less allergenic preparations are currently favored, especially iron sucrose [31].
   Dose in mg = weight x [normal Hb – actual Hb (g/L)] x 0.24 + 500,31 or [normal Hb – actual Hb (g/dL)] x 200 + 500.4
   Iron dextran is diluted in normal saline at a ratio of 5ml (250mg):100mL saline and administered intravenously initially at 20 drops/min for 5 minutes, then 60 drops/min if no side effects occur. The total dose may be given at once to a maximum of 20mg/kg body weight over 4-6 hours or in divided doses on alternate days (preferably) [4, 31]. The author found that administering Hydrocortisone 100mg i.v. 15 minutes before iron dextran, and diluting 5ml (250mg) of iron dextran in 250-500mL of normal saline successfully averts allergic reactions, even in a patient who previously reacted when those measures were not taken [31].

   Iron sucrose is less allergenic and is also administered safely in normal saline infusion 100mg:50mL or 200mg:100mL over 30 minutes, or 500mg:250mL administered over 3 hours. The total dose may be given at once to a maximum of 7mg/kg body weight over 3-3.5 hours (some workers have given 1000mg safely) or in divided doses on alternate days [4].

3. **Erythropoietin alfa** which was in use for blood conservation in oncology since 1989 was approved for perioperative use in the US in 1996. Beta preparations are also available. In general surgery 100-150U/kg s.c. for 6 doses (e.g. twice weekly for 3 weeks) is recommended. [4] In oncology 150U/kg s.c. 3 times weekly or 40,000U s.c. weekly is the recommended starting dose [33]. Darbopoietin alfa is a long-acting ESA that can be administered s.c. weekly (2.25µg/kg) or 3 weekly (500µg). Intravenous iron is recommended in conjunction with ESAs as it potentiates the response and averts functional iron deficiency [4, 34]. ESAs stimulate RBC production by up to 4 times the basal marrow rate. Reticulocyte count increases by Day 3 and hemoglobin typically increases at 1g/dL every 4-7 days [34]. Use of ESAs is not recommended when the hemoglobin is above 12g/dl in oncology [33].

Optimizing the hemoglobin with the appropriate medication is indicated in virtually all surgical patients, in elective and emergency cases, as it is in treatment and prophylaxis of anemia in non-surgical patients [4] Interventions in this regard do not start working slowly after 21 days as some may imagine, but start working immediately and build up over time [31, 34]. Provided the main pathology is properly and promptly treated, the patient's improvement with bloodless care is sometimes dramatic, compared with patients who are transfused.

3.2 Minimizing blood loss

Efforts towards minimizing blood loss in the surgical patient start from the first contact and span through the entire perioperative period.

a. **Good history, physical examination, and laboratory investigations** are essential even in emergencies, taking note of the following among others:

   i. History of bleeding disorders
   ii. Anticoagulant therapy
   iii. Site of external hemorrhage (to be promptly arrested)
   iv. Estimate of blood loss
   v. Full Blood Count
   vi. Clotting profile (if indicated)

b. **Pharmacological agents t**hat can reduce hemorrhage include: [4]

   i. **Vitamin K** 10mg (2.5-50mg) p.o., i.m., s.c., i.v.
   ii. **Tranexamic acid** 1.5g 3x/day – 1g 6x/day for 5-7 days, first i.v. then p.o. (for prophylaxis, 1g p.o. preop).
   iii. **Aprotinin** 500,000KIU i.v. then 150,000KIU/h in infusion (low-dose regimen, for noncardiac surgery); or 2,000,000KIU i.v. then 2,000,000KIU in CPB prime, then 500,000KIU in infusion for duration of surgery (Hammersmith high-dose regimen for cardiac surgery).
   iv. **Desmopressin** (1 –deamino-8-D-arginine vasopressin or DDAVP) 0.3µg/kg i.v. or s.c. x2 periop, second dose 6-8 hours after the first; or 2 intranasal "standard puffs" totaling 300µg for home use (e.g. menorrhagia), repeated as necessary after 8-12 hours.
   v. **Recombinant Factor VIIa** 90µg/kg i.v., repeat dose every 2-3 hours or as needed.
   vi. **Somatostatin**
   vii. **Vasopressin**
   ix. **Misoprostol** 600 µg p.o. to prevent postpartum hemorrhage

c. **Non-invasive monitoring s**uch as pulse oximetry, whenever possible, minimizes blood loss.

d. **Restriction of diagnostic phlebotomies** reduces blood wastage. **Microsampling** is a recent technique that drastically reduces the volume of blood needed for tests, with obvious benefits in blood conservation.

d. **Intraoperative strategies** that could be employed to reduce blood loss include:

   i. **Normothermia** averts coagulopathy due to hypothermia [1, 4, 35] and may be achieved by

      1. Maintaining room temperature above 270 C
      2. Thermal suits or blankets
      3. Warming of intravenous infusions

   ii. **Acute Normovolemic Hemodilution (ANH)** involves withdrawal of some of the patient's blood in the operating room prior to incision, and replacement with colloids and/or crystalloids, so that intraoperatively the patient loses dilute blood with less effect on the total red cell mass. The withdrawn blood is kept within view in the operating room and is re-infused at the end of surgery.
   Up to 4 units may be withdrawn safely using the formula V = [Baseline HCT – Target HCT]/Average HCT x EBV. (V = volume, HCT = hematocrit, EBV = estimated blood volume) [36].
   iii. **Regional anesthesia** results in less intraoperative blood loss than general anesthesia through mechanisms not yet fully elucidated [4].
   iv. **Positioning** of patients to minimise blood loss is guided by two principles: [2]

      1. Elevate the operation site above the right atrium e.g. Trendelenburg for prostatectomy, reverse Trendelenburg for thyroidectomy;
      2. Avoid compression of venous drainage e.g. tilting patient in supine position slightly to the left to avoid compression of inferior vena cava in abdominal surgery.

v. **Meticulous hemostasis** and good operative technique can save up to 1 or more units of blood [1]. Simple techniques like Pringle's manoeuvre in liver surgery and B-lynch suture in postpartum haemorrhage can be employed to great benefit. Use of diathermy and topical adhesives like fibrin glue and Surgicel® (Johnson & Johnson, Somerville, NJ, USA) limits blood loss, as does judicious use of tourniquet. Argon Beam Coagulator and Cavitron Ultrasonic Surgical Aspirator (CUSA) are blood conserving innovations in hemostasis and dissection respectively [1, 4, 37]

vi. **Cell salvage and autotransfusion** can be performed effectively by techniques ranging from simple manual scooping of blood from a wound, filtration then reinfusion, to use of sophisticated computerized cell salvage machines that return washed blood into the patient.

vii. **Laparascopic surgery** and **interventional radiology** can effectively reduce blood loss in many surgical procedures.

viii. Other techniques like **controlled hypotension** and **hypothermia** may be used cautiously in selected patients [2, 4]

3.3 Optimizing tissue oxygenation

This principle is often omitted from the "pillars" of BMS or Patient Blood Management [6, 7]. Nevertheless, it can be deduced as a separate and indispensable element since tissue oxygenation is the major function of blood.

Many clinicians transfuse blood in the hope of improving the patient's tissue oxygenation. However, allogeneic blood transfusion has been shown not to improve but to decrease tissue oxygenation.27-29 Rather, tissue oxygenation can be improved by other methods avoiding blood transfusion by considering the equation for oxygen delivery: [38] $DO_2 = CO \times CaO_2 = CO \times \{(Hb \times SaO_2 \times 1.39) + (PaO_2 \times 0.003)\}$. ($DO_2$ = oxygen delivery, CO = cardiac output, CaO_2 = arterial O_2 content, Hb = hemoglobin concentration, SaO_2 = fraction of hemoglobin saturated with O_2, PaO_2 = partial pressure of O_2 dissolved in arterial blood). Thus, even when Hb is low, DO_2 can be improved by improving the CO and CaO_2 (SaO_2 and PaO_2).

a. **Volume replacement** with crystalloids (e.g. normal saline and Ringer's lactate) or colloids (e.g. Hetastarch, Hemacel®, Dextran, and Isoplasma®) reduces blood viscosity and improves cardiac output. Crystalloid requirement is 3 times blood volume lost, while colloid requirement is equivalent to volume lost and is therefore preferable when there is danger of circulatory overload with crystalloids.

b. **Oxygen therapy** increases SaO_2 and PaO_2. Intraoperative hyperoxic ventilation not only improves tissue oxygenation but also can augment ANH and avert allogeneic blood transfusion [2, 4]. Hyperbaric oxygen is rarely needed but may be used when indicated and available [2, 4].

c. **Minimizing oxygen consumption** may be achieved through appropriate interventions such as:

   i. Maintaining room temperature above 270 C
   ii. Thermal suits or blankets
   iii. Warming of intravenous infusions

d. **Treating causes of tissue hypoxia** promptly e.g. pneumonia, bronchial asthma.

e. **Inotropic and vasoactive agents** may be used in extreme cases to improve cardiac output. Low dose dopamine (2-5µg/kg/minute) also improves renal perfusion, but higher doses cause vasoconstriction.

f. **Artificial Oxygen carriers a**re still largely experimental. They include Perflourocarbon emulsions and modified hemoglobin-based solutions. They have been used successfully in Augmented ANH (A-ANH) [2, 4].

4 Bloodless medicine and surgery programs

Bloodless medicine and surgery programs (BMSPs) are specialized programs offering non-blood treatment by a committed multidisciplinary staff to a wide variety of registered patients within a hospital setting. There are up to 240 of such programs worldwide [42]. Depending on the emphasis, various institutions have adopted various names for their program, such as Blood Conservation Program or Transfusion-Free Medicine Program. These programs provide the standard of care for patients without the use of allogeneic blood products. They invariably record superior results [2].

5 Newer innovations in bloodless medicine & surgery

One of the selling points of robotic surgery is a drastic reduction in blood loss due to the increased precision obtainable (figure 1).

Non-invasive continuous monitoring of total hemoglobin is now possible with the Rainbow Pulse CO-Oximeter® by Masimo® Corporation (figure 2), licensed for use in the US in 2010. This is of great advantage during certain types of surgeries traditionally associated with much blood loss like cardiac surgery, liver surgery, and in monitoring ANH.

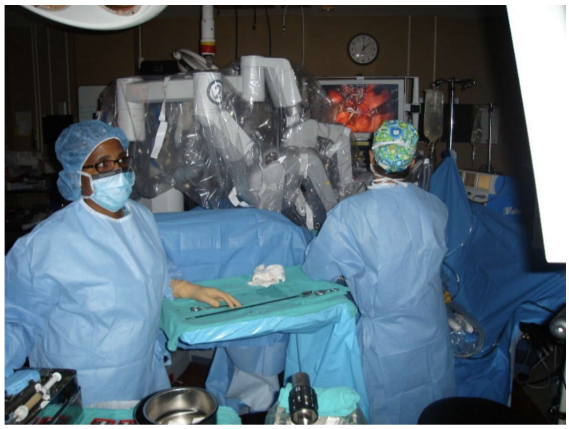

Fig. 1. Robotic surgery

Fig. 2. Pulse CO-Oximeter®

Thromboelastometry during cardiac surgery, liver transplantation and other similar surgeries has greatly reduced transfusion rates [43, 44]. It monitors the coagulation status of the patient and greatly minimizes undue intervention with blood products.

Plasmajet® by Plasma Surgical Limited is the product of newer technology for hemostasis during surgery (figure 3). It works in a similar manner to the argon beam coagulator.

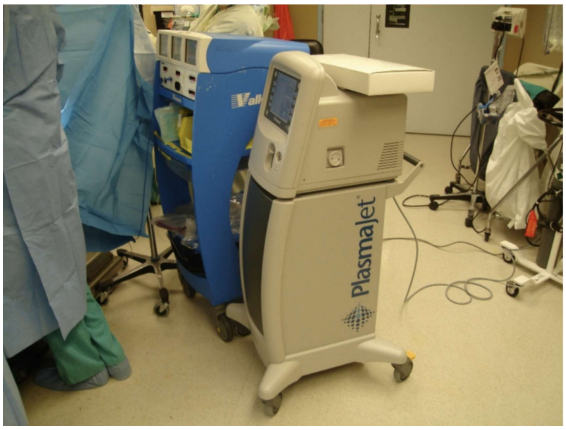

Fig. 3. Plasmajet®

5 The future of bloodless medicine and surgery

BMS is evidence-based [7]. It results in faster recovery, lower morbidity, lower mortality, shorter hospital stay, lower cost and better patient (and physician) satisfaction [1, 2]. Furthermore, patient autonomy is respected and the hazards of allogeneic blood transfusion are avoided, in accordance with the principles of nonmaleficence and beneficence in the Hippocratic Oath [7, 41, 45]. Understandably then, BMS is no longer an 'alternative' but the current standard of care.4 BMS may also be considered a crucial step in the journey towards universal ethical, scientific, and evidence-based practice of medicine.

The Government of Western Australia is the first in the world to implement Patient Blood Management as an official policy starting from 2008 [7]. In 2010 the 63rd World Health Assembly of the World Health Organization officially recognized and adopted the "pillars" of Patient Blood Management [6]. BMS is obviously therefore the universal standard of future ethical practice of medicine, having survived prejudice and being propelled by scientific evidence.

Blood conservation in BMS is not 'a technique' but a combination of techniques tailored to the needs and physiological status of the individual patient in order to avoid transfusion of allogeneic blood. It requires planning and a multidisciplinary team approach, but usually little technology, to achieve the best results. Setting up a BMSP with written protocols, standardizes the practice of bloodless medicine and surgery, thus ensuring that patients receive the best care.

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Table 1 *Infectious agents transmissible by blood transfusion16*

Viruses	Hepatitis viruses Hepatitis A virus (HAV) Hepatitis B virus (HBV) Hepatitis C virus (HCV) Hepatitis D virus (HDV) (requires co-infection with HBV) Hepatitis E virus (HEV) Retroviruses Human immunodeficiency virus (HIV) 1 and +2 (+ + other sub-types) Human T-cell leukemia virus (HTLV) I and II Herpes viruses Human cytomegalovirus (HCMV) Epstein–Barr virus (EBV) Human herpes virus 8 (HHV-8) Parvoviruses Parvovirus B19 Miscellaneous viruses GBV-C [previously referred to as hepatitis G virus (HGV)] TTV West Nile virus
Bacteria	**Endogenuous** Treponema pallidum (syphilis) Borrelia burgdorferi (Lyme disease) Brucella melitensis (brucellosis) Yersinia enterocolitica Salmonella spp. **Exogenous (environmental species and skin commensals)** Staphylococcal spp. Pseudomonas Serratia spp. Rickettsiae Rickettsia rickettsii (Rocky Mountain spotted fever) Coxiella burnettii (Q fever)
Protozoa	Plasmodium spp. (malaria) Trypanosoma cruzi (Chagas disease) Toxoplasma gondii (toxoplasmosis) Babesia microti/divergens (babesiosis) Leishmania spp. (leishmaniasis)
Prions	Variant Creutzfeldt–Jakob disease (vCJD)

Table 2 *Noninfectious Serious Hazards of Transfusion (NISHOTs)17*

Immune mediated	Hemolytic transfusion reactions Febrile nonhemolytic transfusion reactions Allergic/urticarial/anaphylactic transfusion reactions Transfusion-related acute lung injury (TRALI) Posttransfusion purpura (PTP) Transfusion-associated graft versus host disease (TA-GVHD) Microchimerism Transfusion-related immunomodulation (TRIM) Alloimmunization
Nonimmune mediated	Septic transfusion reactions Nonimmune hemolysis Mistransfusion Transfusion-associated circulatory overload (TACO) Metabolic derangements Coagulopathic complications from massive transfusion Complications from red cell storage lesions Over/undertransfusion Iron overload

Table 3 *Approximate contributions of selected modalities to blood conservation in the surgical patient (adapted from Goodnough et al, 20031)*

Options	Number of Units of blood conserved
Preoperative	
Tolerance of anemia ((lowering the transfusion trigger)	1-2
Increasing preoperative RBC mass	2
Intraoperative	
Meticulous hemostasis and operative technique	1 or more
ANH	1-2
Blood salvage	1 or more
Postoperative	
Restricted phlebotomy	1
Blood salvage	1