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New horizons for reduction of blood use: Patient blood management

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Abstract:

A countrywide study over the eras indicates overuse of blood transfusion can have considerable risks to patients accompanied by significant costs of blood transfusion for patients, hospitals, and health-care systems. Besides, more than 30% of the world's population is anemic. Typically, blood transfusion helps continue suitable oxygen transfer in anemia, i.e., more and more documented as a threatening factor with several adverse outcomes including long hospitalization, morbidity, and mortality. Transplantation of allogeneic blood is thus like a two-edged sword. There is no doubt that the blood transfusion is a life-saving treatment, but it should be underpinned by much of up-to-date health-care services. The new theory considered for patient blood management (PBM) also discusses the timely application of evidence-based surgical and clinical theories and focuses on patient outcomes. Furthermore, PBM involves a multidisciplinary methodology to reduce unnecessary transfusions, minimize costs, and cut risks.

Keywords:

Blood transfusion, maximum surgical blood ordering schedule, patient blood management

Introduction

The first case of a successful human-to-human blood transfusion was performed by James Blundell in 1818. During the 20th century, blood use was escalated to save patients' lives across the world.[1] However, a fundamental question remained unanswered, that is to say; Is Blood transfusion considered to be safe or not?[2]

It should be noted that misdistribution of oxygen in a tissue can result in oxygen deficiency, ischemia, and expiry. Therefore, allogenic blood transfusion (ABT) may be requested to eliminate critical severe anemia and restore oxygenation and protect patients against bleeding in clinical settings. Evidence has also demonstrated an association between ABT and unsatisfactory clinical outcomes.[3-5] Accordingly, ABT is correlated with transfusion reactions both infective, for example, hepatitis C virus, hepatitis B virus (HBV) or acquired human immunodeficiency virus (HIV)[6] and noninfective, for example, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and, Transfusion-Associated Graft Versus Host Disease (TA-GVHD) and transfusion-related immunomodulation (TRIM).[7] In this regard, a study established that the length of stays in hospitals and intensive care units (ICUs) as well as mortality rates, were reported to be higher in blood recipients.[8,9]

In addition, ABT is deemed as one of the costly supportive cures imposing significant economic burdens on health-care systems.[10] Shander *et al*. demonstrated that the total cost of red blood cell (RBC) unit transfusion in administration processes was $761 USD in surgical situations at four hospitals. In this

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study, some costs such as long-term adverse effects of treatment and hospitalization charges were neglected.[11]

Besides, Jehovah's Witnesses (JW) were well-known for their rejection of allogenic blood components based on their beliefs. Great experience has been thus gained from JW patients who have been severely anemic or even bleeding patients that described bloodless medical and surgical management. These approaches, known as patient blood management (PBM),[12] have been effectively exploited to reduce ABT use in health-care services for other patients. Accordingly, PBM is an approach to minimize patients' need to ABT. The given approach sets a patient on the axis of choices for the best treatment and ensures their safety. Correct implementation of PBM can also lead to the moderation of inappropriate use of blood components, their adverse effects, as well as their associated costs.[12]

Blood Transfusion Epidemiology

So far, few studies have been published on the epidemiology of blood use, but this limited literature shows bear significant variations (0%–100%) associated with the consumption of blood products in different hospitals and countries due to differences in transfusion practices in health-care centers[13,14] regarding diagnosis, type of surgery, surgeon's skills, use of advanced surgical and anesthesia techniques, geographical site and hospital ranking.[15]

In a recent observational cohort study of 102470 cases experiencing coronary artery bypass graft (CABG) surgery in 798 geographical regions in the United States; rates of RBC, fresh frozen plasma (FFP), and platelet (PLT) blood count transfusion varied from 0% to 97.5% between 2008 and 2010.[14] Cobain *et al*. also performed a retrospective study in the United States, England, Australia, and Denmark and reported that most RBC and plasma transfusion rates had been included in 24% and 34% of cardiovascular surgeries in the United States, respectively. Moreover, RBC and plasma transfusion rates were assessed in 39.7% and 62.7% of surgical treatments in England, respectively. In the other two countries, RBC transfusion rates were, respectively, reported to be 20.7% and 25.7% for malignant diseases; and plasma transfusion rates were 26% and 39.2% for trauma and circulatory diseases, respectively. Furthermore, neoplasms and hematologic diseases had the most usage of PLT in the United States, Australia, and Denmark.[13] In three hospitals in the city of Yazd; Javadzadeh *et al*. reported that the epidemiology of PLT and RBC use in Iranian patients with malignancy was 82% and 42%, respectively.[16] The use of RBC in surgical settings especially in cardiovascular surgeries and neoplasms was correspondingly significant. In all countries, PLT was mainly used for hematologic diseases and neoplasms, and plasma was almost used in cardiovascular surgeries.

Blood Transfusion and Medical Treatment

Some patients, such as those with major thalassemia and hemophilia, cases on chemotherapy, and patients undergoing hematopoietic stem cell transplantation have a long-lasting dependence on blood components.[17-19] Early hemophilic treatment was associated with the use of FFP; later, cryoprecipitate and plasma-derived concentrates of clotting factors also became common.[20] The introduction of recombinant activated factor VII and Activated Prothrombin Complex Concentrate significantly enhanced hemorrhage control in patients developing inhibitors and thus reducing the need for transfusion therapy in these patients.[21]

A study indicated that the average transfusion in leukemic cases was 1.6 PLT concentrates and 2.5 RBC units per week. Both high doses of PLT and packed RBC transfusion were linked to less clinical responses and an increase in quick death after the induction phase in chemotherapy.[22] It must be noted that, following high-dosage chemotherapy in leukemia, bone marrow is suppressed and leads to the increased rates of RBC and PLT transfusion. Seeking chemotherapy for solid tumors may also need a blood transfusion, but less than leukemia.[23]

Gene therapy mainly corrects malfunctioning genes accounting for genetic syndrome through several approaches.[24] According to the studies, gene therapy can discount blood transfusion or minimize it in hemoglobinopathic, hemophilic, and, thalassemic patients who are frequently need RBC transfusion.[25-28]

Blood Transfusion and Surgery

Preoperative anemia is considered a risk factor for infection, and acute kidney injury. It makes the need for RBC transfusion and causes prolonged stay in healthcare centers. Moreover, management of acute symptomatic anemia is particularly challenging when the administration of blood transfusions fails.[29] Excessive hemorrhage can be also attributed to other causes of trauma which contributes in almost 30% of death cases.[30] Gupta *et al*. reported that blood loss rates >250 ml in patients experiencing laparoscopic liver incision resulted in clinical status failure.[31] Rankin *et al*. also demonstrated that massive transfusion was a major need in elective surgery, for example, orthopedic and central nervous system surgeries. Accordingly, surgery candidates had lost about 11 L of blood intraoperatively whose average of administrated units was 24.5 units of RBC

and plasma products as well as 4.5 units of PLT orders.[32] Another investigation indicated that blood transfusion is a significant predictor of increased morbidity and mortality rates in patients with liver cancers and surgery candidates.[33] According to another investigation, the adverse effects associated with transfusion after hepatectomy-associated colorectal metastases were dose-dependent. The researchers found that single-dose or no-unit recipients had shown better outcomes when compared to two-unit recipients. Mortality in the former group was 2.5% and 1.2%, and it was 11.1% in the latter. Moreover, they found that the transfusion of more units cause longer hospitalization however it should be considered that it may be confounding factors in which patient requiring more blood may already be compromised.[34]

According to a number of studies, the need for blood transfusion was higher in on-pump CABG and combined CABG and valve surgery, since more extensive tissue injury might result in a greater amount of clotting factor and PLT consumption whose effect on bleeding risk higher.[35,36] It should be noted that great blood loss is common during orthopedic surgery such as neuromuscular scoliosis cases due to the reduction of clotting factor levels and increased risk of bleeding in underlying neuromuscular diseases.[37] Another study had correspondingly found a relationship between the need for blood transfusion and the prescription of serotonergic antidepressants among patients with orthopedic surgical experiences. These drugs could inhibit serotonin-mediated PLT activation and increase more blood loss.[38] In surgical settings, multiple factors including pre- and post-operative anemia incidence, intraoperative blood loss, underlying diseases, patients coagulation statue, the type of surgery, site of surgery, redo or combining of surgery, as well as some surgical techniques increase the need for transfusion.[35-37]

Risks of Transfusion

ABT may be assumed very safe, but this is not always entirely true. It can lead to significant adverse effects and needs cautious attention. ABT is related to transfusion events with both infective and noninfective difficulties. The infectious complications are caused by bloodborne pathogens which include viral infections, for example, cytomegalovirus, human T-cell lymphotropic virus 1,2, HIV (1, 2), hepatitis virus including B,[39] C, and E types, Creutzfeldt-Jakob Disease, and more novel Ebola and Zika viruses along with emerging infectious diseases.[40] A study reported that the risk of bacterial infections and short-term mortality in perioperative transfusion recipients was more than nonrecipient patients after surgery.[41] However, some studies did not demonstrate a constant relationship between postoperative infection and blood transfusion therapy.[41,42] Scientific advances in this field have severely reduced the likelihood of microbial bloodborne disease but some of the risks have remained the same containing TRALI, TRIM, TA-GVHD, and TACO and other serious complications.[43] However, these problems can be partly diminished using the prescription of leukodepletion transfusion, irradiation, and cautious donor/recipient selection.[7] Evidence even showed that hemorrhage and transfusion may increase the risks of relapse after liver resection for hepatocellular carcinoma.[44] As suggested by Schwann *et al*., the use of transfusion in CABG surgery could augment mortality risk.[45] A number of studies had further confirmed that the use of blood transfusion in orthopedic surgeries make delays in wound healing[46,47] and consequently increases hospitalization up to 1.5 times.[46] It should be noted that transfusion can modify host immunity which makes morbidity or mortality possible. Recurrent tumors, secondary infections, and metastases are examples of immunosuppressive effects. The logic is that ABT can result in intensifying metastasis possibility and cancer development by down-regulating the immune system in patients.[48]

Costs of Transfusion

ABT accounts for up to 5% of the whole health-care charges in advanced countries.[10] Costs associated with blood transfusion can thus significantly increase the burden of health-care system costs, for example, increasing ICU residency and hospitalization days, postoperative use of blood components, adverse effects of ABT treatment, frequency of laboratory tests, and overall blood production up to administration costs. Therefore, unnecessary blood product transfusion needs to be reduced to mitigate health-care costs.[49] Forbes *et al*. found that the patient's average charges and hospital's average costs per unit transfused were $219 and $155, respectively. In this study, most costs were associated with the laboratory tests.[50] The related literature had also calculated the total cost of RBC transfusion in outpatients with solid tumors and leukemia. In solid tumors, less cost by $474 per BRC unit had been spent when compared to $512 per RBC transfusion in patients with leukemia. Thus, the type of cancer, patient's age, and environmental differences might have increased transfusion-associated costs.[51] It should be noted that costs associated with transfusion practices annually rise along with scientific advances, for example, nucleic acid amplification test routinization.[52] Since ABT-associated costs are annually increasing, cost-effective approaches should be used as alternatives for blood transfusion considering price adjustment.

What is Patient Blood Management?

Some reasons about why PBM exists including an increasing gap between supply and order of blood

components, lack of safety, and adverse effects of blood products as well as increasing costs of transfusion.[53] PBM can thus, reduce inappropriate transfusion. It is also known as an evidence-based and a patient-centered multidisciplinary program that concurrently helps ensuring patient safety and blood use reduction. As well, PBM focuses on three pillars: improving hematopoiesis, minimizing blood loss, optimizing coagulation and increasing biological tolerance of anemia in patients. PBM approaches in surgery can be divided into three stages; pre-, peri-, and post-operative procedures.[54]

PBM means beyond the conception of proper use of blood components because it significantly decreases frequent transfusions by reducing possible risk factors that may result in repeated transfusion.[53] Hence, PBM is a universally recognized concept validated by the World Health Organization (WHO) and aimed to manage transfusion practices, decrease charges, and improve hospitalization days. It is also applicable in surgical and clinical settings to provide access to blood and blood components for patients who actually need a transfusion.[55] Gallagher *et al*. implemented a PBM program in hospitals and investigated effects of PBM strategies in Western Australia from 2008 to 2015. The given project began with team training for physicians and nurses, revising patients' clinical information, and improving clinical care such as preoperative anemia improvement. This intervention led to a significant reduction in blood transfusion incidence and demonstrated that staff training played a key role in the efficiency of PBM program.[56]

Anemia Correction

The definition of anemia provided by WHO is a hemoglobin (Hb) threshold of 12 g/dl in females and 13 g/dl in males.[57] The first step in PBM is the identification of patients who are at higher risk of developing anemia and bleeding disorders in clinical examinations and taking a history. Subsequently, proper decisions need to be made and proper measures should be made based on patients' clinical conditions.[58] Anemia is also a common complication in patients undergoing surgery, acute hemorrhage cases, old individuals, as well as cardiac patients. Thus, low Hb is considered an important and independent factor in predicting needs for ABT as well as increasing rates of mortality and morbidity during surgeries.[59] In 2015, Lasocki *et al*. observed that most of the patients experiencing selective orthopedic operation had standard Hb thresholds but they had become anemic after surgery. They found that the presence of anemia before surgery might result in the worsening of diseases and complications associated with blood transfusion. The prevalence of its adverse effects in anemic patients was 36.9% and in nonanemic cases was also reported by 22.2%. In addition, patients with anemia before surgery had experienced longer hospital stay.[60] Hence, it is important to correct anemia to acceptable iron stores, through preoperative administration of adequate Vitamin B12, folic acid, and erythropoiesis-stimulating agent (ESA).[4] Cuenca *et al*. reported that the need for ABT after the operation had been minimized once patients underwent total knee replacement treated with folate (5 mg/day), ferrous sulfate (256 mg/day), and ascorbic acid (1000 mg/day) at least 4 weeks before the surgery.[61] Lidder *et al*. conducted a clinical trial examining ferrous sulfate (200 mg) oral treatment for 14 days before colorectal surgery and found it to be an easy and low-cost care instead of ABT reduction.[62] Hence, if patients have oral iron absorption deficiency, iron intolerance, or because of a small opportunity for surgery need faster treatments, iron injection must be used to increase its stores. Today, there are several types of intravenous iron formulations. Counter-indication of iron treatment can be mentioned as iron sensitivity, iron overload, and anemia disassociated with iron.[63] Adkinson *et al*. conducted a pilot study comparing the efficacy of ferric carboxymaltose with intravenous ferumoxytol in patients with iron deficiency anemia as nonresponsive individuals to oral iron. The patients treated with ferric carboxymaltose or ferumoxytol intravenously over 15 min on days 1 and 8 or 9 for full respective dosages of 1.02 g and 1.50 g. Ferric carboxymaltose had more allergic responses than ferumoxytol.[64]

Erythropoiesis-stimulated agents (ESAs) such as erythropoietin derivatives (α-epoetin and α-darbepoetin) can also increase RBC mass in an anemic patient to reduce the risk of the need for transfusion during surgery. However, investigations have raised worries about the use of ESAs to be added to Hb concentrations in patients undergoing hemodialysis above a level intended solely to prevent them from inappropriate RBC transfusions.[65] Anti-erythropoietin (anti-EPO) immunoglobulin associated with pure RBC aplasia is also a severe adverse effect that can happen in the treatments by ESAs.[66] RBC aplasia mediated by anti-EPO can mainly occur in cases undergoing treatment by epoetin alfa. The incidence percentage of aplasia was also reported in a study in which aplasia related to EPO administration was a rare episode that had happened among some patients with kidney failure.[67] Similarly, in a meta-analysis, it was observed that ESAs in cancer patients might augment mortality and degrade survival rates. The mortality associated with treatment by ESAs needed to be stabilized versus their profits.[68] Evidence also revealed that EPO therapy could be cost-effective, with or without autologous blood obtained in perioperative settings.[69]

It should be noted that packed cell (PC) transfusion and anemia are correlated with illness worsening and death likelihood. Anemia correction in patients may also progress operation safety and outcomes in patients more than PC transfusion.[4]

Point-of-Care Testing

Intraoperative homeostatic regulation is essential as it can prevent probable problems associated with transfusion and surgery in anemic patients.[70] Hence, Point-of-Care Testing (POCT) has numerous benefits when compared to usual laboratory tests for quicker turn-around times as well as well-timed choices on coagulation interference. The most common POCT is the activated clotting time, used to monitor heparin therapy during cardiopulmonary bypass. Viscoelastic coagulation assessments including thromboelastography and Rotational thromboelastometry (ROTEM) have been also suggested for the treatment of postoperative bleeding. ROTEM is a POCT device that can be used to calculate viscoelastic properties on various features of blood coagulation in traumas and surgeries.[71] Khalaf Adeli *et al*. conducted an investigation on changes in POC tests in elective valve coronary cardiac operation. They revealed that PLT count and PLT aggregation were reduced during surgery, leading to augmented bleeding and transfusion rate, postoperatively.[72] A cohort study conducted by Smith *et al*. correspondingly revealed that POCT had statistically and significantly diminished blood components received during lung-transplantation surgeries.[73] In a systematic review and meta-analysis, it was further validated that the routine use of POCT reduced PLT and RBC transfusion, death rates, hospitalization days, duration of ICU stays, reoperation for blood loss, and critical kidney damage in cardiac operations. The Group Reading Assessment and Diagnostic Evaluation™ as a diagnostic reading test valuation demonstrated that the value of the evidence was "low" or "very low" for all results.[74] Furthermore, Forestier *et al*. recommended that POCT needed to be routinized for cardiac operations without any excessive bleeding.[75]

Antifibrinolytics

To reduce blood transfusion, blood loss should be reduced by administering pharmacological drugs including antifibrinolytic factors, tranexamic acid (TXA), epsilon-aminocaproic acid (EACA), protease inhibitor, for example, aprotinin and desmopressin that increase plasma levels of factor VIII and von Willebrand factor.[76] A systematic review by Henry *et al*. compared TXA, EACA, and aprotinin with each other. They assessed the rate of intraoperative bleeding, need for transfusion, and their adverse effects and mortality rates. The study indicated that lysine derivatives such as TXA were safer than aprotinin but more effective than TXA in terms of improvement of blood use and hemorrhage.[77] TXA also inhibited fibrinolysis and needed to be used for prophylaxis in surgery with excessive bleeding and trauma since it could significantly reduce blood loss.[78]

Reduction of Iatrogenic Blood Loss

Laboratory testing is the main reason for iatrogenic anemia after surgery. Nonpharmacologic policies can be thus applied to decrease frequent transfusion. Most of these policies benefit from little charge and can be simply employed when surgeons and nurses are encouraged to minimalize transfusion ordering. In a cohort study by Raad *et al*., it was indicated that hospital staff training about the removal of unnecessary laboratory tests except for arterial blood gas could be the cause of anemia reduction in ICU patients.[79] Eliminating the effect of diagnostic phlebotomy on the progress of anemia, particularly in pediatric patients is another policy;[80] for example, Myles *et al*. in a cohort study demonstrated that low-volume sampling tubes were related to a 42% saving of blood equal to 180 ml of blood over 21 days of admission.[81]

Autologous Transfusion

Three main techniques are applied for autologous transfusion including preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), and cell salvage.

PAD is one of the approaches that can lead to averting the needs for allogeneic RBC transfusion in some patients experiencing selective surgery. Patients can normally donate 1–3 units of packed RBCs over a course lasting 21–28 days before their surgery.[82] In this regard, a study demonstrated that the average cost associated with the blood donation up to transfusion of PAD was $338 per unit although; the effectiveness and cost-effectiveness of PAD have remained questionable.[83]

ANH is a technique in which blood is collected perioperatively and exchanged with colloid or crystalloid diluents.[84] Among the presently-used PBM policies, ANH is assumed as a rather safe strategy. ANH can remove postponement between bloodletting and surgery. It is also taken into account as a cost-effective method with no administration or store charges.[85,86] Colloid fluids, as albumin, hydroxyl-ethyl starch, and gelatin are also known as current replacements. The merits of colloids include their leaking into the unsuitable area of interstitial space less than crystalloids and thus less volume is used. However, these fluids have particular contrary side effects such as vomiting,

itchiness, coagulopathy, fever and chills, renal problems, and rare responses like bronchospasm.[87] Evidence in this respect described that the process of ANH contains the boost of cardiac efficiency.[88] In a systematic review and meta-analysis in this field, also it was reported that ANH could decrease the number of patients transfused, RBC transfusion, and bleeding in cardiac operations.[89]

JW and cases with infrequent blood groups or RBC immunoglobulins, for whom finding well-matched blood units are hard, can use cell salvage.[90,91] There are some experimental studies supporting cell salvage usage in tumor surgery. In gynecologic malignancy, the removal of the uterus and tumor recurrence rates can delete tumor cells via a leuckoreducing filter.[91-93] This technique is assumed suitable for any patient whose blood loss is estimated by >1000 ml.[91] Sickle-cell anemia, hemostatic factors (e.g., thrombin and fibrin), and chemical contamination of collected blood coupled with alcohol and betadine are also introduced as contraindications to cell salvage. However, in a report, sickle-cell trait had been mentioned as one of the indications for cell salvage depending on clinical situations.[91,94] It must be noted that the given method has become uncommon due to the development of surgical approaches and blood loss reduction.[95]

Blood Ordering Guidelines

The Maximum surgical blood order schedule (MSBOS) is known as a list that helps to limit preoperative over-cross-matching of RBC units. MSBOS is a table of the frequently done selective surgical implements in a hospital with the most number of blood units which can be cross-matched for each operation.[96] In 1974, Friedman *et al*. conducted a study in Michigan and observed that the same number of cross-matched units had been consumed in similar surgeries. Subsequently, they established one MSBOS guideline to normalize blood product over-ordering according to patients' requirements. The outcomes of the MSBOS presentation were successful and caused a reduction in RBC units from 6.5% to 4.5% via the removal of over-ordering.[96] To create the MSBOS, the data also needed to be examined for each operation. Regarding each elective surgery, blood usage could be evaluated using various indices such as cross-match-to-transfusion (C:T) ratio.[97] This index was computed by the formulation:

$$\text{C : T ratio} = \frac{\text{No. of units cross - matched}}{\text{No. of units transfused}}$$

The perfect rate for the C: T ratio is 1.0. The upper value also leads to more blood that is being cross-matched unreasonably. A truthful target for surgical measures is a C: T ratio between 2 and 3: 1, which is linked to blood use between 30% and 50%.[97] One of the conditions to implement this guideline is to routinize an antibody screening test or type and screen (T/S) in blood banks.[98] The order of T/S, which usually takes 1 h, also includes defining patient's ABO grouping, RhD type, and plasma screening for clinically important immunoglobulins.[99] Regarding certain patients and procedures (e.g., laparoscopy, cesarean section and lobectomy), T/S is a safe alternative for type and cross-match because it helps better consumption of blood products and is less expensive. T/S is also performed on the patient's plasma, not RBC units.[98] However, the MSBOS scheme does not include changes in transfusion needs among patients with similar surgeries, and many blood banks of hospitals still have high C: T ratios. Therefore, alternative mechanisms increasing the odds of transfusing cross-matched blood and thus, minimizing wastage of reserved blood units should be adopted. Accordingly, the surgical blood order equation (SBOE) was developed for the first time in a retrospective study about ordering RBC units for patient's requirements of total hip arthroplasty.[100] In 1998, Nuttall *et al*. compared SBOE with MSBOS and revealed that SBOE had a lower C:T ratio when compared to MSBOS (0.83 vs. 4.12). Charges were also lower due to SBOE implementation.[101]

Summary

A PBM program is a conservative approach to improve the outcome of hospitalized patients. As with other therapeutic procedures, comprehensive clinical indications for PBM are constantly evolving and new indications are being identified. Therefore, more evidence and documentation are needed to optimize the methods used in PBM for surgical and nonsurgical patients. At the same time, effective regulations and regulatory measures and guidelines should be implemented by medical associations and national and international health authorities to promote and motivate the effective implementation of PBM programs.

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Conflicts of interest

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