

Transfusion dependency in cardiac surgery – update 2006

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Summary

In developed countries perioperative blood transfusion requirements for red blood cell concentrates (RBC), platelet concentrates (PC), fresh frozen plasma (FFP) and stable plasma derivatives have now levelled off with more patients requiring less or no products whilst fewer patients need the larger proportion of donations. This text explores the reasons for such a development in patients undergoing cardiovascular surgery where the transfusion requirement has drastically declined in recent years. A reduced requirement of a mean of 2 RBCs is now the need per patient in most centers. Such a reduction is possible through various recent perioperative improvements: (i) thorough preoperative haematological checks in order to equip the patient for blood loss, surgical trauma and extracorporeal circulation (ECC) in which heparinized blood is pumped at high speed through an oxygenator, heat exchanger, reservoirs, tubings and connectors. (ii) Perioperative administration of inhibitors of fibrinolysis (aprotinin, ε-aminocaproic acid) reduce profuse haemorrhagic tendency.

Successful attempts to minimise ECCs, including foamless aspiration of wound blood, refined surgical technology, tissue glue, and point-of-care laboratory testing (POCT) in the operating theatre all contribute to a reduced transfusion requirement. A substantial proportion of patients can now be operated on without ECC. New thrombelastography analysis allows for real-time monitoring of haemorrhagic/thrombogenic risk. Modern blood product quality contributes to limiting blood product usage. (iii) During the postoperative recovery phase, anaemia can be corrected by i.v.iron and recombinant human erythropoietin.

Such measures allow the transfusion trigger, based on haemoglobin concentration, to be set as low as 70 g/l in suitable patients.

Key words: blood transfusion; cardiovascular surgery; transfusion trigger; extracorporeal circulation; ECC; anaemia; point-of-care testing; POCT; minimal extracorporeal circulation; MECC

Introduction

Surgical interventions on the heart and great vessels are major invasive procedures designed for treatment of congenital and acquired diseases, e.g. coronary artery disease (CAD), valve repair/replacement as well as treatment of aortic aneurysms. The procedures have become routine not least due to unrestricted blood transfusion support once a lower haemoglobin concentration is reached, referred to as the transfusion trigger [1, 2].

Initially, feasibility of extracorporeal circulation (ECC) and tolerance to its side effects described in the 1950s, depended on the availability of banked whole blood. At that time, whole blood was used both for volume replacement and for anaemia prophylaxis/treatment. Since the earliest days of the clinical use of ECC, there have been concerns about the relatively large amounts of whole blood used for this purpose, although later replaced by cellular blood components, such as red

blood cell (RBC), platelet concentrates (PC) in addition to fresh frozen plasma (FFP) with its fractionated protein derivatives albumin and clotting factors. Such concerns relate to the safety, availability and cost of donor blood and led health professionals to examine techniques in blood conservation and alternatives to blood transfusion.

The viral risks discovered in the early 1980s are now reduced in countries that employ rigorous testing of donated blood. There are however, new concerns such as West Nile virus, avian flu [3], variant Creutzfeld-Jakob diseases (vCJD) and severe acute respiratory distress syndrome (SARS) known to be transmissible by blood products [4].

A substantial number of cardiac operations, in particular those performed without opening the heart, such as coronary artery bypass grafting (CABG) can now be performed without any transfusion requirement. This remains true even with

the increasing proportion of patients suffering from co-morbidities and elderly patients eligible for such operations [5] and may also pertain to paediatric heart surgery [6]. Off-pump CABG on a beating heart (OPCAB) as well as the development of miniaturised ECC systems (M-ECC) [7], contributed to further reduction of transfusion in cardiac patients. In most hospitals, the tracking of blood product use to a specific patient group or sub-group is still not comprehensive, in spite of bar coded information. Accordingly, blood banks often lack the possibility to learn whether the products they released were in fact transfused unless haemovigilance programs (www.swissmedic.ch) call for such a requirement. Currently, in developed centers, patients involved in elective heart

surgery on ECC, need a mean of 1.9 RBCs/procedure and 2.0 RBCs/patient, a requirement which is quite similar to that observed at the Berne Clinic (1.58 RBCs/patient in a collective of 200 patients on ECC) [8].

For now, it should not be forgotten that blood products may be required for O₂ transport and to maintain haemostatic safety in times of need and urgency. As a result of the lack of evidence based medicine supporting transfusion decisions, with additional need for strict definition of endpoints in clinical studies [9], the worldwide use of blood products during CABG varies widely [10]. The present review focuses on the achievements in reducing homologous blood product need in modern cardiovascular surgery.

The beginnings

In the early 1950s, the development of the first blood oxygenators and subsequently the first ECC systems allowed John Gibbon to successfully operate on a patient and repair his atrial septum defect. He thus confirmed the previously reported successful use of an ECC in two dogs by Senning [11]. Independently from Gibbon's landmark operation, the development of ECC was also pursued in China by Su Hong-Xi in Xi'an who also carried out animal experiments [12] even though China was isolated before the 1980s. In Russia, similar ideas to create ECC for heart surgery was established independently from what was happening elsewhere. Priming of the ECC circuit was accomplished with heparinized and/or citrated whole blood, the availability of which became routine in the wake of professional blood banking after world war II [13]. The Zurich Blood Bank had a category of overweight male donors from which to draw as much as 600 mL fresh whole blood (FWB) at a time [14].

It is difficult to assess the transfusion requirements from the literature concerning the first phase of ECC-development. Surgeons and anaesthetists took it for granted that sufficient blood

products were available for restoring lost blood. Thus transfusion therapy was an essential pillar during the development of ECC systems controlled by surgeons need at that time. As recently as 1985, it was common practice to prepare 8 units of virus-marker untested, heparinized FWB II from established donors, for elective adult heart surgery. The blood was stored between 4 and 6 °C and used when not older than 48 hours post-donation. In addition 4 units of FWB I were prepared, with a shelf-life of <24 hours, stored between 20–24 °C. The latter FWB I was intended to provide sufficient platelets since at that time it was already known that platelets required to be stored at room temperature but purified platelet concentrates were not yet available on a routine basis. Screening of donations for anti-HTLVIII (now anti-HIV) was introduced in 1984 and meant that blood banks had to allow for a 48 hour laboratory testing period before releasing the units [14]. With this new requirement, preparation of heparinized FWB fell out of favour, because the anticoagulatory effect of heparin diminished during this 48 hour period.

Preoperative monitoring of transfusion dependency

For each patient, the time lapse between establishing the indication for heart surgery and its initiation has become part of surgical care to a certain extent. As a rule CABG and surgery involving the cardiac valves are elective procedures and constitute the most frequent cardiac operations. A strategy to reduce blood loss and transfusion requirements can thus be planned prospectively. Often, percutaneous transluminal catheterization, followed by cardiac surgery rather than by coronary angioplasty (PTCA) will set the stage for subse-

quent care. The preoperative management focussing on transfusion requirements depends on the diagnosis. Candidate patients for surgery are usually anticoagulated and/or receive anti-platelet therapy to prevent acute coronary obstruction whilst waiting for bypass grafting. Dosage of drugs such as aspirin, clopidogrel (Plavix[®]) or anti-fibrinogen receptor monoclonal antibody (ReoPro[®]) needs to be adapted individually. Continuing aspirin and clopidogrel therapy combined with intraoperative aprotinin may reduce postoperative

blood loss and avoids delaying surgical treatment, by preventing major adverse cardiac events before surgery [15]. By the same token, haemoglobin concentrations will be determined preoperatively because some types of anaemia might be corrected in the short term by iron substitution and/or boosts with recombinant human erythropoietin (r-hu-EPO). This increases a patient's haemoglobin concentration above designated transfusion-trigger values. Iron deficiency without anaemia can now be identified with ferritin levels <50 micrograms/mL and haemocytometers that measure haemoglobin plus size of individual erythrocytes. The resulting histograms reveal any alterations in cell Hb, plus number, and size. Combined with haemoglobin measurement in reticulocytes (CHr/Ret-He) a finely tuned preoperative diagnostic tool exists, with which to estimate patients iron equilibrium [16]. Using POCT, a recent study underlines the importance of pre- *versus* intra-

operative RCV measurements as factors in triggering RBC transfusion [17]. Preoperative plasma fibrinogen levels have recently been proposed to impact on postoperative bleeding [18]; appropriate preoperative monitoring may thus result in reduced intra-/postoperative transfusion requirements.

Preoperative appreciation of rarer conditions like antiphospholipid syndrome, factor V Leiden or factor V Cambridge mutations associated with low levels of protein C resistance is now possible thanks to improved laboratory diagnosis, currently moving towards genotyping with real time PCR technology. Congenital antithrombin deficiency can be corrected using recombinant human antithrombin and/or FFP [19]. Certainly, such investigations will not become routine preoperative screening tests but they are valuable tools in cases of known anamnestic facts in high-risk patients.

Intraoperative transfusion: the mainstay

Oxygen delivery to tissues is defined as the product of blood flow (cardiac output, or ECC pump flow speed with artificial lung membrane index) and arterial O₂ content. The latter depends on haemoglobin concentration, the binding coefficient of haemoglobin (1.39 mL O₂ are contained in one gram of haemoglobin), the saturation of the haemoglobin and the physically dissolved O₂. Should any of these factors fail in a patient undergoing heart surgery, then the therapeutic goal of blood transfusion is to ensure adequate O₂ delivery according to the physiologic need. Because cardiac output is so decisive in contributing to O₂ delivery

to any tissue, including the heart itself, this organ is primarily at risk in acute anaemia. Guidelines for blood transfusions [20] generally do not focus on individual patient groups; an international agreement recommends RBC not to be transfused prophylactically. The transfusion trigger haemoglobin concentration or haematocrit below which anaesthetists consider RBC transfusions, varies from patient to patient but for cardiac patients this should be set between 70 and 90 g/L [21, 22] and between 90 and 100 g/L for patients undergoing elective aortic or infrainguinal arterial reconstructive surgical procedures [23].

Surgeons and anaesthetists techniques to save on blood products

Recent advances in surgical techniques not only progressively reduced the operation time but also helped to decrease the tissue damage. Consequently, blood loss was also significantly reduced. Today, the estimated blood loss averages ~300 mL during CABG procedure and ~400 mL during valve replacement or repair. For example, the development of tissue glue, such as fibrin, complements the precision in sutures and inline seams and reduces haemorrhagic properties by improving tissue adhesiveness and scarring of structural edges.

Another possibility is the use of pericard patches to consolidate particularly fragile anastomoses. Cardioplegic solution pharmacology has now switched from larger volume crystalloid formulation, of which at least 2 litres were used, to as few as ~200 mL of KCl- and amino acid-enriched warm autologous blood cardioplegia. This has allowed reduction of haemodilution by large volumes of crystalloid solution reaching the ECC with the effect of reducing the haematocrit.

Extracorporeal circulation

Traditional ECC circuitry, an assembly of oxygenator, heat exchanger, and reservoir brought together by tubing and connectors represents an immense foreign surface for blood [24]. Obviously, the patient must be fully heparinized to prevent clotting in the circuitry with possible subsequent arterial embolization (see below). Activation of inflammatory and complement protein cascade systems and trauma to blood cells, mainly platelets [25] might also occur with ECC.

A wide variety of developments and improvements are currently being introduced with ECC technology, the most drastic being deliberate omission of ECC to perform CABG procedures, i.e. off-pump (OP)CAB on the beating heart (table 1). This technique has been shown to greatly reduce complications, transfusion requirements [26] and recovery time compared with the traditional on-pump bypass surgery. Transfusion requirements in OPCAB were recently suggested to depend also on the intraoperative warming system employed [27]. A thermoregulation system using a blanket wrapped around the patient's body transferring heat via conduction led to substantial reduction of overall blood loss and transfusion requirements. The patient population eligible for OPCAB is quite restricted; a large proportion of cardiovascular surgery patients still depend on ECC. In this respect, ECC has gone through considerable improvements on its own. The major side effects of ECC being based on bioincompatibility phenomena, research efforts aim at improving biocompatibility. To reduce activation of the coagulation and complement cascades and to protect blood cells, more particularly platelets, from damage, heparin-coated ECC has been developed to allow a reduction of the patients systemic heparinization [28]. Even it is known that reduced heparinization may favour embolus formation in the ECC-reservoir, about one third of cardiac surgeons still use heparin-coated systems.

The development of a mini-ECC (MECC,

Cardiosmart®) for intraoperative clinical care of heart surgery patients has now reached routine status. The MECC is a compressed circuit with a reduced artificial surface consisting of a special suction pump that aspirates shed wound blood only when the suction tube-tip is immersed [7]. No air is aspirated together with blood, avoiding foam formation that therefore reduces haemolysis due to the air-blood interface [8]. A retrospective study covering 200 patients with CAPG under conventional ECC *viz* 207 patients with MECC has shown that the RBC transfusion requirement in the former group was 1.46 RBC/patient falling to 0.058 RBC/patient in the patients with MECC [8].

Case report: An 84-year of Jehova Witness was operated on with CABG because of unstable angina pectoris and received an intraaortic balloon pump, but later needed bypass surgery. Since a previous examination using the femoral artery led to an anaemia of 21% haematocrit, MECC was applied. Addition of aprotinin helped to save blood such that the patient survived the operation and recovered quite rapidly from her anaemia due to injection of r-hu-EPO. This case illustrates that not one but often several of the recent elements of progress used on the same patient lead to successful avoidance of blood transfusion. Between 1991 and 2003, 200 adult Jehova Witnesses were followed up in France and Spain using Euroscore and were maintained with haemoglobin values >14 g/dl using r-hu-EPO. Thanks to MECC usage, warm cardioplegia and early extubation, the authors concluded that despite a heightened operative risk, blood saving protocols might now have reached evidence-based status [29, 30].

However, a word of caution is imperative: the Jehova Witness patients cited in scientific publications are almost exclusively the successful survivors of transient anaemia whereas those who suffered complications from withheld transfusions, even fatal ones, are unpublished.

Table 1
Recent achievements to reduce use of blood products in cardiovascular surgery.

	Preoperative period	Perioperative period	Postoperative period
Surgical Means		Suture technique Tissue glue	
Clinical Pathological Laboratory Procedures	Haematological checkup	Point of Care Testing (POCT) (thrombelastography, haematocrit, blood gases, coagulation parameters)	Surveillance of iron status
Drug Prophylaxis/Therapy	r-hu-EPO	Aprotinin ε-amino-caproic acid	r-hu EPO i.v. iron
Extracorporeal Circulation (ECC)		Off-pump coronary artery bypass (OPCAB) Heparin-coated circuits M (minimal-)ECC	

Volume replacement and cell salvage

For substitution of lost volume, an array of acellular and protein-free solutions are available, such as electrolyte (crystalloid) solutions, gelatine, dextrans and hydroxyethyl starch; they can be administered as single products or in combinations [31, 32]. With such immediate volume replacement, haemodilution occurs, correction of which calls for cell saving. Autologous red blood cells of the patient are washed from aspirated shed blood and enter a collection reservoir. The time delay until haemodilution is corrected may be acceptable provided appropriate tissue O₂ supply is maintained by the patients circulation.

Red cell salvage technology has found its way into different fields of major surgery, including cardiac surgery. Intraoperative cell salvage may be performed using different blood processing devices that aspirate, anticoagulate, wash and concentrate intraoperative shed blood. These devices, bulky and complex at the outset, have now been replaced by small, fully automated, and easy-to-use cell saver devices such as OrthoPAT[®] (Haemonetics), AutoLog[™] (Medtronic) or CATS (Con-

tinuousAutoTransfusion System, Fresenius). Cell saving is considered standard in some centers but is called into question in others mainly due to cost effectiveness concerns. At the Bern University Hospital Cardiovascular Surgery Clinic, retransfusion of shed mediastinal blood is considered not to confer any benefit and at worst produces harmful effects from impaired platelet function, activated inflammation processes and increased fibrinolysis.

Anaesthetists and cardiotechnicians have learned to use the patients' own venous compartment as a reservoir. Alpha blockade and beta-blockade using drugs such as phentolamin and nitroglycerin, opens the periphery and the pre-load-compartment which, supported by orthostatic inclination of the operation table feet-down, permits the surgeon to complete CABG by creating autologous blood reserves in the venous compartment. Sometimes a short, transient drug-induced arterial hypotonus down to as low as systolic 60 mm Hg, helps to reduce haemorrhagic diathesis on its own.

Improvements in drugs and blood products

There is no great mystery in this matter- the facts allow only one type of anticoagulation persisting from the early days: heparinization using unfractionated heparin with reversal of its anti-thrombin effect by protamin remains the cornerstone of systemic anticoagulation for heart surgery. Heparin inactivates thrombin by binding and activating antithrombin as well as inducing release of tissue factor pathway inhibitor from endogenous sources. With rare, but much feared side effects of unfractionated heparin, such as heparin-induced thrombocytopenia and its effects on thrombin generation, important implications of heparin also impinge on postoperative haemostasis after ECC [33]. Therefore its role as the ideal anticoagulant during ECC has been questioned but the developments of newer anticoagulants, good for indications other than ECC have not even achieved a status of investigational new drugs in cardiac surgery. Low molecular weight heparin or oligosaccharide moieties of glycosaminoglycans e.g. the active pentasaccharide fondaparinux [34], are not introduced into the management of patients undergoing ECC. Fortunately, substantial progress has been achieved by balancing embolism and haemorrhage using antifibrinolytic agents, its most prominent representative being aprotinin, a naturally occurring serine protease inhibitor [35, 36]. Efficacy of aprotinin in limiting blood transfusion is well established for adults and blood loss in OPCAB surgery. In a prospective, double-blind, randomized study with 47 patients at Bern clinic,

only two patients (10%) needed RBC, whereas 8 (35%) did so in the group of patients not receiving aprotinin [37]. Some centers use ε-amino caproic acid or tranexamic acid, instead of aprotinin, but comparative studies are lacking. Aprotinin has now found widespread application during cardiac surgical procedures with an favourable risk-benefit ratio [36-38].

The homologous blood products transfused have been also improved. During the 1970s, whole blood transfusions were replaced by RBCs, FFP and later PCs, a practice now known as component therapy. In 1969, the Geneva Blood Center was the first in Switzerland to switch from whole blood in glass bottles to components in PVC bags. RBCs are stored in CPD-Adenine to reduce storage lesions, of which potassium release from red cells is one of the earliest along with reduction in 2,3-DPG. Leukofiltration of blood or cellular blood products removes microbial organism-carrying white blood cells and appears to reduce the incidence of pulmonary tract infections in patients undergoing CABG [39].

Fresh frozen plasma (FFP) and/or purified procoagulants are efficient products with which to regulate haemostasis. Unfractionated quarantine or virus-inactivated FFP contains procoagulants and coagulation control proteins in physiological constellation and therefore this blood component is bound to stop excessive bleeding without risk of thrombosis. Single donor FFP bears the risk of side effects, such as transfusion associated lung injury,

TRALI [40, 41], or posttransfusion purpura [42, 43]; pooled plasma treated with solvent/detergent [44] or using the Intercept System [45] may replace quarantine FFP; the quality of FFP transfused still differs depending on the donor population and on the viral-inactivation procedure and/or pooling [46–48]. In recent years, the potential of purified or recombinant factor VII (rFVIIa), to reduce perioperative bleeding and RBC transfusion requirement in nonhaemophilic patients has been studied

in several clinical trials [49]. Cardiac surgery has been one of the more common situations for the treatment of surgical bleeding using purified plasma proteins and recombinant FVIIa [50]. This may be of benefit in infants and elderly people [51] and its efficacy on reducing postoperative haemorrhage [52] or upon removal of intra-aortic balloon pump [53] has been documented. The optimal dosage for factor VII is yet to be found [54].

Laboratory procedures

Clinical laboratory medicine has made its way into the operating theatre. Although offending the sensibilities of regular laboratory staff, state-of-the-art heart surgery cannot be done without POCT during cardiovascular surgery; the most important tests carried out for control of haemorrhagic diathesis are listed in table 2.

The monitoring of heparin-activity during ECC is performed by a fast assay on a POCT device. The single most reliable procedure to estimate appropriate heparinization during cardiac surgery is quantitative estimation of activated clotting time. The circulating heparin concentration

can also be measured using the heparin/protamine titration method with Hepcon/HMSplus [55]. Because the assays used for heparin often cannot be used to monitor the new drugs (aprotinin, ϵ -amino caproic acid), new instruments and assays have been developed (table 2). POCT in the operating theatre also includes blood gas analysis and haematocrit measurements [17, 56]. Advice from the clinical laboratory experts and industry in placing quality-controlled laboratory equipment for POCT in the operating theatres has helped to improve on-site patient care and to monitor transfusion requirements.

Table 2

Instruments and assays for monitoring anticoagulants in cardiopulmonary bypass.

Instrument	Assay	Drug
Hemochron	Activated Clotting Time	Heparin
HemoTec	Activated clotting time	Heparin
TAS analyzer	Heparin management test	Heparin
TAS analyzer	Ecarin clotting time	Thrombin inhibitors
Platelet Function Analyzer	Platelet function	Aspirin, gpIIb/IIIa inhibitors
Thrombelastograph	Clot signature and platelet function	Aspirin, gpIIb/IIIa inhibitors, aprotinin
Hepcon	Protamine neutralization	Protamine

See also: [56].

Early and late postoperative appraisal, conclusions

Once the operating wound is closed, the patient needs to be followed for appropriate O₂ delivery to tissues. After exclusion of surgical bleeding requiring revision of the operation site, postoperative anaemia is currently being treated with modern drugs reducing the need for relieving RBC transfusions. The two compounds in the limelight in the year 2006 are intravenous iron and r-hu-EPO. The latter glycoprotein growth factor, produced in the kidney is available for subcutaneous or i.v. injection and its beneficial effects beyond raising the haemoglobin concentration have been described in the fields of neuro- [57, 58] and cardioprotective [59] applications.

In conclusion, with fewer patients on cardiac bypass surgery requiring RBC transfusions, the decision about when to transfuse has not become

easier the more so as RBC utilization may impact on patient morbidity and mortality. A recent Canadian study with questionnaires answered for 642 intra- and postoperative case scenarios revealed mean haemoglobin concentrations as transfusion triggers at 70 g/L for intraoperative and at 72 g/L for postoperative case scenarios. In their answers, physicians ranked myocardial ischaemia as the most relevant factor affecting transfusion decision [60]. The numerous possibilities to manage transfusion requirements for cardiovascular surgery patients including surgical, technical-blood circuitry and pharmacological developments make that their application to patient care is specific to each surgical team; they remain far from being able to be included in treatment guidelines written by international expert panels.

Note added in proof

A working party on perioperative haemostaseology has been founded recently within the Society for Thrombosis and Haemostasis Research (www.gth-online.org) and holds biannual meetings.

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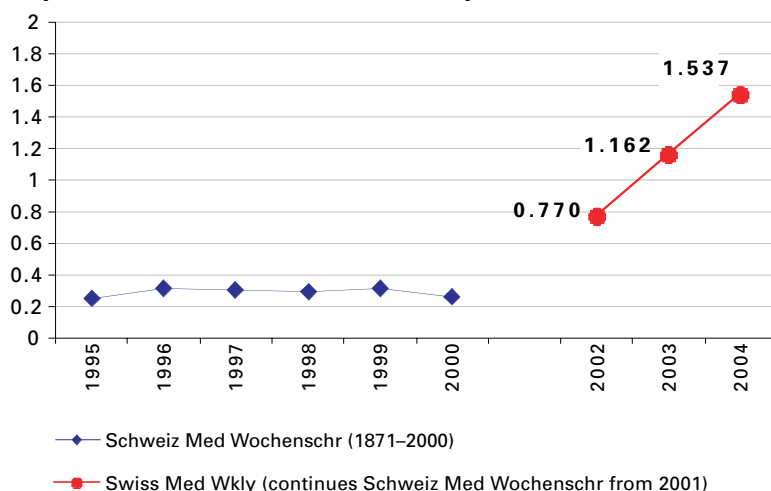
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