Transfusion Medicine and Surgery

VINCENZO DE ANGELIS, M.D., ASSOCIATE DIRECTOR
LUIGI DE MARCO, M.D., DIRECTOR
BLOOD BANK AND CLINICAL PATHOLOGY LABORATORY
IRCCS CENTRO DI RIFERIMENTO ONCOLOGICO
AVIANO, ITALY

Mortality after surgery in patients with severe and progressive anemia is an entity[1]: risks related to blood loss and insufficient oxygen delivery to tissues are still a major concern in surgery. Risks of blood transfusion parallel those of blood loss: blood-borne infectious diseases and immunological side effects[2] may frustrate therapeutic efforts of surgery. Thus, blood transfusion in surgery must be kept to a level in which both risks are reduced to a minimum (or theoretically even absent). This review will deal with two relevant questions: ***(a) how to define the lowest amount of blood transfusion needed for surgery and (b) how to reduce or abolish post-transfusion risks of this amount.***

THE AMOUNT OF BLOOD NEEDED IN SURGERY

The 1988 Consensus Conference on perioperative red cell transfusion[3] provided several guidelines supporting the decision-making process. Unfortunately, these and other guidelines have had a limited impact in optimizing transfusion practice[4]; a surprisingly high variability among comparable surgical teams in perioperative blood transfusion needs has been shown. Results from the SANGUIS (Safe and Good Use of Blood in Surgery) study[5] indicate a use of transfusion resources as much as 30 times greater in some hospitals than in others, for the same intervention; the probability of a patient being transfused still differs significantly among hospitals after adjustment for age, gender, preoperative hematocrit (Hct) and blood loss. Moreover, only 23% of the clinical records of patients receiving red cell units contain any documented reason for transfusion; in the large majority of the cases, this is low Hct or excessive bleeding. A recent study[6] on a 1-year cohort of patients undergoing hip or knee total joint arthroplasty showed significant gender-related differences in blood transfusion. Although male patients presented with higher hematocrit values than females (thus making transfusion in theory less probable), once the transfusion decision was made, the amount of blood given in each procedure did not show sex-related variation. Moreover, hematocrit values at discharge were quite comparable for all transfused patients, thus suggesting that men had relatively less blood replaced than women. These differences in transfusion practice could not be associated with identifiable changes in the clinical outcome.

These studies suggest that the variability in transfusion practice is not linked with biological factors but rather with the medical attitude toward transfusion.[5] Different kinds of efforts may be pursued to define when a significant benefit of transfusion can be expected (and therefore transfusion should not be withheld).

Physiologic Indexes for Body's Oxygen Demand

The indication for red cell transfusion is an inadequate oxygen-carrying capacity. Patients with good cardiac function may compensate for acute anemia by increasing cardiac output and arterial oxygen saturation. The main limiting factor to compensation appears to be the oxygen extraction ratio at which myocardial lactate production occurs, signaling an inadequate oxygen delivery and therefore a risk for the heart due to acute anemia.[7] Empirical hemoglobin/hematocrit thresholds are limited clinical indicators of impaired oxygen metabolism and therefore of the need for red cell transfusion. This results from the fact that they do not closely correlate with oxygen metabolism. An increase by 1 or 2 g/dL in Hb concentration in the range of a moderate anemia (between 7 and 10 g/dL) only marginally affects oxygen consumption;[8,9] it is noteworthy that the oxygen extraction ratio neither is markedly deranged before transfusion (indicating that the moderate anemia is well compensated) nor shows relevant changes after transfusion.[9] Therefore, the physiologic consequence of increasing Hb does not support the widely accepted use of Hb concentration as the unique transfusion trigger. More physiologic data such as arterial oxygenation, mixed venous oxygen tension, cardiac output, oxygen extraction ratio, and blood volume may characterize the limits of the body to compensate for anemia. Several reports suggest that an oxygen extraction ratio higher than 50% should indicate the need for increasing red cell mass, being associated with hemodynamic instability and marginal myocardial reserves.[7,10] This critical value is reached at lower Hb concentrations (3.5 to 4 g/dL) in physiologic than in pathologic states (for instance at 6-7 g/dL in a model for coronary stenosis in dog).[7,10-12] Clearly, this would make the oxygen extraction ratio much more reliable than the Hb level for the assessment of the transfusion need. Unfortunately, these studies are mainly experimental and the validity of such an indicator in more complex situations that alter oxygen metabolism remains to be investigated.

All these results are very promising for a future possibility of laboratory-aided clinical assessment of transfusion need, which is however limited by the lack of timely availability and the lack of studies evaluating their effectiveness. Nevertheless, the recommendation of the 1988 Consensus Conference[3] must be reasserted that researchers must try to identify a set of monitors for inadequacy of oxygen delivery (mainly for those organs more sensitive to the consequences of anemia) and to compel them in a set of data, timely available for surgeons and anesthesiologists.

Decision-Making Analyses and Algorithms

A number of studies have been performed to define algorithms intended to preassess blood need and to define when transfusion cannot be withheld. They are mainly based on analyses of the surgical procedures, maximum surgical blood ordering schedule, pharmacological approaches to bleeding, patient status, and patient suitability for autologous donation. Also, they comprise a number of data which are either preoperatively known or timely available during operations, with special regard to blood loss and hemostatic function, whose impairment maintains bleeding.[13] Tests for hemostatic function are of relevance in cardiac surgery requiring cardiopulmonary bypass and in hepatic surgery; consequently, they represent an important decision trigger in the algorithm constructed by Despotis et al.[14,15] In the study by Matsumata et al.,[16] aside from intraoperative blood loss and patients' body weight, preoperative prothrombin time is a predictor of perioperative blood transfusion, and the recommendation to correct hemostatic abnormalities is made. A relevant help in constructing algorithms comes from the Maximum Schedule Ordering Blood for Surgery (MSBOS), originally intended to avoid the waste of blood and work in the Blood Banks. Instead of cross-matching in advance the maximum of blood units eventually needed during an operation, a calculation is made after a review of ratio of cross-matched to transfused units which defines the average of units normally transfused during any intervention; all the extra-units eventually required are issued by the "type & screen" protocol.[17] The use of the MSBOS practice effectively works in saving resources in the Blood Banks[18] but it can also help surgeons to define the minimum amount needed for surgery. Thus, the installation of an algorithm based on a careful review of the MSBOS allowed Spence et al. to choose appropriate transfusion guidelines and to maximize both allogeneic and autologous blood resources.[19,20] Retrospective analyses may also allow critical evaluations of otherwise inexplicable differences in transfusion requirements. Bracey et al.,[21] analyzing 65 patients who had repeat procedures of coronary artery bypass grafting, were able to determine a 31% greater blood loss than that observed in 196 patients who underwent primary procedures but a 73% greater use of red cell transfusion. Although other variables (as prolonged time on cardiopulmonary bypass, preoperative Hb, and aspirin exposure) showed a predictive value on red cell transfusion, the physician's anticipation of excessive blood loss may result in a more liberal attitude toward transfusion. Retrospective analyses can be used to develop a transfusion prediction assessment, as demonstrated by Moenning et al. for orthognathic surgery[22] and by Weber in head and neck cancer surgery.[23] In this latter study, 12 variables available prior to the surgical procedure were retrospectively analyzed in a group of 436 patients over a 4-year period. Oropharyngeal or hypopharyngeal primary tumor sites, T3 or T4 tumor stage, need for flap reconstruction, and abnormal preoperative hemoglobin were significantly associated with the need for transfusion. Based on these data, an algorithm has been developed which is intended as a guideline for transfusion planning. Decision-making criteria seem not to be restricted to the field of elective surgery, but may be also used in intensive care medicine. In the study by Bein et al.,[24] different clinical variables (e.g., the Acute Physiology and Chronic Health Evaluation [APACHE-II], the Mortality Prediction Model, and the presence of neurosurgical diseases) were evaluated and compared with transfusion requirements in 117 prospectively studied patients admitted to an intensive care unit. Again, the results suggest that, apart from hematocrit, other clinical parameters are predictive of the need for blood transfusion.

Overall these results seem to validate the algorithms as useful tools for assessing transfusion needs and a strong suggestion is made to implement clinical judgement with algorithms for transfusion needs.[25] However, an "installed algorithm" is a clinical decision support that must be followed and implemented by the cooperation of anesthesia, surgery, laboratory, and blood transfusion service teams.[26] Secondly, it must be frequently reviewed for emerging situations; in this respect, an algorithm is a part of audit and education in transfusion medicine, as are meetings between transfusion medicine physicians and surgeons, teaching at scheduled conferences, clinical rounds on patients receiving blood transfusion, and reviewing of order for transfusion prior to issuing blood.[27] Finally, the validity of statistical analyses must be carefully checked, since misuse of statistics may lead to the presentation of incorrect results which, at best, generate controversies.[28]

AUTOLOGOUS TRANSFUSION

Preoperative Hemodilution

Preoperative or acute normovolemic hemodilution (ANH) is a logistically simple method for autologous procurement of blood needed during surgery.[29] It avoids the risks of disease transmission and those of transfusion to an unintended recipient, since it is performed immediately before or shortly after induction of anesthesia. Blood is then transfused when blood loss ceases or before, if needed. Basically, it consists in the removal of a predetermined volume of blood (which can be confidently calculated[29,30]) and in the simultaneous infusion of colloids or crystalloids to maintain a normal blood volume. In this way, blood shed during surgery has a lower RBC concentration and the loss of red cells is decreased. The resulting hemodilution is well tolerated by means of different physiologic compensatory mechanisms: increased cardiac output, heart rate, stroke volume, and increased heart and brain blood flow more than proportional as compared to the increase in cardiac output.[31] A variety of studies have reported on the feasibility of ANH and the great decrease (or even avoidance) in allogeneic transfusions when using acute normovolemic hemodilution in open heart surgery,[32] spine surgery,[33,34] hepatic surgery,[35] hip arthroplasty,[36] major colon surgery,[37] urologic[38,39] and vascular surgery.[40,41] The main problem of the majority of these reports lies in the fact that their results are mainly compared with historical controls, most often with different "transfusion triggers," which makes very difficult the interpretation of any difference found in transfusion requirements between ANH patients and controls. Nevertheless, the few prospective, randomized studies (three in urologic and one in colon surgery[37-39,42]) seem to suggest that in some instances ANH is a truly effective and less costly alternative to preoperative autologous blood donation as a blood conservation strategy. However, two major concerns have been raised against ANH. The first is related to myocardial ischemia as a side effect of the maneuver.[43] Detrimental effects of hemodilution on myocardial function[44,45] have been described and myocardial infarction has also been reported in association with ANH[46]; recent studies have revealed silent pre-existing ischemic heart disease in different sets of surgical patients[47,48] and this offers a strong argument for cautious thinking regarding ANH.

The second question deals with the red cell mass conserved by ANH.[49] Two mathematical models, in contrast with the clinical observations described above, seem to negate the possibility of obtaining, by ANH, a sufficient amount of red cells to fulfill transfusion requirements during surgery.[50,51] The discussion on this problem is flawed by two facts: one is that mathematical models are subject to all simplifications needed to force biological complexities in any sort of model[52]; the second is that transfusion requirements during surgery are far from being defined in a precise way. Once again, the first question to be answered is not "what" but "when" to transfuse.

Although the merits of ANH have been proven in several circumstances,[53] ANH is only part of a comprehensive blood conservation program and in the absence of a defined protocol has limited efficacy.[54] Nevertheless, ANH is likely to deserve a wider use,[55] provided that clinical studies are planned to define the benefits and risks associated with hemodilution and anemia under anesthesia, and patient selection criteria are developed.[56]

Intraoperative Blood Salvage

As this important source of conserved blood has been recently reviewed,[57] it will be purposefully excluded from this review, except for the aspect of blood salvage in malignancy, which deserves further comments. The efforts to avoid allogeneic blood transfusion in malignancy surgery mainly come from studies which suggested an earlier recurrence of cancer after allogeneic transfusion.[58,59] Mechanisms for allogeneic transfusion-related earlier cancer recurrence have been debated, but no conclusive evidence has been obtained.[60] While animal models provide evidence that blood transfusion-induced immunosuppression can promote tumor spread,[61] clinical studies give conflicting results. In two recent reviews,[62,63] a large number of studies are summarized which strongly suggest, but do not prove, a causal relationship between transfusion (mainly of white blood cell-containing components) and recurrence of a large variety of malignancies (colorectal, breast, lung, prostate, stomach, bone, soft tissues, bone, and liver metastases). About 65% of these studies report adverse effect of allogeneic blood transfusion, while 35% fail to do so. The authors correctly state that "final acceptance of the causal nature of transfusion influence on cancer recurrence awaits further conclusive reproducible studies."[62] Therefore, the main indication for efforts to prevent allogeneic blood exposition in cancer patients remains to be proven.[64]

On the other hand, the controversy on intraoperative blood collection in cancer surgery concerns the possibility that tumor cells not removed by washing techniques may result in a risk of metastases.[65,66] A study on intraoperative blood collection performed in the surgical treatment of 71 patients with early cancer of the uterine cervix was unable to detect tumor cells either in peritoneal or in salvaged blood cytology. Moreover, 3 pelvic recurrences of the disease were registered in a 24-month follow up, 1 in the autotransfused, and 2 in the nontransfused patients.[67] Another experimental model, in which radiolabelled cancer cell lines are mixed with red cells, demonstrated a very low (but not absent) retrieval of the initial radioactivity after separation with cell saver and membrane filters.[68] Experimental studies demonstrating a complete inhibition of the proliferative activity of tumor cell by irradiation with 50 Gy of blood collected intraoperatively seem to suggest that this approach may facilitate intraoperative blood salvage in cancer patients, but this promising tool remains to be clinically investigated.[69] A good, but not complete, removal of tumor cells, together with an impaired viability of cells not retained by filters, has been demonstrated in laboratory experiments by Karczewsky et al.[70]; they demonstrated, in a subsequent clinical study on three patients, a retention of 50-68% of tumor cells harvested, together with blood, during surgery. These results are presented as indicating a metastatic inefficiency of cotransfused tumor cells. Clearly, intraoperative blood salvage in cancer patients is an underinvestigated field, mainly for the absence of prospective studies addressing this important issue. However, a possible risk of earlier tumor recurrence induced by allogeneic transfusion seems counterparted by a possible risk of metastatic diffusion by salvaged blood. A strong suggestion for the use of leucodepleted component seems, however, to emerge.[63]

Preoperative Autologous Blood Donation

Preoperative autologous blood donation (PABD) is probably the most familiar form of autotransfusion and is considered a standard of care, especially for orthopedic and urologic[71-73] surgery. It is not the aim of this review to summarize all conditions in which PABD has been used. It is, however, worth considering the controversies surrounding PABD highlighted by the recent literature.

1. Safety.

The paradigm of discussion on PABD safety is represented by atherosclerotic coronary artery disease, which is a reason for rejecting volunteer blood donors but is a well-studied condition for PABD use.[74,75] While significantly reducing allogeneic blood exposure,[76,77] PABD is not generally acknowledged as a safe maneuver in cardiac patients.[78,79]

A comparable safety of blood collection in high risk and non-risk autologous donors has been reported by Hailer et al.[80] In their study the authors compare 665 donations from non-high risk autologous donors and 551 direct donations from donors who met the criteria for allogeneic donation with 207 donations from patients in whom blood withdrawal may be a potential risk (due to a history of significant coronary artery or cerebral vascular disease, recent seizures, cardiac arrhythmia, chronic heart failure, valvular or congenital heart disease, symptomatic dyspnea, insulin-dependent diabetes and hypertension requiring two or more antihypertensive drugs). The authors conclude that autologous donation by the high risk donors is as safe as that by donors who met homologous donation criteria. Similar results in terms of severe side effects have been reported by Adegboyega and Potter,[81] who, reviewing the literature on high risk predonating patients, have been able to record only 10 mild and 9 moderate reactions (including 5 episodes of severe hypotension), thus concluding that autologous blood donation is safe in carefully selected and well-compensated cardiac patients, including those with severe coronary artery disease. However, as reported in the same review, 4.3% of the donations were accompanied by some reactions, and about 1% of predonating patients described by Owings et al.[76] and Dzik et al.[82] required hospitalization because of severe reactions. Britton et al. found that 10 out of 82 patients with coronary artery disease had to discontinue predonations because of increasing angina; however, they do not report on symptoms occurring in the control group of patients who did not choose to predonate blood.[83] In a study by Van Dyck et al.[84] on patients scheduled for coronary artery bypass grafting, Holter monitoring performed 24 hours before and after blood donation showed ischemic events before and after donation in 9 out of 24 patients, although their duration and intensity were significantly higher after donation. Of relevance, ischemic events in this latter study were not only related to blood donation, but also to a trip to the hospital. Altogether, the magnitude of these side effects does not seem very different from the 2 to 5% complications occurring in non-high risk donors,[85] but their consequences might be more serious in cardiovascular patients.[86] Another concern on PABD efficacy is related to the rate of mortality of patients waiting for cardiac and cancer surgery; as stated by Goodnough,[87] any mortality during the autologous blood collection period must be regarded as a complication of PABD. This is not trivial, considering that in the report by Suttorp et al.,[88] 2 out of 288 patients on a medium priority list for CABG, with a mean waiting period of 39 days (approximately the storage period of blood) died before operation. Clearly, this risk would decrease with reduced blood donation intervals, and this approach should ameliorate preoperative blood collection, once the results by Wittig et al.[89] are confirmed. The authors randomly assigned a total of 40 consecutive patients scheduled for hip arthroplasty to two groups: with the aim of collecting 3 units, the first group gave blood at weekly intervals and the second at days 0, 3, and 7. Short donation intervals resulted in a higher preoperative erythrocyte mass after similar preoperative deposit.

Finally, some risks of PABD, such as bacterial contamination, circulatory overload and clerical errors which lead to transfuse the unit into an unintended recipient,[90] are common to allogeneic blood transfusion. At least for clerical errors, a device based on the forcing function concept can be used for an univocal identification of the autologous blood recipient[91]; concerns about the risks, either immunologic or infective, of transfusing an autologous unit to an unintended recipient are probably overestimated.[92]

2. Utilization.

In the past decade, a dramatic increase in the request of predonating blood has been observed. The percentage of total blood supply by PABD was 8.1% in the US in 1992, nearly doubled when compared to 1989.[93] As the first aim of medical work is not to do harm, a series of criteria for the eligibility of predonating patients has been established, which results in an estimate of the potential effect of PABD on blood supply. Interestingly, two different studies, using different criteria of eligibility, conclude with the same estimate of the total potential effect of PABD on the total blood supply, which is considered about 10%.[94,95] Remarkably, units collected by PABD represent only about 5% of the total transfused units in the U.S. in 1992,[93] which is about half the total potential effect of PABD on the blood supply. Data from either European[5,96] or American[93] sources clearly indicate that this approach is both over- and underutilized. They show that a considerable amount of autologous blood units collected are left untransfused, whereas many patients who would otherwise benefit from this approach are not entailed in the protocol. This latter event seems to suggest that the safety of the procedure is a matter of feeling among surgeons and physicians (see above) and some reluctance to approach PABD is present.[97] AuBuchon et al.[98] reported that in 40% of the cases in which an allogeneic transfusion was made during surgery, the reason for not ordering a PABD was medical ineligibility (including anemia), as also reported by different studies.[99,94,100] Many factors may contribute to explain these findings. Emergence of HIV infection has had a great impact on physicians' practice regarding blood transfusion and a study by Atlas et al.[101] demonstrates that in about 10 years the exposure to allogeneic blood for patients undergoing hip surgery decreased from 90% to 16%. Although this was due in part to a change in transfusion triggers and in operative technique improvement, the availability of autologous blood increased from near zero to 82% of total blood used. Similar results have been obtained by Biesma et al.[96] Medico-legal reasons urge physicians to inform patients when autologous donation is available,[102] and overestimation of unknown risks regarding blood safety by patients has probably led to an overcollection of autologous units even when blood use is highly improbable. Another reason for increasing autologous unit wastage is that the number of units to be collected per patient is often determined by a schedule of optimal preoperative collection of autologous blood (SOPCAB)[103] instead of a standard surgical blood ordering schedule (derived by the MSBOS)[104] in order to cover more than 95% of the transfusion need by PABD (for instance, 5 units for coronary artery bypass grafting instead of 3).[94] Clearly, this increases autologous blood wastage and might also lead to an increased probability for anemic patients to be transfused with allogeneic blood, despite autologous blood donation.[105,106] This latter implication is not confirmed by other investigators,[107] who found that availability of autologous blood results in a pattern of more conservative use of red cells despite similar Hct pretransfusion levels (about 24%) in the two groups of patients transfused with autologous or allogeneic blood. Once again, these apparent conflicting observations are related to the controversy on whether indications for autologous blood transfusion might be more liberally advocated.[108,109]

Use of Recombinant Erythropoietin

Recombinant human erythropoietin (rHuEPO) increases red blood cell production and its clinical use in therapy is generally accepted in the treatment of anemia of chronic renal failure, zidovudine induced anemia in HIV-infected patients, and anemia related to cancer and cancer chemotherapy.[110] However, clinical uses of rHuEPO are evolving and its role in surgery is now emerging. As reported by many studies, a standard phlebotomy schedule of one autologous blood donation every week for surgical procedures makes many patients unable to produce, within the necessary time, the number of required units and expose them to the risk of allogeneic blood transfusion. Anemia at the beginning of donations adds a concomitant risk for subsequent allogeneic blood transfusion.[111,112] Treatment with rHuEPO has proven to be effective in increasing the volume of autologous blood collected from patients with low basal hematocrits, although its efficacy in avoiding subsequent allogeneic exposure in patients with normal basal hematocrit levels remains questionable.[113-116] An indication has been made for rHuEPO also in the perioperative anemia.[117] More extensive applications can be performed by using rHuEPO in combination with pharmacological approaches to surgical bleeding.[118] Many concerns remain, however, over the use of rHuEPO in surgery, as reviewed by Goodnough[119]: adequate iron supplementation to optimize erythropoietic response, dose, route, and interval of administration, prevalence of adverse effects (as a possible increased prevalence of thrombotic events), and finally cost-effectiveness of the procedure. Present guidelines restrict the use of rHuEPO to defined subgroups of patients, such as patients with reduced preoperative red cell volume (anemic and pediatric patients), patients for whom standard or longer donation intervals are not feasible, patients with rare alloantibodies or at risk for alloimmunization, and patients who refuse blood transfusion for religious opinions.[120]

Cost-Effectiveness

Looking at the costs associated with blood collection, inventory, storage, and issuing, there is no doubt that an autologous unit has a higher cost than an allogeneic one.[120] Not surprisingly, PABD has raised a great controversy on its cost-effectiveness. However, as stated above, risks of allogeneic transfusion (although overestimated), medico-legal instances, or patient's request have made autologous blood donation a standard of care, regardless of its cost. As safety of allogeneic blood transfusion has increased in the last 10 years[121], cost-effectiveness of PADB must be considered on the basis of true risks (HIV, HCV, and other clinically relevant infectious agents transmitted by blood) and speculative risks (postoperative infections or cancer recurrence due to immunomodulation effect of transfusion). The literature on increased postoperative infections in autologous versus allogeneic transfused patients is contradictory,[63] and earlier cancer recurrence has been already discussed in this review. Hence, data presented by Etchason et al.,[122] Goodnough,[123] and Birkmeyer et al.[124] correctly suggest that the limited healthcare resources have to be used judiciously and that, from this point of view, PABD is a very poorly cost-effective practice, as compared to other medical interventions.

On the other hand, two concerns have been raised: the first is that costs as calculated by Etchason et al.[122] are related to an autologous donation modeled on allogeneic donation, which should be avoided to make PABD more cost-effective.[125] The second is that many medical and non-medical factors[125-127], less readily quantifiable, should be considered: patients with rare blood group or with multiple alloantibodies, emerging blood-borne infections, personal and/or religious reasons, ethical issues in transfusion medicine, and "peace of mind."[55] As correctly stated by Goodnough,[123] this discussion probably overwhelms the merits of PABD but may be useful in redefining all strategies in the transfusion practice.

CONCLUSIONS

The analysis of these issues on transfusion medicine in the field of surgery has yielded important results for future clinical researches:

- the debate on the risks and benefits of autologous blood donation has been renewed, mainly in those fields of surgery (cancer and cardiac surgery) in which an inappropriate choice would produce harmful consequences;
- the redefinition of autologous blood programs has been claimed in order to render them more cost-effective and more precisely addressed to maximize autologous blood use, minimizing the cost of its management;
- the definition and the testing for efficacy have been urged of combined approaches using quantitative data, algorithms, and point of care information which help the physician in the decision to transfuse, either with allogeneic or autologous blood. A continuous monitoring and audit of medical approaches is awaited and welcome to help physician's behavior be effective.[128,129] STI

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