Techniques of reducing perioperative blood loss

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Prevention of allogeneic blood utilization in surgical patients has become an important topic in transfusion medicine owing to the lack of absolute safety and, more recently, to the increasing problem of donor blood availability. For these reasons in the last decades a number of different strategies involving transfusion practice at different level have been proposed, evaluated and utilized to reduce allogeneic transfusion surgical patient.

Basically these strategies can be divided into 2 groups according to the mechanism they affect the patient's RBCs transfusion requirement:

a) Strategies reducing the patient's perioperative RBCs loss; or

b) Strategies increasing the amount of RBCs that the patient can tolerate to loss before requiring RBCs transfusion support.

The aim of this paper is to review same of the most utilized or promising strategies to preserve allogeneic transfusion by limiting the total volume of RBC that the patients lose during surgery and in the early postoperative period (Tab I).

Tab. I Strategies to reduce perioperative RBCs loss

Identification and correction of coagulation impairment
Less invasive surgical procedures
Accurate surgical hemostasis
Optimal anesthesiological techniques
Regional anesthetic technique
Hypotensive general anesthetic technique
Topical hemostatic agents
Procoagulant drugs
Desmopressin
Aprotinin
Antifibrinolytics drugs
Loss of RBCs poor blood (acute normovolemic hemodilution)
Intra and postoperative blood salvage

Topical Hemostatic Agents

Enhancement of the hemostasis at the site of the surgical wound represents, since long time, a very attractive way to limit perioperative bleeding and to reduce the need for blood transfusion support. A number of natural or synthetic topical hemostatic agent have been developed through the years, including collagen products (i.e. collagen fleece), absorbable gelatin sponges, oxidized cellulose, and synthetic cyanoacrylate-based glue. Among these product fibrin glue has been advocated by many surgeon as the material that best approaches the ideal operative sealant. Fibrin glue, also called fibrin sealant or fibrin adhesive, is a 2 component sealant composed of a variously obtained fibrinogen concentrate (usually containing also other factors such as aprotinin) and thrombin. At the time of utilization the 2 components are mixed in the presence of calcium chloride, thus reproducing the last step of coagulation cascade: thrombin-induced activation of fibrinogen results in the formation of a fibrin clot that consolidates and adheres to the site of application.

As a naturally occurring and human-derived product the material appear to have no tissue toxicity, promotes a firm seal in seconds to minutes, is reabsorbed in days to week and appear to promote local tissue growth and repair (1).

Different types of fibrin glues are currently in use, these products can be basically subdivided into two categories, the commercially prepared and the home-made prepared fibrin glues, that differ for the methods of preparing fibrinogen concentrate. In the commercially prepared fibrin glues, fibrinogen is obtained from fraction I paste obtained through Cohn's fractionation process (2), while in the home-made products fibrinogen is concentrated through the method of cryoprecipitation of allogeneic or autologous plasma (3). Both types of products utilize commercially prepared human thrombin concentrates. Commercially prepared fibrin glues have optimally high fibrinogen concentration, are safe (virus-inactivated), are easy to use but very costly. Home made products conversely, have lower and high variable fibrinogen content, their preparation is time-consuming, can not undergo virus inactivation process but are cheaper.

Beside the large number of experiences demonstrating the efficacy of fibrin glue as adhesive agents in maxillofacial and plastic surgery, numerous reports can be found concerning the hemostatic efficacy of fibrin glue, particularly in European literature. However studies reviewing experiences in human subjects generally fail to compare fibrin glue-treated group with control group. Altogether, despite considerable variation in experimental design these studies have generally shown fibrin sealant systems to be efficacious in controlling slowly bleeding foci, diffuse oozing bleeding from needle puncture site and diffuse parenchymal organ hemorrhage (4).

For these reason fibrin glue has found its most extensive application in the field of cardiothoragic (5) and vascular surgery (6) where it has been successfully used to seal the foci of microvascular bleeding (form anastomoses and needle puncture sites) and in prosthetic valve implantation. Moreover fibrin sealant have been successfully used to control bleeding at the site of dental extraction or minor surgical procedures in patients who are at increased risk for bleeding because of congenital coagulopathies or the use of anticoagulants (7).

Few experiences and reliable data on efficacy have been collected in the field of major bleeding surgery. Recently the efficacy of fibrin glue obtained from cryoprecipitate of autologous plasma has been evaluated in our Institute in patient's undergoing major orthopedic surgery. In this experiment a recently developed automatic device to produce cryoprecipitate has been utilized. The device (Thermogenesis-Dideco Cryoseal) allows to obtain the production of 7-10 mL of cryo from 250 mL of plasma in 30-40 minutes. Cryo was topically applied into the femour canal before the prosthesis installation through a delivery kit allowing the mixing of cryo with a solution of 100U/mL of human thrombin (Ortho Diagnostics) in a 1:1 ratio. The efficacy of the fibrin glue utilization has been determined by comparing between the 2 groups the perioperative RBCs loss calculated as the reduction of the circulating RBCs mass from presurgery to the 5th postoperative day plus the volume of RBCs transfused during this period. Despite age, body mass, baseline and preoperative Hct were comparable in the 2 groups, patients receiving intraoperative application of fibrin glue had significantly lower perioperative RBCs loss (640 ± 121 mL vs 904 ± 152 mL of RBCs; $p = 0.000$), with a mean saving of 264mL of RBCs per patient. Moreover patients in fibrin glue group had a reduced transfusion requirement (2.2 ± 1 vs 2.9 ± 0.9 units of blood) The difference was not statistically significant due to the limited number of cases. None of the patients had any adverse effect related to the use of the study agent. These results, although preliminary, seem to indicate that fibrin glue may represent an effective further strategy to reduce perioperative blood loss also in major bleeding surgery. However further studies are needed to define the cost-effectiveness of the procedure and the role that fibrin gluing may have in transfusion medicine.

Perioperative salvage

Perioperative salvage refers to the collection and reinfusion of autologous RBCs lost by a patients during surgery (intraoperative salvage) or in the early postoperative period from surgical drains (postoperative salvage).

Two kinds of systems are currently available for these procedures. The basic difference is whether or not cells are washed before they are returned to the patient. In the washing systems, aspirated RBCs are concentrated in a centrifuge and then washed with saline. The end product, the patient's own red cells suspended in saline, is then spun off into a concentrated pack for reinfusion. These systems represent by far the most extensively utilised method for intraoperative salvage. In the systems for transfusion of unwashed RBCs, the collected shed blood, mixed or not with anticoagulant, is returned to the patient through filters. The use of these systems is generally restricted to the postoperative salvage.

When the safety profile is concerned it has been observed that if the shed blood is collected by sterile methods and properly transfused the procedure has few risks. In particular it has been claimed that the risk of clerical error is practically non existent if blood collection and patient are at the same site and reinfusion is conducted without the blood having left the patient side (9). There are, however some contraindications to the use of perioperative salvage (infection, cancer) and some medical controversial hazards (coagulation derangement after reinfusion of salvaged blood).

Infection in the operative field is widely regarded as an absolute contraindication to perioperative blood salvage. Indeed, no existing system of blood filtering or washing can completely eliminate bacteria. Although some reports refer of positive outcome of patients receiving contaminated salvaged blood the use of blood recovered from a contaminated field is justified only for life-threatening bleeding with no available banked blood.

The use of blood salvage is regarded as contraindicated in cancer surgery as concern exists that tumour cells harvested during perioperative salvage would be reinfused to the patient and promote metastatic disease (10). Although an increased incidence of recurrence or metastasis in cancer patients receiving salvaged blood during cancer resection surgery has not been documented, the safety of the technique has not been established and the transfusion of blood contaminated with malignant cells should be avoided. Recently, very promising results have been obtained with blood irradiation. Experimental studies have shown that blood irradiation with 50Gy is very efficient in eliminating cancer cells that contaminate the surgical field. This effective strategy suffers from relevant problem of feasibility (availability of the blood irradiator close to the operating room; special transfusion bags) and exposes to an increased risk of mistaken exchange; however several hospital in Europe are now utilising successfully blood irradiation for intraoperative salvage in cancer surgery (11).

A long standing controversy focuses on the coagulation risk to the patient who receives unwashed salvaged blood as the product is partially hemolyzed and defibrinated and may contain high concentration of cytokines, vasoactive contaminants, activated clotting factors and fibrin degradation products. Moreover when large volume of unwashed salvaged blood are reinfused the amount of anticoagulant (heparin or ACD) may be clinically relevant (10). A number of animal and human studies addressed the issue of whether or not it is safer to wash salvaged blood prior to reinfusion but no conclusive results have been obtained. Taking the different studies together it can be concluded that although unwashed blood may contain potentially harmful soluble products, its use appears to be safe if transfusion is limited to small quantities (< 1000-1400mL of whole blood) and to appropriate circumstances, avoiding transfusion of unwashed blood in the presence of shock, acidosis or hypoperfusion (12,13).

One of the major advantages of perioperative salvage is that is logistically easier to organise than other autotransfusion technique and it is not affected by cancellation of operation and is applicable in emergency cases. The salvaging of blood does not in itself involve any manipulation of the patient's physiology and it is therefore applicable in patients where acute normovolemic hemodilution and PABD are not, for example when the patient is already anemic. However, specially when washing systems are utilised, to ensure a quality blood component for transfusion, a well-designed program and an appropriately trained staff are necessary.

When the efficacy of technique is concerned it can be observed that it provides a ready supply of blood that is available in proportion to the losses that are occurring and, in the event of massive haemorrhage, its use may occasionally be lifesaving if the rate of blood loss outstrips the availability of the allogeneic supply. Moreover, numerous studies have shown that perioperative salvage reduces allogeneic blood transfusions, especially in high-volume blood loss situations such as liver transplantation, extensive scoliosis repair, and complex cardiac (coronary artery graft and valve replacement) and major vascular surgery (9). More controversial is the efficacy of perioperative salvage in other major orthopedic work as major joint replacement and trauma (14,15). In our Institute it has been calculated that, in orthopedic surgery, the recovery varies between 30% and 45% of the blood lost during operation time (tab 1) and constitutes the 5% - 32% of all the blood transfused in patients undergoing different major orthopedic procedures.

Tab. 1 Total perioperative RBCs loss, RBCs loss the day of surgery and mL of RBCs salvaged during surgery and in the early postoperative period (mean ± standard deviation) in different major orthopedic surgical procedures

Type of Surgery	*n° Pts (F/M)*	*Total perioperative RBcs loss (mL of RBCs)*	*RBCs loss the day of surgery (mL of RBCs)*	*Perioperative RBCs salvage (mL of RBCs)*	*% of RBCs salvaged*
Total Hip Replacement	614 (414/200)	866 ± 316	592 ± 255	176 ± 138	29
Hip Revision	58 46/12)	1276 ± 484	959 ± 473	421 ± 265	44
Bilateral Hip Replacement	38 (34/4)	1831 ± 449	1357 ± 562	464 ± 190	34
Total Knee	84 (66/18)	766 ± 224	509 ± 218	178 ± 124	34

The subject of cost-effectiveness for intraoperative and postoperative salvage, including washed versus unprocessed blood, is a complex one, and has not been adequately addressed in any large prospective controlled study. Most researchers have sought to show whether or not the technique achieves cost equivalence with allogeneic blood as the determining measure of its effectiveness. With the use of automated cell-washing devices, it is generally agreed that the equivalent of at least 1.5 – 2 units of blood needs to be recovered in order for the method to be cost-effective (16,17). Thus selective use of the method in situations in which large perioperative blood loss are anticipated would improve the cost-effectiveness of the procedure, but such blood losses are difficult to predict. Indeed, the amount of blood that is lost during surgery and that can be recovered depends on a number of unpredictable variables, beside the type of operation. Consequently the identification of the cases in which the salvaging procedures have to be performed may be erroneous when based only on the type of operation.

To offer all the patients the benefit of salvaging their own blood but maintaining a favourable cost-benefit ratio the "stand-by procedure" is utilised. It consists in mounting the collection set in all the procedures where transfusion is expected and proceed to the washing cycle only if enough blood has been recovered. However, the estimation of the volume of RBCs that can be actually rendered available for transfusion may be fallacious when it simply relies on the volume collected into the reservoir. To estimate the volume of RBCs that can be saved and transfused before proceed to the washing cycle we defined a mathematical approach (18) that takes into account the total volume collected into the reservoir (Vol in reserv) the volume of anticoagulant solution (anticoag), the volume of solutions used to irrigate the surgical field (irrig solut), the patient's preoperative hematocrit (preop Hct), and the expected hemolysis, expressed as a ratio, occurring throughout the process (hemolis ratio); according to the following formula:

Expected volume of salvaged RBCs =

= Š(Blood in reserv - anticoag - irrig solut) x Preop HctĆ x (1 - hemol ratio)

We prospectively compared the estimated volume of salvaged RBCs (calculated with the formula assuming an hemolisys ratio of 0,3 Š30%Ć) with the volume of RBCs actually salvaged in 99 patients undergoing different orthopedic surgical procedures. An optimal correlation between the estimated and the actually collected salvaged RBCs was obtained ($r = 0,957$). Out of 27 cases where the expected RBCs yield was > 180mL only in 3 cases (11%) we actually obtain less than 180mL, while out of 72 cases where the estimated yield was < 180mL of RBCs only in 8 cases (11%) the actual yield was higher (Pearson's chi square = 54.3; $p=0.000$). The formula seems to represent a simple and precise method to estimate the volume of RBCs that can be saved and can be used during a "stand by" procedure to base the decision to process the collected blood, thus improving the cost-effectiveness of the technique.

Acute normovolemic hemodilution (ANH)

Acute normovolemic hemodilution (ANH) is the technique in which whole blood is removed from a patient while the circulating blood volume is maintained with acellular fluid shortly before a surgical procedure that is anticipated to result in significant blood loss. In adults the technique is most commonly used when blood loss of > 1 litre is anticipated, and usually moderate hemodilution is employed, the target hematocrit at commencement of surgery being 0,25- 0,3 (19,20).

The rationale of its use is that the blood lost during surgery after hemodilution has a lower hemoglobin concentration, which decreases the amount of hemoglobin lost and thus potentially decreases the need for allogeneic transfusion.

The proponents of ANH observe that the technique can be safely performed in a large number of patients without significant hemodinamic changes because when normovolemia is preserved, the reduction in RBCs results in a decreased blood viscosity and systemic vascular resistance that are associated with preservation of O_2 delivery.

However ANH carries the potential for a variety of adverse effects, even when the use is limited in extent (Hct>0,20). These effects include the occurrence of peripheral edema, and an increase in lung water when crystalloid is used for replacement. The latter effect may have implications for wound healing and post-operative lung function, although no studies have been reported (20).

The most significant potential risk with ANH is that of myocardial ischemia, the risk of which increases with decreasing hematocrit, in patients with impaired compensatory mechanisms to anemia. In patient with abnormal ventricular function ANH may induce ischaemic ECG changes and in patients with cardiovascular diseases the risk of

silent myocardial ischaemia in the perioperative period can be possible. It has been found that myocardial ischaemia is frequent in this group of patients even in the absence of hemodilution(21). At even greater risk are the patients with pre-existing heart diseases. However in one randomised study of patients with coronary artery disease undergoing aortic reconstruction it appeared that ANH-treated patients were less likely to develop myocardial dysfunction at the time of cross-charging than controls (22).

Another relevant issue regarding the safety of ANH is the chance of clerical errors. While many Authors claim that ANH minimise the risk (as the blood units generally remain in the operating room) concern exists on proper and safe management of blood units when many procedures are performed daily at the same time and from each patient a relevant number of blood units are collected (and some of them have to be transfused in the recovery room). Consequently an initial training, performed by the personal of the blood transfusion service, can be necessary for blood collection, management of the bags, patients and units identification and storage

There is no doubt that ANH has several logistic advantages over other modalities of autologous transfusion. Scheduling difficulties may preclude the use of PABD in urgent or emergent circumstances while are not limit to the use of ANH. Moreover when PABD is undesiderable or impossible (e.g. there is a potential for bacteremia or too little time for donation) ANH may be the appropriate solution. ANH can also be considered when malignancy or infection at the operative site precludes the use of perioperative salvage. Finally, ANH may also be convenient for patients and saves them from having travel to the centre to make donations.

It has been claimed that ANH is simple to perform, has not impact on staffing because usually is performed by anaesthesiologist and does not prolong operating room time (23-25). The latter, however, is an argument of debate. As ANH can be performed in awake and anaesthetised patients it can be implemented both in a surgical "prep" area- or in the OR. In order not to impact overall OR time, by delaying the onset of surgery, it is suggested to initiate ANH immediately following tracheal intubation and complete it after the induction of anaesthesia, during the initial period of the operation when blood loss is minimal. However taking into account that approximately 10 minutes are required to collect one unit of blood, when extensive hemodilution is carried out the time required to collect the required amount of blood may be not compatible with the surgical timetables. When ANH is performed an adequate preoperative evaluation of patient's cardiovascular condition and a careful monitoring during hemodilution are mandatory. The monitoring required depends upon hemodilution and the physical condition of the patient. Placement of a pulmonary artery catheter is usually indicated if extreme hemodilution is to be employed; it is not necessary for moderate hemodilution. However, the procedure must be performed by experienced personnel. ANH requires vigilance, clinical expertise, and an understanding of the physiologic consequences.

The efficacy of ANH in reducing allogeneic blood requirements is highly controversial. Early studies claimed to document the ANH effectiveness in allogeneic blood conservation, however many of these studies used small group of patients, historic or literature controls and were accompanied by changes in transfusion practice, with lower final hematocrit levels in ANH group compared with control.

A recent metaanalysis of 24 randomized, prospective studies of ANH in 1218 patients concluded that ANH reduced the likelihood of allogeneic exposure and the total number of allogeneic blood transfused. However, in trilas using a protocol to guide transfusion, ANH failed to show benefit (26).

Interesting results have been obtained in studies utilising mathematical modelling to evaluate the clinical efficacy of ANH (27-28). These studies suggest that moderate hemodilution to maintain a preoperative hematocrit of 25% results in the preservation of small volumes of RBCs (equivalent to 0.5 – 1 unit of blood) when the perioperative

blood loss is in the range of 1 – 1.5 litres of whole blood. Only when more substantial hemodilution (Hct <20%) is performed in patients with greater blood loses the savings become more substantial. However such a severe hemodilution requires the collection of very large volume of blood that involves safety concerns in a relevant numeber of patients.

Even more difficult is to define the cost-effectiveness of ANH. As indicated above, studies of ANH are few in number, with small numbers of patients and poorly selected controls. It seems unlikely that studies large enough to determine the relationship between the risks of ANH and the benefits of the reductions in allogeneic blood use achieved by its use will ever be carried out. ANH is a relatively inexpensive form of autologous blood transfusion. However its cost-effectiveness seems questionable as a results of theoretical and observational studies showing that the ability of the procedure in reducing allogeneic blood transfusion is limited.

Presently ANH seems safe, efficacious and cost-effective only when undertaken very aggressively (target Hct<20%) in healthy, young patients undergoing surgery with large (higher than 2 liter) expected blood losses. Such extensive hemodilution cannot be applied in elderly patients because in this case has the potential for adverse event. ANH should therefore be reserved for patients under 40 or for patients over 40 who are at low risk of ischemic heart disease unable to deposit preoperatively sufficient blood to meet their transfusion need or for whom allogeneic blood is unavailable.

Conclusions

In conclusion different strategies to reduce perioperative RBCs loss are currently available whose knowledge is very important to achieve the best from their use. The choice of the most appropriate techniques to be used in the specific patient should be based on the clinical condition of the patient, the type of surgery the patient is undergoing, the logistical conditions and on the availability of the different strategies in the specific setting, their efficacy and cost-effectiveness. As the different strategies to reduce perioperative RBCs loss involve the activity of different medical specialists, a strict co-operation between them is of paramount importance to obtain successfully clinical results without wasting precious resources.

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