Perioperative Autotransfusion and its Correlation to Hemostasis and Coagulopathies

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Abstract

The use of autologous blood techniques affords the reduction or elimination of homologous blood transfusions for most patients. In addition, for certain religious faiths such as Jehovah’s Witnesses or those patients with rare blood types, intraoperative salvage and return of the patient’s own blood is the only source of available blood. Autologous blood salvage in the perioperative period includes:

• Hemodilution
• Intraoperative salvage of lost blood
• Postoperative collection of shed blood

Perioperatively, autologous blood is salvaged and returned and the volumes involved do not create any hematological problems for the patient. In those cases involving large volumes of blood being processed and returned to the patient, the autotransfusionist must be aware of the possible alterations that may occur in the patient’s coagulation system. The collection and reinfusion of wound drainage fluids from operative sites has the potential to cause severe bleeding problems. This paper will present an overview of autologous blood salvage techniques in the perioperative period along with a review of the clinical effects of autotransfusion on hemostasis. Also discussed will be possible coagulopathies that can be caused by returning collected autologous blood.

Perioperative Autotransfusion

Generally, perioperative autotransfusion involves the collection and processing of blood lost during the intraoperative and postoperative periods and should be an integral part of any autologous blood program. Perioperative autotransfusion involves the following procedures:

• Preoperatively

Preoperative Hemodilution/Sequestration

There are two methods of preoperative hemodilution.

1. Hemodilution Combined with Whole Blood Sequestration
   One technique of preoperative hemodilution involves whole blood sequestration. With this method, while the patient is being anesthetized, whole blood (usually one or more units) is drawn into anticoagulated storage bag(s) and kept at room temperature (20° to 24° C). The patient is then given an equivalent volume of crystalloid or colloidal fluids to replace the collected blood and to maintain proper circulating volume. The whole blood is given back to the patient at the end of the surgical procedure.

2. Hemodilution Combined with (PRP) Platelet Rich Plasma Sequestration
   A second preoperative hemodilution involves the use of plasmapheresis (in the form of PRP). In this technique, blood is withdrawn from the patient and separated into packed red cells and platelet rich plasma. Usually one thousand milliliters of platelet rich plasma is processed (approximately 20-25 percent of the patients plasma volume). Volume replacement as required, is usually a crystalloid solution or colloidal solution such as 5 percent albumin to maintain the patient’s hemodynamic stability. The red cells separated during this procedure can be utilized during cardiopulmonary bypass to help maintain adequate hematocrit levels without the use of homologous blood products. The plasma portion containing clotting factors and platelets is...
returned following the administration of protamine to reverse the circulating heparin.4

• Intraoperatively

**Standard Hemodilution**

Generally, standard hemodilution is utilized with patients who have a normal pre-operative hematocrit. As blood is lost during the surgical procedure, crystalloid or colloidal fluids such as saline, lactated ringers and albumin are added to maintain proper fluid balance.5,6

**Intraoperative Blood Salvage**

During the operation, blood aspirated from the wound is suctioned into and collected in a sterile reservoir, separated and washed to recover the oxygen-carrying red cells, which are then given back to the patient. Some hospitals have their own intraoperative autotransfusion (IAT) equipment and staff technicians. Other hospitals utilize machines and operators from the American Red Cross or other Autotransfusion technology/processing agencies. This salvaging technique is appropriate when blood from the operative site is not contaminated. It should not be used during surgery on the bowel, in infected wounds, or in cancer surgery for fear of spreading cancer cells.7 Some physicians, however, have successfully utilized intraoperative autotransfusion in cancer patients.8 Autotransfusion also should not be used in Caesarean section operations.

• Postoperatively

Wound drainage is collected during the initial postoperative period. This blood should then be centrifuged to concentrate the red cells. Following concentration, the red cells should be thoroughly washed to remove any debris, then reinfused as required to the patient.5,10,11

**Blood Components Involved in Perioperative Autotransfusion**

**Red Cells**

Red cells (erythrocytes) are the key blood element saved during perioperative autotransfusion. Normally red blood cells are approximately 7 to 8 microns in diameter and 1 to 2 microns thick. The red cell is a non-nucleated flat cell with a bi-concave shape. The red cell is produced in the bone marrow at a rate of 1,000,000 red cells per second. Normally they are present in the peripheral blood in concentrations of 4 to 6 million red cells per microliter of blood. The normal circulating life span of the erythrocytes is about 120 days. The primary function of the red cell is to carry oxygen and carbon dioxide. One of the questions frequently asked about blood salvage from the wound is how does perioperative autotransfusion affect the red cell life span. There have been several studies done with Isotope tagging of blood salvaged from drainage of an orthopedic wound. A study by Ray et al. showed no significant difference in the lifespan of red cells processed by a cell washing system as compared to the patient's normal circulating red cells.12

**White Cells**

White cells (leukocytes) normally are present in the blood with a range of 5,000 to 12,000 cells per microliter of blood. The bone marrow produces leukocytes at the same rate as red cells, about one million per second. A common question is why, if so many white cells are produced, is the number of circulating white cells lower than red cells? One of the reasons is that white cells have the ability to squeeze through the pores of vessels and into the tissue bed where they are attracted to foreign bodies such as bacteria, viruses, etc. The white cells engulf the object and digest them with the enzymes contained in the cytoplasmic granules. White cells have a very short life span once they leave the vascular system. When they become activated in the tissue bed the life span is about 24 hours. One of the concerns expressed by those new to perioperative autotransfusion is the fact that in the washing process a majority of the leukocytes are being washed away. This is really in the best interest of the patient since these white cells have been exposed to tissue in the wound. When this happens they become activated. Once activated, these white cells go through a self-destructive process, liberating digestive enzymes into the circulation, which causes complement activation. This can lead to Adult Respiratory Distress Syndrome (ARDS) and other complement related complications.13

**Platelets**

The third cellular component in the blood is the platelet. Platelets are generally about 1 to 2 microns in diameter. Primary hemostasis depends upon the response of the platelet and blood vessel wall to injury. The platelets are the first line of defense against any violation in the integrity of the vascular system. They become activated, accumulate at the injury site and occlude the break in the vessel. Platelets also release components that initiate the activation of the clotting cascade, forming fibrin which gives the clot some of its structural strength.14

**Plasma**

Plasma is the fluid segment of the blood in which the
red and white blood cells are suspended along with platelets and numerous dissolved chemical compounds. Some of these compounds include clotting factors, calcium and other electrolytes, phospholipids and other materials required for the blood to clot.

**Coagulation System Overview**

Alteration of the coagulation pathway (cascade) is probably the most common problem the autotransfusionist will have to face during perioperative autotransfusion. Therefore, a brief review of the coagulation system is in order. One of the major functions of blood is to maintain tissue stability, thereby keeping the internal environment of the body constant so that normal physiological processes may occur. In order to maintain this stability, blood must remain fluid within the confines of the circulatory system. Should an abnormal vascular condition occur, certain changes take place which stop the flow of blood to the vessel wall. Therefore, hemostasis can be defined as the process by which the body maintains blood in the fluid state within the vascular compartment and prevents excess blood loss when the vascular lining is breached. There are three basic facets of hemostasis: vascular, platelets, and plasma coagulation factors. This is called the triad of hemostasis since the vascular component, the coagulation factors, and the platelets all intermingle and interact with each other. The vascular portion is composed of arteries, which are muscular and resistant to severe trauma and rupture and veins, which are thinner, less resilient and may rupture with moderate trauma. There is also the microcirculatory system, which is comprised of arterioles, capillaries, and venules. The integrity of the vascular system is also dependent upon the internal action of platelets. Platelets must be adequate in number and function properly. Following vessel injury, platelets adhere to the exposed surface beneath the damaged endothelium. Platelet aggregation serves two functions:

1. sealing of the ruptured vessel with a platelet plug, and
2. the release of several indigenous components.

One platelet component interacts with clotting factors to produce thrombin which ultimately results in the formation of fibrin. There are eleven plasma coagulation factors. A deficiency of one or more factors and/or their activity may result in an abnormal hemostatic response. An increase in concentration of these factors in association with changes in blood flow can result in thrombin formation.

In 1904 Dr. Morowitz presented, based on experimental data, what he called the "Classical Theory of Blood Coagulation." He stated that prothrombin, calcium, and fibrinogen were all present in the circulating blood. He theorized that blood remained fluid in the absence of thromboplasmin which had the ability to convert prothrombin to thrombin with subsequent fibrin formation.

Between 1904 and 1950 not much research was done on thromboplastic activity. In 1950, it was postulated that there are two types of thromboplasmin, resulting in two avenues of coagulation. These are defined as the intrinsic and extrinsic pathways. There is a third pathway involved in the clotting process called the final or common pathway. The processes and reactions that occur in this final pathway are common to the final formation of a clot, independent of whether it was the intrinsic or extrinsic pathway which initiated the coagulation.

The intrinsic pathway is triggered by many stimuli which are not clearly understood, but usually is a result of some disruption of the vascular wall or contact with a foreign surface. Denuded epithelium at the injury site releases plasma thromboplasmin which causes platelet activation resulting in the initiation of the intrinsic coagulation cascade. Once the clotting process is started by the intrinsic mechanism, the clotting process moves to the common pathway where the clot is formed. Many steps are required to form a clot initiated by the intrinsic coagulation pathway. This makes it extremely difficult for the coagulation system to become hyperactivated and form unnecessary clots.

The extrinsic pathway is activated by a tissue extract called tissue thromboplasmin. When tissue thromboplasmin is released from an injury, such as a cut, the platelets are immediately activated starting the clotting process and proceeding into the final common pathway to form the clot. Since external injury is usually more severe, nature has made this pathway so that very few steps are required to form a clot.

Almost all of the coagulation factors are proteolytic enzymes called serine proteases. They circulate in an inactive state until they are activated. The important thing to remember is that these factors must be sufficient in concentration to properly activate each other and complete the cascade to the point of forming a normal stable clot. All pathways also require the presence of ionized calcium. If ionized calcium is not present in adequate amounts, the cascade will not continue and a clot will not be formed.

**Fibrinolytic System Overview**

When the vascular system is compromised, the body activates the coagulation system to form clots and stop blood loss. Massive activation of the coagulation system is accompanied by activation of the fibrinolytic system.
This prevents the patient's body from totally clotting the entire circulatory system. After a clot has stopped the loss of blood at the injury site, the process of tissue rebuilding is initiated. As the injury heals and the clot is no longer needed, the fibrinolytic system breaks down and dissolves the clot. Sometimes problems develop when the fibrinolytic system becomes overly activated (fibrinolysis). In this situation the patient will also have bleeding problems. As fast as the clot is formed, the fibrinolytic system breaks it down. Therefore the clot is never fully formed and is not able to occlude the break in the vessel.

Anticoagulation Therapy Overview

Blood collected for autotransfusion requires that an anticoagulant be added in sufficient quantities at the time of collection. Generally, two anticoagulants are utilized for autotransfusion procedures.

Heparin

Heparin is usually the most recognized anticoagulant, and is utilized in surgical areas such as open heart, vascular, and catheterization laboratories. Medical personnel are familiar with heparin since it has been readily available since 1935.

Heparin is a systemic anticoagulant with up to a four hour half-life in the body. It is derived from either beef lung or pork mucosal sources. The beef lung type is the more expensive and potent of the two types. To anticoagulate the blood, heparin requires the presence of a plasma component called Antithrombin III or heparin cofactor. Antithrombin III is normally present in the blood and is the agent that normally binds with the clotting factors at a constant rate to prevent clotting. Heparin speeds up and enhances this bonding process of Antithrombin III, thereby limiting the availability of clotting factors for forming clots. Without the presence of ATIII or with reduced ATIII levels, heparin is unable to properly anticoagulate the blood. Another problem with using heparin for anticoagulation is the need to monitor heparin levels and reverse the anticoagulation effect of heparin with protamine. Protamine is a very potent drug which can cause adverse patient reactions. Some of the adverse effects of protamine include hypotension, platelet dysfunction, complement activation, and other negative reactions. In a survey of perfusionists it was reported that "the most common complication that resulted in the greatest number of patient injuries or deaths was a protamine reaction." In large doses protamine can even act as an anticoagulant and cause bleeding. Studies have shown that inadequate levels of heparin can cause the formation of procoagulant and leukoattractant materials during perioperative autotransfusion. If not properly neutralized, heparin rebound can cause bleeding problems postoperatively. Because of the effects of heparin, and especially protamine on the platelets, heparin should not be the anticoagulant of choice for (PRP) Platelet Rich Plasma sequestration procedures. In situations like cardiac surgery, if the patient has been systemically heparinized when the blood is collected, CPD must still be added to the collected blood. CPD's method of anticoagulation offers some protective action for the platelets. Although heparin is utilized extensively as a systemic anticoagulant, it is not approved by the American Association of Blood Banks (AABB) for the storage of blood.

CPD (Citrate Phosphate Dextrose)

The second anticoagulant available for autotransfusion and PRP procedures is Citrate Phosphate Dextrose Solution, USP. CPD is a sterile, nonpyrogenic solution of citric acid, sodium citrate, monobasic sodium phosphate and dextrose in water. It is a local anticoagulant, intended for use in blood banks for anticoagulating stored blood or blood products. It may also be used for autologous blood transfusion procedures and perioperative autotransfusion systems. CPD anticoagulates by the action of the citrate ion chelating calcium in the blood, thereby making calcium unavailable to the coagulation system. When mixed with autologous blood collected for reinfusion in a ratio of one part CPD Solution to seven parts blood (14-15 ml solution per 100 ml of whole blood), CPD prevents coagulation by inhibiting the calcium dependent steps of the coagulation cascade. The chelation of the calcium as the mechanism for anticoagulation offers several advantages for using CPD in perioperative autotransfusion procedures. Heparin, and especially protamine, are known to have detrimental effects on platelets (Protamine Sulphate-Induced Platelet Agglutination. Unpublished Manuscript by Robert Baugh c/o Hemotec Inc., Englewood, CO 80112). The use of CPD not only eliminates the need for heparin and protamine, but by binding the calcium which is needed in the coagulation cascade, protection for the platelets is further enhanced. Heparin is also known, in some instances, to activate the complement cascade. CPD, on the other hand, tends to inhibit complement cascade activation.

As described above, the anticoagulant action of CPD is related to its ability to chelate or bind with available calcium, inhibiting the coagulation cascade. Since calcium is required for many of the physiologic processes of the body, it is not possible to use CPD as a systemic anticoagulant because the large scale binding of calcium in the body would have disastrous results. Therefore, CPD is never to be directly infused intravenously. The reinfusion of properly washed red cells contains only traces of CPD anticoagulant solution which presents no problem to the normal patient. In any
case in which the patient receives quantities of whole blood, PRP, or in patients with impaired liver function, the autotransfusionist must adequately monitor for CPD toxicity with frequent blood samples to check pH and serum calcium (ionized) levels to assure that the patient does not develop citrate toxicity and circulatory depression. Normal plasma levels of ionized calcium are approximately five milliequivalents per liter. In the event of overinfusion or solute overload following reinfusion of autologous blood anticoagulated with CPD solution, evaluate the patient and institute appropriate corrective measures. CPD anticoagulant is fully compatible with heparinized blood and can be used safely in collection of blood from heparinized patients. Table 1 shows the advantages and disadvantages of both heparin and CPD.

Due to the many advantages of CPD anticoagulation for autotransfusion procedures, it is recommended that CPD be utilized for almost all autologous blood collection and storage procedures. One major exception would be in cases where electrolyte containing fluids, such as lactated ringers, are utilized as a rinse solution in the wound and will be mixed with the collected blood. If it is impossible to change to a normal saline irrigating solution, then heparin must be used as the anticoagulant in these cases. Another exception would be in patients with impaired liver function or in liver transplants; the autotransfusionist must be careful to adequately monitor for CPD toxicity with frequent blood samples to check pH and serum calcium (ionized) levels.

ACD (Acid Citrate Dextrose) is used widely in apheresis procedures and may also be used in place of CPD for autotransfusion procedures, since blood collected in perioperative autotransfusion procedures will not be stored longer than six hours.

**Hemostasis and Coagulopathy**

In the process of perioperative autotransfusion, blood lost from the circulation either during surgery or from the wound postoperatively, is collected in a holding reservoir. The blood is then processed using a centrifuging procedure in which the red cells are concentrated and the plasma is washed away. The removal of the plasma is necessary since the plasma contains suspended debris and plasma bound agents. In normal operative or post-operative situations, one or two 225 ml "bowls" are processed. With a typical collected blood hematocrit of 22-28% this represents a removal of approximately 800-1500 ml of plasma volume. Since the normal adult blood volume is five to six liters, the removal of 800 to 1500 ml of plasma usually presents no problems for the coagulation system. The plasma volume should be replaced by crystalloid or colloidal fluids such as saline, lactated ringers or albumin. These solutions are added in quantities sufficient to maintain proper fluid balance.

**Bleeding Disorders Common to Perioperative Autotransfusion**

**Dilution of Clotting Factors**

Most of the eleven clotting factors are able to function at minimum hemostatic levels of five to thirty percent of normal concentration levels. Some require as much as 40 to 50 percent levels to function adequately. In addition, adequate levels of functional platelets must also be maintained. One of the most common bleeding problems in perioperative autotransfusion is the removal of over forty to fifty percent of a patient's total plasma volume during processing. If only the processed red cells are replaced and no consideration is given to the plasma or platelets lost, bleeding may occur due to the dilution of the clotting factors and the loss of platelets. It is important that the autotransfusionist keep track of the volumes of blood being processed and have an estimate of the patient's total blood volume. It must be kept in mind that the lower the patient's hematocrit, more plasma must be washed away to collect enough red cells to fill the autotransfusion bowl. Generally, if the patient's hematocrit is in the range of 24-28 percent, lab studies should be ordered to measure coagulation status, platelet function and quantity after the collection of approximately 2000 ml of whole blood (or after two to
three 225 ml bowls of packed cells have been processed). Coagulation testing should be undertaken at any time the patient exhibits any signs of abnormal bleeding tendencies.

**Coagulation Tests to be Evaluated**

- **PTT** - The PTT or Partial Thromboplastin Time is prolonged in patients with deficiencies in clotting factors in the intrinsic or common pathway. Normal values range from 13.3-15.2 seconds.
- **PT** - The PT test or the Prothrombin Time tests factors involved in the extrinsic or common pathway. Normal values range from 32-38 seconds.
- **TT** - The TT test or Thrombin Time is used to evaluate the final phase of blood coagulation. The two tests above measure the intrinsic and extrinsic pathways. The TT measures the final phase of the common pathway through the formation of the fibrin clot. This test is affected by abnormal fibrinogen levels. Normal values range from 20-25 seconds.
- **ACT** - The ACT or Activated Clotting Time Test measures the effectiveness of anticoagulants. This is the test of choice during cardiopulmonary bypass or when heparin is being utilized systemically as an anticoagulant, because the PT, PTT and TT are not linear at higher heparin levels. Baseline ACT values range from 110-145 seconds.

All of the above test results may be extended in patients whose clotting factors have been diluted.

**Platelet Quantity and Function**

Problems encountered with platelets during perioperative autotransfusion can consist of excessive dilution of the patient's platelets when large quantities of fluids are given for hemodilution during surgery. When a patient receives large amounts of packed red cells (either from the blood bank or from washed red cells from autotransfusion), platelet dilution can occur. Patients who have been on cardiopulmonary bypass will exhibit both lower platelet volume (thrombocytopenia) from hemodilution and will sometimes experience decreased function for several hours in the remaining platelets. Excessive platelet consumption can also occur in certain pathologic conditions such as DIC (disseminated intravascular coagulation).

**Platelet Tests to be Evaluated**

- **Platelet Count**
  This test reports the quantitative number of platelets in the circulation. Reductions of platelet counts to below 50,000 per µl may precipitate bleeding. Platelet counts normally range from 150,000 to 450,000 µl with a mean of approximately 250,000µl.

**Platelet Aggregation**

Measures the tendency of platelets to aggregate to form a hemostatic plug. Results are reported as normal or abnormal.

**Platelet Adhesion**

Measures the ability of platelets to adhere to a surface. Results are reported as normal or abnormal.

**Bleeding Time**

The bleeding time is the classic test for platelet and vascular response to injury, i.e., the ability to form an effective platelet plug. It is not often used during surgical procedures. A prolonged bleeding time will be found when the platelet count is below 100,000µl. With the Duke method, a normal time is 3-3.5 minutes or less. Using the Ivy method, normal times range from 2-12.5 minutes with a mean of 6.2 minutes. Results are generally reported as normal or abnormal.

**Thromboelastograph**

**Sonoclot**

Both of these devices are classified as viscoelastic monitors of the coagulation phenomenon. They measure platelet function.

**DIC - Disseminated Intravascular Coagulation and Primary Fibrinolysis**

Precipitated thromboplastic activity will initiate Disseminated Intravascular Coagulation or DIC. The intensity depends on the amount of precipitating agent, whether it is acute, subacute, or chronic. In DIC a clot promoting agent enters the circulation where it can cause the following problems: fibrin formation and a consumption of platelets. There is also a consumption of clotting factors I, II, V, VIII, and XIII. There will be a reduction of platelets and these factors to concentrations below normal levels in fibrin formations which will lead to bleeding or hemorrhage. At this point the fibrinolytic system becomes activated, causing the production of FDP (Fibrinogen Degradation Products). Clinical and laboratory findings in Disseminated Intravascular Coagulation and primary fibrinolysis are similar because both processes are characterized by depletion of fibrinogen, clotting factors V and VIII and the presence of FDP's. Differentiation must be made between the two syndromes, since therapeutic measures for both are specific and may, for the protection of the patient, need to be started promptly. Table 2 shows a differential...
Table 2

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<thead>
<tr>
<th>TEST</th>
<th>DIC</th>
<th>Primary Fibrinolysis</th>
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<td>Abnormally long</td>
</tr>
<tr>
<td>PT</td>
<td>Abnormally long</td>
<td>Abnormally long</td>
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<tr>
<td>TT</td>
<td>Abnormally long</td>
<td>Abnormally long</td>
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<tr>
<td>Platelets</td>
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<td>Normal</td>
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<td>Factor II</td>
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<td>Factor V</td>
<td>Reduced</td>
<td>Reduced</td>
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<tr>
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<td>Profibrinolysin</td>
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<tr>
<td>FDP</td>
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diagnosis chart of coagulation test results in evaluating DIC and fibrinolysis.

Tests to Evaluate the Fibrinolytic System

D-Dimers
Measurement of cross linked fractions of a fibrin clot. Normal range 0-0.5 µg/ml

FDP (fibrin degradation products)
Measurement of the split byproducts of fibrinogen by plasmin. Normal range 0-5 µg/ml

ELT (euglobulin clot lysis time)
This test is used to evaluate systemic fibrinolysis. All inhibitors of fibrinolysis are removed from the plasma, and the time necessary for the clot lysis is measured. A shortened ELT indicates that enhanced fibrinolysis is occurring. If the ELT time is extended, there is diminished fibrinolytic activity. Normal control range is 230-240 minutes.

Conclusion
In cases of massive bleeding in which collection of the blood and the subsequent washing of the red cells removes platelets and plasma, fresh plasma, fresh frozen plasma, platelet concentrates, cryoprecipitate, or other blood components may need to be given to replace those products lost during processing or diluted by added fluid volumes. Thor-ough evaluation of the patient's coagulation system should be undertaken prior to the administration of plasma or other blood components. There is no evidence that the prophylactic administration of FFP decreases transfusion requirements in multiple-trans-fused patients who do not have documented coagulation defects. There is no justification for the use of FFP as a volume expander or as a nutritional source. It is not required that an autotransfus-ionist be able to correctly diagnose the bleeding disorders discussed in this paper; however, it is important that the autotransfusionist have an understand-ing of the etiology of bleeding problems associated with perioperative autotransfusion. This knowledge will allow the avoidance of many situations which could initiate a serious bleeding problem.

References


