Recommendations for the transfusion management of patients in the peri-operative period. I. The pre-operative period

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Evaluation and management of patients in the pre-operative period

Introduction

A thorough pre-operative evaluation is fundamental for stratifying haemorrhagic risk, for predicting transfusion needs in relation to the type of surgical intervention, as well as for evaluating the indications and eligibility of a patient for autotransfusion procedures, and the need for any adjuvant therapies (*Grade of recommendation: 2C*)[1-3].

The pre-operative assessment must include a careful review of the patient's clinical documentation, a thorough personal and family history, focused particularly on revealing a suspected bleeding disorder, as well as a control of the laboratory tests.

The evaluation must be carried out a reasonable time before the planned date of the intervention, for example 30 days before, in order to allow detailed diagnostic investigations or planning of appropriate therapeutic measures (*Grade of recommendation: 2C*)[4].

Evaluation of haemorrhagic risk

A detailed personal and family history of any bleeding episodes must be taken from all patients who are candidates for surgery or invasive procedures (Figures 1-3, Table I) (*Grade of recommendation: 2C*)[5-10].

A well-conducted clinical interview should elicit information on any spontaneous, post-traumatic or post-surgical bleeding, any use of anticoagulant and anti-aggregant drugs (*Grade of recommendation: 2C*)[2] and include the family history (*Grade of recommendation: 2C*)[2,11].

For those patients with a positive history of bleeding, it may be helpful to use a structured questionnaire[12], such as the one shown in Table I[13], and a scheme to evaluate menorrhagia (Figure 2) in order to quantify the haemorrhagic risk (*Grade of recommendation: 2C*)[14,15].

Indiscriminate screening of coagulation parameters in unselected patients who are candidates for surgery or invasive procedures, in the absence of a history suggestive of bleeding, cannot be recommended (*Grade of recommendation: 2C+*)[2,16,17]. In the presence of a history of bleeding or a clear indication (for example, liver disease) further diagnostic laboratory tests are necessary; these should be guided by clinical findings and the history and clinical features of the patient (*Grade of recommendation: 2C*)[2]. A platelet count is, however, advisable before surgery and invasive procedures (excluding diagnostic endoscopies) (*Grade of recommendation: 2C*)[18].

The contemporaneous presence of anaemia and thrombocytopenia increases haemorrhagic risk[19-31]. In anaemic and thrombocytopenic patients (platelet count $\leq 20 \times 10^9$/L) who are candidates for surgery or invasive procedures, the haemorrhagic risk can be reduced by increasing the haematocrit to around 30% (besides correcting the platelet count to levels appropriate for the management of the procedure to be carried out) (*Grade of recommendation: 1C+*)[19-31].

Blood Transfus 2011;9:19-40 DOI 10.2450/2010.0074-10

Laboratory tests

The laboratory tests commonly used to evaluate haemorrhagic risk are the prothrombin time (PT)[32], which explores the extrinsic and common coagulation cascades, the activated partial thromboplastin time (aPTT), which explores the intrinsic and common coagulation cascades, and the platelet count. Both the PT and the aPTT can be altered in various situations, which may lead to a physiological response being masked. For example, the levels of factor VIII (FVIII) increase during pregnancy and in response to stress and inflammatory states.

This causes a shortening in the aPTT, which can mask a mild form of haemophilia or von Willebrand's disease. Contrariwise, lengthening of the aPTT due to the presence of a lupus inhibitor is not associated with an increased risk of bleeding.

Further examinations are assays of fibrinogen and the clotting factors [von Willebrand factor (vWF), factor II, factor V, factor VII, FVIII, factor IX, factor X, and factor XI], the bleeding time, and platelet function tests[33,34]. The utility of the bleeding time, even when standardised, is limited by the poor sensitivity and specificity of this test[2].

Figure 3 is a flow diagram illustrating the procedures to adopt for the initial evaluation and investigation of coagulation status (*Grade of recommendation: 2C*)[35-37].

A lack of factor XII does not increase haemorrhagic risk, while, in selected cases in which no laboratory anomalies are apparent but there is a history of significant bleeding, it is suggested that platelet function is evaluated and factor XIII assayed (*Grade of recommendation: 2C*)[38,39].

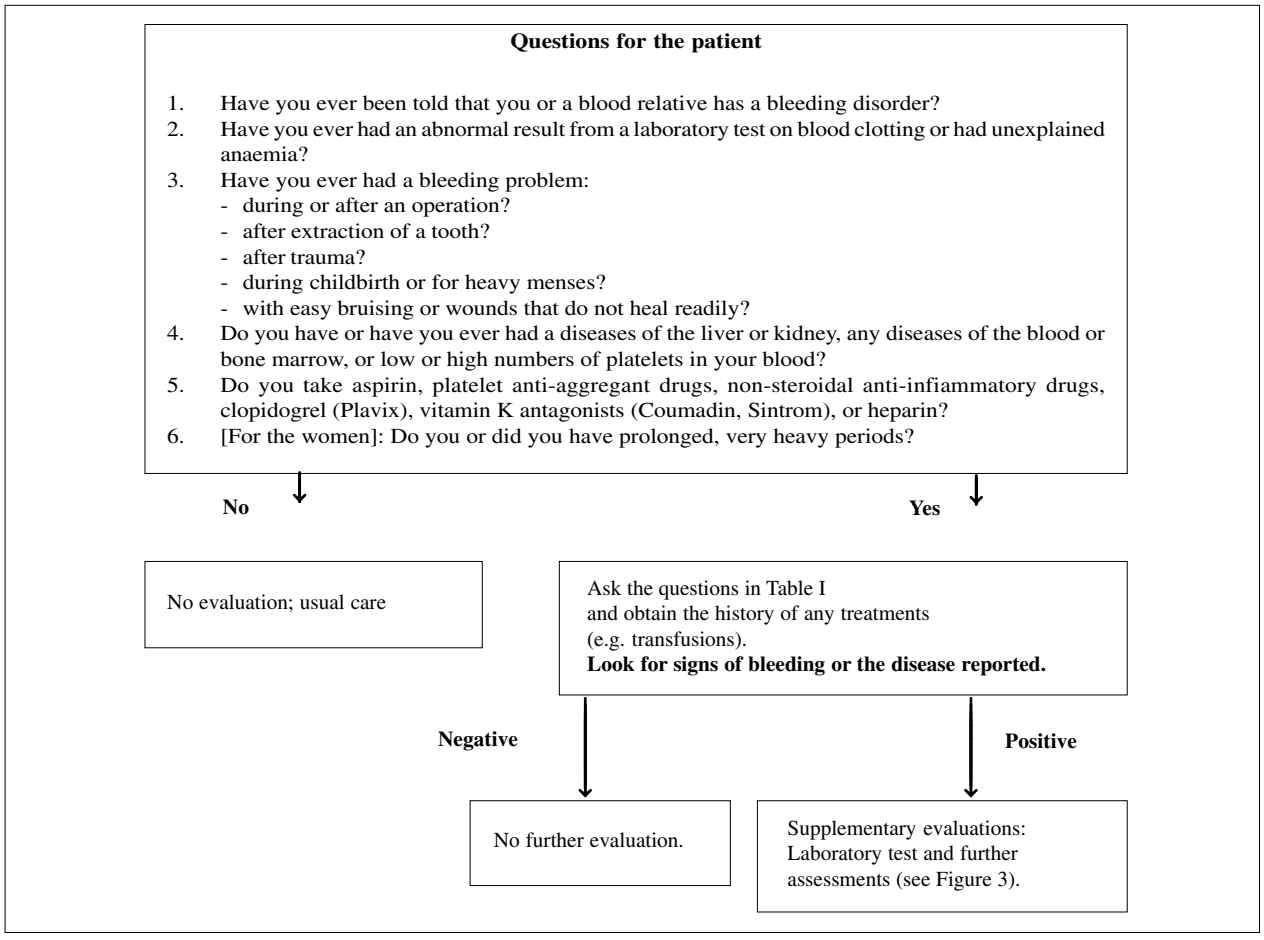


Figure 1 - Initial evaluation of bleeding disorders[35].

Table I - Bleeding score[12].

Patient's ID _____ **sex** _____ **date of birth** _____

Epistaxis	**Bleeding from minor wounds**	**Oral cavity**
0 None or rare (<5 episodes)	0 None or mild (<5 episodes)	0 No
1 >5 episodes or >10 min/episode	1 >5 episodes or >5 min/episode	1 Reported at least 1 episode
2 Only medical consultation	2 Only medical consultation	2 Only medical consultation
3 Packing or cauterisation or antifibrinolytic	3 Surgical haemostasis	3 Surgical haemostasis or antifibrinolytic
4 Transfusion or replacement therapy or DDAVP	4 Transfusion or replacement therapy or DDAVP	4 Transfusion or replacement therapy or DDAVP
Menorrhagia	**Muscle haematomas**	**Joint bleeds**
0 No	0 None	0 None
1 Only medical consultation	1 After trauma, no treatment	1 After trauma, no treatment
2 Antifibrinolytic and OC	2 Spontaneous, no treatment	2 Spontaneous, no treatment
3 DDAVP or replacement therapy or iron treatment	3 Spontaneous or traumatic, requiring treatment	3 Spontaneous or traumatic, requiring treatment
4 Transfusion or replacement therapy or DDAVP or hysterectomy	4 Spontaneous or traumatic, requiring surgery or transfusions	4 Spontaneous or traumatic, requiring surgery or transfusions
Dental extractions	**Surgery**	**Post-partum bleeding**
–1 No bleeding after ≥2 extractions	–1 No haemorrhage in ≥2 operations	–1 No haemorrhage in ≥2 deliveries
0 No extractions or no bleeding after 1 extraction	0 No surgery or no haemorrhage in = 1 operation	0 No deliveries or no haemorrhage after 1 delivery
1 Reported in <25% of all procedures	1 Reported in <25% of all operations	1 Only medical consultation
2 Reported in >25% of all procedures, no intervention	2 Reported in >25% of all operations	2 DDAVP or replacement therapy or iron treatment or antifibrinolytic
3 Re-suturing or packing	3 Surgical haemostasis or antifibrinolytic	3 Transfusion or replacement therapy or DDAVP
4 Transfusion or replacement therapy or DDAVP	4 Transfusion or replacement therapy or DDAVP	4 Hysterectomy
Skin Gastrointestinal bleeding	**CNS bleeding**	
0 None or mild (<1 cm)	0 None	0 None
1 >1 cm and without trauma	1 Associated with ulcer, portal hypertension, haemorrhoids, angiodysplasia	1 -
2 Only medical consultation	2 Spontaneous	2 -
3 -	3 Surgical haemostasis or transfusion or replacement therapy or DDAVP or antifibrinolytic	3 Subdural, any intervention
4 -	4 -	4 Intracerebral, any intervention

Total score:_____
(attention if >0)

Legend: DDAVP = desmopressin; ID = identity code; CNS = central nervous system; OC = oral contraceptive.

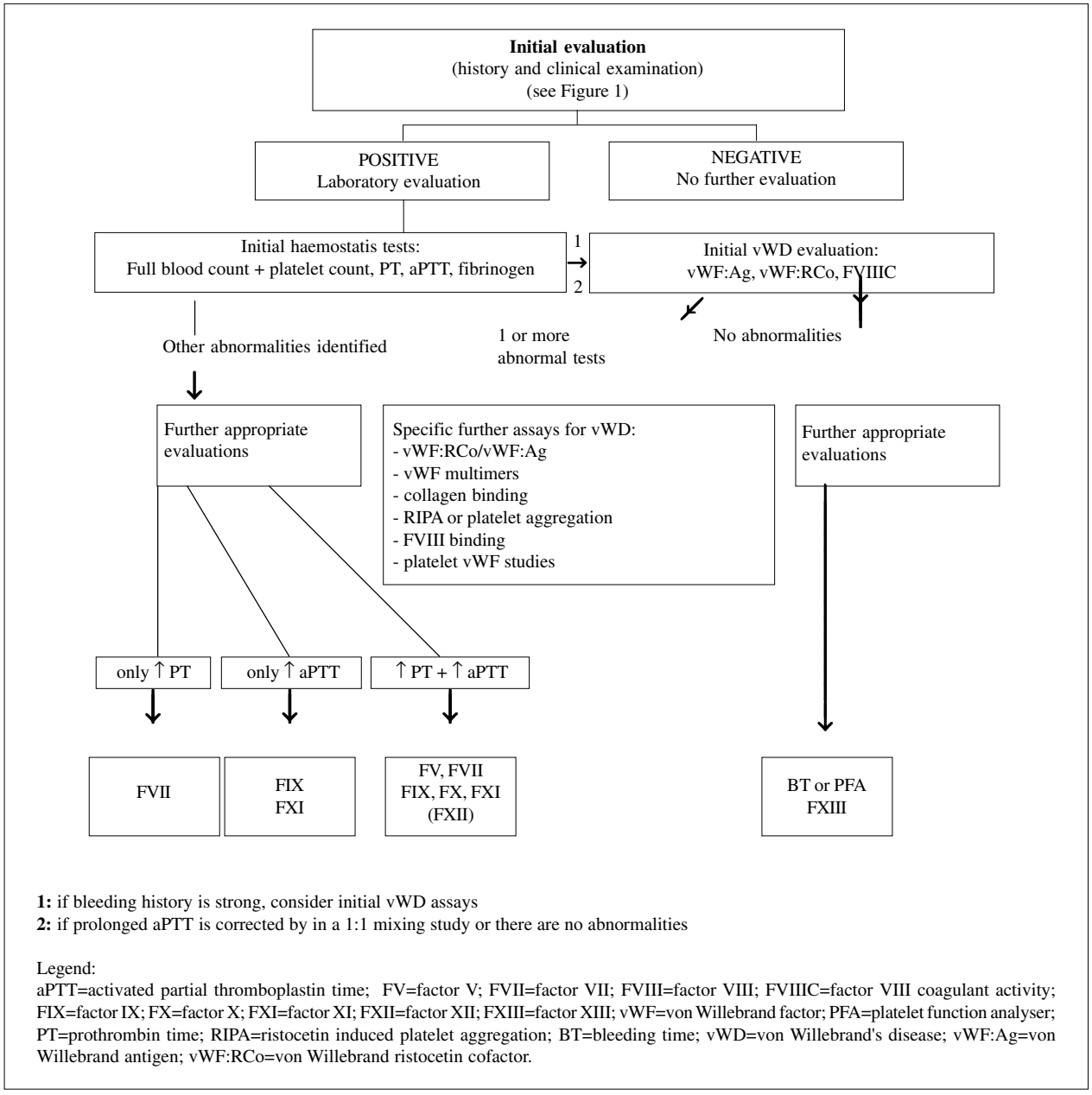
Score	Number of pads/day	1st	2nd	3rd	4th	5th	6th	7th	8th
x1									
x5									
x20									
total	_____								

Attention if score >100.

Score	Number of tampons/day	1st	2nd	3rd	4th	5th	6th	7th	8th
x1									
x5									
x20									
total	_____								

Attention if score >100.

Figure 2 - Evaluation of menorrhagia[14].



1: if bleeding history is strong, consider initial vWD assays
2: if prolonged aPTT is corrected by in a 1:1 mixing study or there are no abnormalities

Legend:
aPTT=activated partial thromboplastin time; FV=factor V; FVII=factor VII; FVIII=factor VIII; FVIIIC=factor VIII coagulant activity; FIX=factor IX; FX=factor X; FXI=factor XI; FXII=factor XII; FXIII=factor XIII; vWF=von Willebrand factor; PFA=platelet function analyser; PT=prothrombin time; RIPA=ristocetin induced platelet aggregation; BT=bleeding time; vWD=von Willebrand's disease; vWF:Ag=von Willebrand antigen; vWF:RCo=von Willebrand ristocetin cofactor.

Figure 3 - Laboratory assessment for von Willebrand's disease or other bleeding disorders[36].

Treatment of defects of haemostasis

In the case of a clotting defect, replacement therapy with the deficient factor should be instituted (*Grade of recommendation: 1A*)[40-44]. Table II lists the inherited bleeding disorders, the haemostatic levels of the deficient factors and the mean dose of the specific factor or plasma necessary for the replacement therapy[41].

In type I von Willebrand's disease, the drug of first choice for patients with vWF levels of 10 IU/dL or higher is desmopressin (DDAVP) (*Grade of recommendation: 2B*)[42]. vWF/FVIII concentrates are indicated for patients who do not respond to DDAVP (patients with severe type 1, types 2 and type 3 von Willebrand's disease) (*Grade of recommendation: 2B*)[42].

vWF concentrates without FVIII can be an alternative to vWF/FVIII concentrates as prophylaxis against bleeding in elective surgery (*Grade of recommendation: 2C*)[42,45].

Table II - Treatment of congenital bleeding disorders based on the plasma levels of the deficient factor in the context of surgery[41].

Deficient factor	Haemostatic plasma levels (IU/dL)	Factor half-life (hours)	Dose of specific concentrate (IU/kg)	PCC (IU/kg)	Dose of plasma (mL/kg)
Fibrinogen	30-50 mg/dL	72	20-30 mg/kg	-	15-20
Prothrombin	20-30	72	-	20-30	15-20
Factor V	10-15	36	-	-	15-20
Factor VII	10-15	4-6	30-40	-	-
Factor VIII	50-100	8-12	50-100	-	-
Factor IX	50-100	20-24	50-100	-	-
Factor X	10-15	40	-	20-30	15-20
Factor XI	5-10	60	15-20	-	15-20

Legend: PCC=prothrombin complex concentrate.

Thrombocytopenia

The suggested **prophylaxis** in the case of thrombocytopenia is as follows[19]:

- major surgery or invasive procedures such as lumbar puncture, epidural anaesthesia, liver biopsy, endoscopy with biopsy, placement of a central venous catheter: bring the platelet count to above $50x10^9$/L (*Grade of recommendation: 2C+*)[46-51];
- operations to critical sites, eye surgery and neurosurgery: administer prophylactic transfusions if the platelet count falls below the threshold of $100x10^9$/L (*Grade of recommendation: 2C*)[19,46-49];
- in patients with acute disseminated intravascular coagulation, in the absence of bleeding: reserve prophylactic platelet transfusions for those cases in which the thrombocytopenia and stratification of haemorrhagic risk indicate a high probability of bleeding (*Grade of recommendation: 2C*)[52].

With regards to the **treatment** of thrombocytopenia:

- the surgical patient who is bleeding usually requires a platelet transfusion if his or her platelet count is below $50x10^9$/L and rarely requires such a transfusion if the platelet count is above $100x10^9$/L (*Grade of recommendation: 2C*)[19,46-48,53];
- during massive transfusions, when the volume of red cell concentrate transfused is approximately double that of the circulating blood volume, a platelet count of $50x10^9$/L can be expected; a transfusion threshold of $75x10^9$/L is, therefore, suggested in those patients with active bleeding, in order to guarantee them a margin of safety and prevent the platelet count from dropping below $50x10^9$/L, the critical threshold for haemostasis. A higher platelet count has been recommended for patients with multiple trauma resulting from high velocity accidents or with lesions involving the central nervous system (*Grade of recommendation: 2C*)[19,54];
- in acute disseminated intravascular coagulation, in the presence of considerable bleeding and thrombocytopenia, besides treatment of the underlying disease and restoration of normal levels of clotting factors, the platelet count must be monitored and coagulation screening tests performed (PT, aPTT, fibrinogen, antithrombin, D-dimer). There is not a consensus on the target platelet count, but in the presence of substantial bleeding, it could be reasonable to maintain the platelet count around $50x10^9$/L (*Grade of recommendation: 2C*)[19,52,55].

Platelet disorders

Platelet transfusions are indicated, independently of the platelet count, for the prophylaxis of haemorrhage in patients with platelet function defects

(congenital or acquired) at high risk of bleeding who must undergo surgery or an invasive procedure at high haemorrhagic risk, as well in the presence of peri-operative haemorrhage (*Grade of recommendation: 2C*)[19,50].

Recombinant activated factor VII

The main indications for the use of recombinant activated factor VII (rFVIIa) are peri-operative prophylaxis and the treatment of bleeding in patients with haemophilia A or B with inhibitors, in whom replacement treatment with the deficient factor is not possible or not indicated (*Grade of recommendation: 2C*)[56,57] and in patients with acquired haemophilia (*Grade of recommendation: 2C+*)[57], inherited FVII deficiency (*Grade of recommendation: 2C+*)[41,58,59], or Glanzmann's thromboasthenia associated with refractoriness to platelet transfusion (*Grade of recommendation: 2C*)[19,46,60].

In recent years there has been a notable increase in the use of rFVIIa for "off label" indications such as the treatment of haemorrhage due to secondary coagulopathies in patients undergoing surgery or in those with multiple trauma[61], despite uncertainty about the risk of thrombotic complications associated with the use of this drug for unregistered indications[62,63].

The use of rFVIIa, mainly in the setting of uncontrolled studies, has also been the subject of recommendations, based on the consensus of experts, for the treatment of massive haemorrhage in surgical, obstetric and gynaecological patients[64-66]. A recent Cochrane systematic review recommended using rFVII only in clinical trials, since its true efficacy as a haemostatic drug, both for prophylaxis and for the treatment of major bleeding, is still uncertain[67]. However, reports of adverse arterial thromboembolic events have recently led the European Medicines Agency (EMEA) to contraindicate the use of rFVIIa for purposes other than the approved indications[68,69].

Desmopressin

According to a review from the Cochrane Library[70], the use of DDAVP limits blood losses in the peri-operative period, but not to a clinically important extent, and does not significantly reduce the transfusion of red cell concentrates. The authors, therefore, concluded that there is not currently evidence to support the use of DDAVP to contain peri-operative blood losses and transfusion requirements in patients who do not have inherited bleeding disorders (*Grade of recommendation: 1C*)[70-73].

Antithrombin deficiency

Replacement therapy with antithrombin (AT) is almost exclusively indicated for patients with congenital AT deficiency in particular situations characterised by an imbalance in haemostasis towards thrombosis (*Grade of recommendation: 2C*)[74-76].

There is no clinical evidence that above normal levels of AT guarantee better protection than physiological levels[75,77,78].

A recent meta-analysis[77,78] on the use of AT in critically ill patients did not demonstrate any significant effect on the reduction of mortality either globally or in the subgroups of studies carried out in obstetric patients or in those with trauma; however, an increase in haemorrhagic risk was revealed[75,77,78].

Calculation of the dose of antithrombin to administer

Before giving replacement therapy with the specific concentrate, it is advisable to assay AT function (*Grade of recommendation: 2C*)[75].

Given that a dose of 1 IU/kg of body weight increases plasma AT activity by 1.5%, the dose to administer can be calculated as follows:

IU of AT = body weight (kg) x [desired level - measured activity(%)]/1.5

Example: 60 kg x (100 –38%)/1.5 = 2,480 IU

The dose and timing of subsequent administrations are based on the results of monitoring the plasma activity of AT every 12-48 hours.

Side effects and adverse reactions

AT infusions are generally well tolerated although allergic reactions are possible[75].

The use of AT concentrates contemporaneously with the administration of heparin increases the risk of bleeding and for this reason careful clinical and laboratory controls are necessary in this situation (*Grade of recommendation: 2C*)[75].

Evaluation of concurrent therapy

Antiplatelet drugs

The patient's drug history must be taken, aimed at determining any use of anti-aggregant therapies

(*Grade of recommendation: 1C+*)[79].

Besides the strictly anti-aggregant drugs (aspirin, clopidogrel, dipyridamole, ticlopidine, abciximab), which inhibit platelet function with different mechanisms, effectiveness and duration[80-82], non-steroidal anti-inflammatory drugs also have an antiplatelet effect through the inhibition of cyclo-oxygenase (COX 1)[45,83].

The anti-aggregant drugs and non-steroidal anti-inflammatory drugs have an irreversible effect and do not have antidotes, so their use must be suspended some days before a planned intervention (*Grade of recommendation: 2C*)[17,45,84-87].

Oral anticoagulants

As for the antiplatelet drugs, oral anticoagulant therapy (warfarin, acenocoumarol) must be suspended at least 4 days before surgery to allow the PT and International Normalised Ratio to return to the norm (*Grade of recommendation: 2C*)[88].

In preparation for surgery that cannot be deferred, patients receiving vitamin K antagonists must be treated with prothrombin complex concentrates, which are the first choice of treatment, or, if these are not available, with fresh-frozen plasma, in order to normalise the parameters of coagulation (*Grade of recommendation: 1C+*)[19,75,89-94].

Heparin and thrombolytic drugs

Low-dose (prophylactic) unfractionated heparin (UFH) seems to be associated with a low risk of haemorrhage during anaesthesia and surgery[95]. Nevertheless, in patients receiving treatment with heparin, spinal anaesthesia and neurosurgical interventions should be avoided for at least 6 hours after suspension of the last dose of UFH and for at least 12 hours after treatment with low molecular weight heparins (LMWH), since the activity of these drugs peaks 4 hours after injection and lasts for 24 hours.

Patients receiving therapeutic doses of heparin have high intra- and post-operative risks of bleeding, so UFH and LMWH should be suspended for 6 and 12 hours, respectively (*Grade of recommendation: 2C+*)[95].

In emergency situations, the anticoagulant effect of heparin can be antagonised by protamine sulphate (*Grade of recommendation: 2C+*)[95].

When necessary, heparin administration can be restarted approximately 12 hours after completion of the intervention (*Grade of recommendation: 2C+*)[96-98].

Surgical procedures should, generally, be postponed in patients receiving thrombolytic drugs, even though these have a short half-life (*Grade of recommendation: 2C*)[96-98].

The effects of herbal remedies

Herbal remedies are very widely used in the population as supplementary or alternative therapies[3,99-102]. The use of such remedies is often not reported, since they are considered dietary integrators; however, many of them can affect coagulation and should, therefore, be suspended before an operation, at different times prior to the intervention depending on their duration of action (*Grade of recommendation: 2C*)[103,104].

Garlic potentiates the effect of warfarin and has antiplatelet properties, so it is advisable to suspend its assumption 7 days before a planned intervention (*Grade of recommendation: 2C*)[105]. *Ginko biloba* has an antiplatelet effect, and it has been suggested that this should be suspended 36 hours before an intervention (*Grade of recommendation: 2C*)[105]. The antiplatelet effect of ginseng is irreversible, so this product should be suspended for 7 days (*Grade of recommendation: 2C*)[105].

Other herbal remedies with antiplatelet effects are blueberries, bromelain, flaxseed oil, ginger and grape seed extract[104]. St. John's wort and green tea, in contrast, accelerate the metabolism of warfarin, reducing its effect.

Evaluation of haemoglobin

The level of haemoglobin, related to other conditions that cause organ ischaemia, such as cardiorespiratory disorders, influences the threshold for transfusion of red blood cells[106,107].

Patients with low levels of haemoglobin (<130 g/L in men and <120 g/L in women) have a higher risk of requiring allogeneic transfusion; to minimise this possibility, pharmacological measures should be used to correct their red cell mass before an operation (*Grade of recommendation: 2C*)[1,4].

A simple strategy for sparing a patient's blood is to limit the frequency of laboratory controls, the volume of blood sampled and the number of tests requested (*Grade of recommendation: 2C*)[108].

Since blood transfusion is associated with an increase in morbidity and mortality in all surgical patients, a considerable amount of research has been carried out on how to limit or eliminate the use of allogeneic transfusions[63,109,110].

Anaemia is a common finding in patients who are candidates for elective surgery[111,112].

The relationship between erythropoiesis, erythropoietin and iron, studied in patients undergoing pre-operative autologous blood donation, shows the bone marrow response to post-haemorrhagic anaemia[113]. In response to the collection of one unit of blood a week, under the standard conditions of an autologous donation regimen, endogenous erythropoietin stimulates the production of 397-568 mL of red blood cells, equivalent to 2-3 units of whole blood. Exogenous erythropoietin treatment in patients pre-depositing autologous blood produces from 358 to 1102 mL of red blood cells, equivalent to 2-5 units of whole blood[33,114].

The response to treatment with exogenous erythropoietin[115] in patients with an adequate iron store is independent of the iron supply, as demonstrated in a cohort of patients with haemochromatosis, who did not have a greater response than that of controls[116]. It is, however, difficult for the iron supply to be increased in healthy subjects to the level necessary to support a rate of erythropoiesis of this degree, whereas this can be achieved in situations such as haemochromatosis or intravenous administration of iron[117].

There is a good correlation between the dose of erythropoietin and red blood cell production[118], which can be estimated to be four times higher than the basal levels, independently of sex and age[119].

In patients with substantial iron deficiency, oral iron assumption is not sufficient to correct the induced dyserythropoiesis and intravenous iron administration should be considered (*Grade of recommendation: 1C+*)[117,120-123].

The so-called "iron-limited" erythropoiesis, which occurs during treatment with erythropoietin, should also be corrected by the intravenous administration of iron (*Grade of recommendation: 1C+*)[116,117].

Numerous, well-designed studies have examined the risks and adverse events related to the use of intravenous iron, particularly allergic and vasomotor reactions, which are independent of the dose and occur in about 5% of the patients: 0.7% of these reactions can be life-threatening[123-125]. Iron gluconate and iron sucrose have a better safety profile than iron dextran[123-128]. The rate of adverse events, in particular allergic reactions, appears to be lower with iron gluconate (the only preparation for intravenous administration available in Italy) than with iron dextran (3.3 and 8.7 episodes per million doses, respectively)[33].

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Pre-operative strategies for limiting the use of allogeneic transfusions

Introduction

Most adults in good health with normal baseline concentrations of haemoglobin do not usually require a transfusion when undergoing surgery if the blood loss during the intervention is less than 1,000 mL and the intravascular volume is maintained with crystalloid or colloid solutions[1,2].

Maximum surgical blood ordering schedule

For those surgical procedures that usually necessitate transfusions, a multidisciplinary team, formed of anaesthetists, surgeons and transfusion medicine specialists, must adopt a standard protocol for requesting blood, which reflects the usual local requirement for blood for each type of operation, the so-called "maximum surgical blood order schedule" (MSBOS) (*Grade of recommendation: 2C*)[3-7].

The indications of the British Committee for Standards in Haematology Blood Transfusion Task Force[5], which reports the maximum acceptable order in standard operating conditions and in the presence of good transfusion practice, can be taken as an initial reference (*Grade of recommendation: 2C*).

It is to be hoped that the MSBOS is adapted to the local situation in each health care structure and that it is periodically reviewed based on an internal audit of blood use (*Grade of recommendation: 2C*)[8-11].

Type and screen

Many surgical interventions rarely necessitate transfusion and there is, therefore, no need to reserve units of compatible blood for the patients who are to undergo these interventions[12]. In cases in which the transfusion probability (number of transfused patients divided by the total number of operated patients) is less than 10%, a "type and screen" procedure should be used (*Grade of recommendation: 2C*)[13-17].

The "type and screen" procedure consists of determining the patient's ABO and Rh blood groups and searching for clinically relevant antibodies to red blood cells (RBC). If no such antibodies are found, RBC units can be assigned without having to carry out the cross match[18,19]. If the screening study for antibodies is positive, the antibody must be identified and units of RBC, lacking the antigen corresponding to the identified antibody, must be found and reserved for the patient (*Grade of recommendation: 1A*)[17,20].

Alternatives to the transfusion of allogeneic blood

Every reasonable effort must always be made to avoid or reduce blood transfusions; furthermore, therapeutic alternatives to the transfusion of allogeneic blood should be available for those patients who refuse transfusions for religious beliefs or other reasons (*Grade of recommendation: 2C*).

Before any major surgical intervention, the patient's clinical condition, pre-operative level of haemoglobin and iron stores should be optimised (*Grade of recommendation: 2C+*)[21].

An integrated programme of management of possible pre-operative anaemia should be arranged for all patients undergoing elective surgery that can be expected to necessitate blood transfusion. Such a programme is intended to limit exposure to allogeneic blood and should include an assessment of the appropriateness of using haematinics, erythropoietin, pharmacological measures to aid haemostasis, volume expanders and possible collection of autologous blood (before, during and/or after the operation) (*Grade of recommendation: 1C+*)[1,22,23].

The role of iron

In situations in which there is a continuous loss of iron, its oral intake is not usually able to guarantee a supply sufficient to correct the iron-deficiency anaemia that develops, so intravenous iron therapy should be considered. Patients with renal failure undergoing dialysis have continuous iron loss and the role of intravenous iron treatment in this context has been well defined in numerous clinical trials[24,25].

Treatment with intravenous iron can be used in the case of bleeding, of medical or surgical origin, for patients who refuse blood transfusions (*Grade of recommendation: 2C+*)[26-28].

Recent studies have demonstrated that the benefits of intravenously administered iron in these situations are notable and have generated renewed interest in this important therapeutic modality[27,28]. Furthermore, intravenously administered iron potentiates the erythropoietic response to erythropoietin; this has important cost-benefit implications since, by using this association, the amount of erythropoietin administered

can be reduced[29-31].

However, intravenously administered iron has been associated with an increased risk of adverse events, such as allergic reactions, infections, and haemodynamic reactions[32], some of which can be fatal[33-36]. The prevalence of these reactions does not seem to be related to the dose of the iron infusion (low doses, equivalent to 100 mg, or high doses, equivalent to 250-500 mg)[37]; the pharmaceutical form most frequently responsible for these adverse events is high molecular weight iron dextran. Other preparations (low molecular weight iron dextran, iron sucrose, ferric gluconate) have better safety profiles[38,39].

Erythropoietin

A previously undiagnosed state of anaemia is present in between 5% and 75% of patients undergoing elective surgery[40]. Optimisation of haemoglobin levels is, therefore, an important strategy for reducing allogeneic blood requirements during or after surgery.

Erythropoietin is the main regulator of RBC production and hypoxia represents the principal stimulus for increasing the production of erythropoietin. This hormone binds to specific receptors present on bone marrow erythroid progenitor cells, thereby increasing the production of RBC[41].

The effect of recombinant erythropoietin is fast; within 2-3 days there is an increase in reticulocytes, the haematocrit starts to rise and the equivalent of one unit of blood is produced in about 7 days[42-44].

There are two possible strategies for the use of erythropoietin in the peri-operative period: it can be given to optimise autologous blood donation or it can be used in patients undergoing elective surgery who cannot carry out a predeposit programme[41]. At present, the prescription of erythropoietin α, β and z is paid for by the National Health Service if used as a treatment to increase the amount of autologous blood pre-deposited in pre-operative donation programme, with the limitations set out in the product information leaflet. Erythropoietin α is also paid for by the National Health Service if prescribed to reduce exposure to transfusions of allogeneic blood in adult patients who are candidates for elective major orthopaedic surgery considered at high risk of transfusion complications, but for whom a pre-operative autologous blood donation programme is not available.

The administration of erythropoietin is suggested for patients who are candidates for elective surgery and undergo a programme of pre-operative autologous blood donation (PABD) if the transfusion of at least three units of whole blood is foreseen (*Grade of recommendation: 2C+*)[42,45].

The use of erythropoietin in both strategies leads to a reduction in the transfusion of allogeneic blood in orthopaedic and cardiac surgery[42,46-53]. However, there is not a unanimous agreement on the optimal dose of erythropoietin to use in PABD programmes and the cost-benefit ratio is negative[21,45,47,54]. For this reason, unless there are other associated indications, such as renal failure, or a contraindication to or refusal of transfusions, the routine use of erythropoietin pre-operatively cannot be recommended (*Grade of recommendation: 2C+*)[55,56].

Pharmacological agents to aid haemostasis

Peri-operative bleeding is a problem very commonly encountered by surgeons, anaesthetists and haematologists who care for trauma patients and patients undergoing surgery. Post-surgical bleeding can have various causes. Multiple haemostatic abnormalities occur frequently in patient undergoing heart surgery, with or without cardiopulmonary bypass. These abnormalities are due to the release of tissue factors and activation of the fibrinolytic cascade[57,58].

Platelet abnormalities have also been demonstrated after heart surgery; furthermore, many patients submitted to heart surgery are taking antiplatelet drugs (such as clopidogrel) regularly, because of their underlying cardiovascular disorder, and these contribute to exacerbating any bleeding[59-61].

Various haemostatic drugs can be administered as prophylaxis in operations at a high risk of bleeding or as treatment in the case of massive haemorrhage[62].

The pharmacological approaches to reducing bleeding and transfusion needs have been extensively studied in heart surgery and orthopaedic surgery and are based on both the prevention and the correction of defects associated with the clotting disorders[63,64]. Fibrinolysis is an important cause of bleeding and, therefore, fibrinolysis inhibitors[63,65], whether lysine analogues such as ε-aminocaproic acid or tranexamic

acid, or broad spectrum serine protease inhibitors such as aprotinin, have been widely used and represent standard therapy in these situations.

Systematic reviews of randomised controlled clinical trials, above all in cardiac and orthopaedic surgery, indicate that the use of these drugs is associated with a reduction in the number of patients transfused and in their transfusion requirements[8,66-70].

Topical agents, such as fibrin glue, have also been used successfully in a variety of surgical procedures, but few clinical trials have been conducted on these products and there is little scientific evidence supporting their use[71].

Aprotinin

Aprotinin is a broad spectrum inhibitor of serine proteases and inhibits plasmin, trypsin, kallikrein, chymotrypsin, activated protein C and thrombin[72,73]. This drug has been widely studied in heart surgery, orthopaedic interventions and liver transplants.

Numerous meta-analyses of controlled trials have shown that aprotinin has favourable effects on reducing mortality and decreasing the risk of stroke and massive haemorrhage[74-76]. However, an observational study on the safety of aprotinin, published in 2006, reported that the use of this drug was associated with increased risks of renal failure, myocardial infarction, stroke and cerebral encephalopathy[77,78]. Aprotinin was withdrawn from the market because of increased mortality found during a randomised, multicentre trial in heart surgery[79,80].

Epsilon aminocaproic acid and tranexamic acid

ε-aminocaproic acid (no longer marketed in Italy since 2006) and tranexamic acid are synthetic analogues of lysine which inhibit fibrinolysis mediated by plasminogen and/or plasmin. Tranexamic acid is ten times more potent than ε-aminocaproic acid and its use is associated with decreased bleeding and transfusions in heart surgery with cardiopulmonary bypass[81,82].

In a review that analysed more than 200 clinical trials[70], not limited to only heart surgery, anti-fibrinolytics used during major surgery reduced bleeding, the need for transfusions and repeat surgery because of bleeding. Lysine analogues are probably equally effective as aprotinin and much cheaper; the evidence supporting the use of tranexamic acid is much stronger than that for ε-aminocaproic acid and, for this reason, its use is suggested in cardiosurgery, in orthopaedic surgery and in liver transplantation (*Grade of recommendation: 2C+*)[78,81,83].

Large differences in the doses used in the various studies analysed make it impossible to evaluate the dose-efficacy relationship[57,64,70,84-87].

Desmopressin

Desmopressin (DDAVP) favours the release of von Willebrand factor (vWF) from endothelial cells and causes an increase in the circulating levels of this factor together with an increase in factor VIII, thus contributing to primary haemostasis[62]. It is the treatment of choice in patients with mild or moderate haemophilia A and in those with responsive types of von Willebrand's disease (*Grade of recommendation: 2B*)[88-90].

DDAVP is also often used in patients with uraemia, with haemostatic defects associated with liver diseases and in patients with congenital defects of platelet function or with bleeding associated with the use of platelet anti-aggregants[89,90], although there is no evidence demonstrating its efficacy in these conditions[91].

The efficacy of DDAVP in surgical interventions in patients who do not have congenital bleeding disorders has not been demonstrated and its routine use is not indicated (*Grade of recommendation: 1C*)[91-97].

Pre-operative autologous blood donation

PABD is the process of collecting and storing the patient's blood before a planned operation, with the purpose of having a personal store in the case the patient develops post-operative anaemia[45]. The autologous blood components can be obtained by pre-operative donations of whole blood in the weeks preceding the operation.

In particular conditions and for selected patients, red cell concentrates can also be collected using cell separators: the equivalent of two or three red cell concentrates can be collected in a single procedure (*Grade of recommendation: 2C*)[98,99].

PABD was recommended in the 1980s because of fears about the possible transfusion-related transmission of human immunodeficiency virus

(HIV)[100]. In recent years there has been a notable decrease in the international use of PABD due to the improved safety of allogeneic blood, the growing use of techniques to recover blood during and after operations, and the poor cost-benefit ratio related to the fact that the proportion of predeposited units actually transfused is low[101,102].

Although PABD reduces the number of allogeneic RBC transfused, various studies have shown that the total number of RBC administered (whether autologous or allogeneic) is usually higher in patients who undergo PABD than in control groups[8,74]. This increases the doubts concerning the real usefulness of PABD[54]. PABD programmes are used most frequently in orthopaedic, vascular, urological and cardiothoracic surgery.

Like all procedures, PABD has advantages and disadvantages.

The most important advantage of PABD is that it reduces the risk of transmission of infections, which has already been greatly reduced in recent years thanks to the introduction of molecular biology techniques used for the biological qualification of blood components[103,104]. Another advantage is the lack of development of alloantibodies to RBC antigens that can occur in the case of transfusion of homologous blood.

There are, however, numerous disadvantages of PABD, including a higher risk of adverse reactions compared to that with homologous transfusions[105-107], iatrogenic anaemia[108,109] and, as for homologous blood, the risks of being given a wrong unit, bacterial contamination, circulatory overload and a possible immunomodulatory effect[110-112]. In addition, patients who give blood in the pre-operative period have a higher probability of receiving a transfusion, and this further increases the possible incidence of potential administration errors[113,114].

It is, therefore, recommended that the decision to transfuse a patient is not based on the availability of autologous blood, but rather that the decision is regulated by the same protocols used for the transfusion of allogeneic blood (*Grade of recommendation: 1C+*)[1-9].

Increased costs, inconvenience for the patients and possible clerical errors, together with improved safety of allogeneic blood, are some of the reasons why PABD has lost much of its importance and is now indicated in only very selected cases[43,54,115-118].

PABD programmes must not, therefore, be part of a policy of achieving blood component self-sufficiency, but must only be used based on clinical evaluations (*Grade of recommendation: 2C*)[102].

Although positivity for markers of transfusion-transmissible viral infections, such as HIV, hepatitis B and hepatitis C virus is not an absolute contraindication to PABD, it does represent a possible risk for the staff involved in collecting and processing the units and aggravates the potential problems if units are erroneously exchanged; for these reasons, PABD is not to be encouraged in patients positive for markers of viral infection (*Grade of recommendation: 2C*)[107,119,120].

Informed consent

An absolute prerequisite for enrolment in a PABD programme is that the patient gives written informed consent to the procedure. In order to be able to give such consent, the patient must be informed about:

- the significance of the requested informed consent, the medical examination, the history and the laboratory tests carried out, including those for HIV, hepatitis C virus and hepatitis B virus;
- the autologous donation procedure and the related risks and benefits;
- the possibility of being excluded from the autologous donation procedure in the presence of risk factors;
- the possible use, if necessary, of homologous transfusion, in the case that the autologous blood components are not sufficient to cover the transfusion requirements;
- the fact that unused units will be destroyed at the end of their shelf-life and cannot be used for other patients;
- the risk of loss of the units because of technical accidents.

Indications for pre-operative autologous blood donation

Although PABD was used in the past in patients undergoing elective orthopaedic, urological and cardiovascular surgery, currently the main indications for PABD (*Grade of recommendation: 1C+*) are[9,54,102,113]:

- patients with rare blood groups for whom it is

difficult to obtain allogeneic blood;
- patients with multiple alloantibodies for whom it is difficult to obtain allogeneic blood;
- patients who refuse consent to allogeneic transfusion for personal reasons;
- scoliosis surgery in children;
- patients with bleeding disorders (but who do not have active bleeding or anaemia at the time of the planned PABD).

For the patients with rare blood groups or with particular immunohaematological problems, such as the presence of mixtures of alloantibodies, the predeposited units can, if necessary, be frozen (*Grade of recommendation: 2C*)[121-123].

Contraindications to pre-operative autologous blood donation

Concomitant medical problems may prevent the enrolment of patients into a PABD programme. The main contraindications are leucocytosis, bacteraemia or a high risk of these (for example, due to the presence of a urinary or other type of catheter) (*Grade of recommendation: 1C+*)[102,124].

Other conditions rendering patients ineligible for PAPD include (*Grade of recommendation: 1C+*)[45,102,125]:
- reported and/or documentable unstable angina or ischaemic heart disease (the asymptomatic patient fully rehabilitated from a prior ischaemic episode can be enrolled if the event occurred more than 6 months previously);
- cyanotic congenital heart diseases;
- severe aortic stenosis;
- severe occlusive cerebral vascular disease;
- severe, uncontrolled hypertension;
- epilepsy.

Special recommendations

There are no absolute age limitations, although PABD is discouraged in patients under 10 years old (because of the difficult venous access and poor collaboration of the patients) and in those over 75 years old (*Grade of recommendation: 1C+*)[54,98,126].

The amount of whole blood collected should be 450 mL ± 10%, just as it is for donations of homologous blood (*Grade of recommendation: 1C+*)[20].

In the case of patients weighing less than 50 kg, the amount of blood collected pre-operatively should be personalised according the subject's circulating blood volume such that it does not exceed 6 mL of blood/kg of body weight; the volume of anticoagulant must be adjusted appropriately (*Grade of recommendation: 2C*)[127].

Unused autologous blood must not be employed for allogeneic transfusions (*Grade of recommendation: 1C+*)[20,54,102].

It is recommended that pre-deposited units are not fractionated, both because of possible technical errors related to the separation process, and because of the impossibility of obtaining therapeutic doses of fresh-frozen plasma (*Grade of recommendation: 1C+*)[2,128].

The eligibility criteria for PABD are less stringent than those for allogeneic blood donation. Baseline values of haemoglobin must be between 120 and 145 g/L in men and between 110 and 145 g/L in women (*Grade of recommendation: 2C*)[54].

The minimum interval between the collection of one unit and another must be at least 1 week and in all cases the last unit must be collected at least 72 hours before the planned operation (*Grade of recommendation: 1C+*)[45,54,129].

PABD must only be proposed when it is possible to guarantee the date of the planned surgery (*Grade of recommendation: 2C+*)[4,54].

The ABO and Rh blood groups of both the patient and the autologous unit must be confirmed prior to the transfusion (*Grade of recommendation: 1C+*)[20,54,130].

Iron supplementation and pre-operative autologous blood donation

Oral iron supplementation, particularly in cases without anaemia at baseline has not been shown to be effective in patients undergoing PABD, and for this reason prophylactic iron therapy is not recommended in subjects with normal iron levels who are going to predeposit autologous blood (*Grade of recommendation: 1C+*)[54,131].

Intravenous iron supplementation is, however, suggested when the PABD is associated with erythropoietin therapy (*Grade of recommendation: 2C+*)[35,41,49,54,55,132-135].

Addendum

The process of developing these

Recommendations, in conformity with the indications in the methodological manual of the national programme for guidelines (Istituto Superiore di Sanità, Agenzia per i Servizi Sanitari Regionali. Programma Nazionale per le Linee Guida – Manuale Metodologico. Milano, Italia, Arti Grafiche Passoni srl; 2002. Available at: http://www.snlg-iss.it/cms/files/Manuale_PNLG_0.pdf. Last accessed: 25/03/2010), made use of systematic literature reviews and updates of already existing recommendations on the subject.

The methodology used to determine the grades of recommendation drew on that presented at the 2004 Consensus Conference of the American College of Chest Physicians (Guyatt G, Schünemann HJ, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. Chest 2004; **126**: S179-87).

The recommendations are classified by **grades**, expressed in Arabic numbers (**1, 2**), according to their strength, and in **letters** (**A, B, C**), reflecting the type of study and evidence provided.

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