Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document"

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Summary of recommendations on alternatives to reduce allogeneic blood transfusion (in descending order of strength)

Grade 1A recommendations

We recommend:

- The use of restrictive transfusion strategies in non-bleeding, euvolaemic anaemic patients.
- Perioperative administration of tranexamic acid to patients undergoing cardiac surgery.
- The administration of intravenous iron to cancer patients, as an adjuvant to erythropoiesis-stimulating agents, for correcting chemotherapy-induced anaemia.
- Preoperative administration of erythropoiesis-stimulating agents to anaemic, orthopaedic surgical patients expected to have moderate blood losses.

We do not recommend:

- The administration of desmopressin to patients undergoing elective surgery.
- The administration of erythropoiesis-stimulating agents to critically ill patients who do not have a previous indication for this therapy.

Grade 1B recommendations

We recommend:

- Perioperative cell salvage in patients undergoing surgery for total hip or knee arthroplasty, cardiac procedures with cardiopulmonary bypass, or abdominal aorta aneurysm repair.
- Perioperative administration of epsilon-aminocaproic acid to patients undergoing cardiac surgery.
- Perioperative administration of tranexamic acid to patients undergoing hepatic surgery or bleeding trauma.
- The administration of intravenous iron to patients with post-partum anaemia or inflammatory bowel disease associated anaemia.

We do not recommend:

- Preoperative autologous blood donation in surgical procedures generally requiring the transfusion of two or fewer units of packed red cells.
- Routine use of acute normovolaemic haemodilution, as the single blood-sparing technique, in major surgery.
- Perioperative administration of epsilon-aminocaproic acid in orthopaedic surgical procedures.
- The administration of oral iron in the postoperative period or in critically ill patients.

Grade 1C recommendations

We recommend:

- Preoperative autologous blood donation in orthopaedic surgical procedures generally requiring the transfusion of three or more units of packed red cells.
- Perioperative cell salvage in complex spinal surgery, in combination with other blood-saving strategies.
- The use of thromboelastography in surgical or trauma patients presenting with severe bleeding.
- The administration of prothrombin complex concentrates to patients treated with vitamin K antagonists and presenting with intracranial haemorrhage.
- Thromboelastography-guided administration of fibrinogen concentrates to surgical or trauma patients presenting with severe bleeding.
- Fluid resuscitation in patients with mild to moderate blood losses.

Grade 2A recommendations

We suggest:

- The administration of prothrombin complex concentrates to patients treated with vitamin K antagonists and presenting with active bleeding or undergoing urgent or emergent surgery.
- Perioperative administration of tranexamic acid to patients undergoing lower limb arthroplasty,

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extensive spinal instrumentation, gynaecological cancer surgery, or radical prostatectomy.
- The administration of tranexamic acid to patients presenting with gastrointestinal bleeding due to ulcer or mucosal erosion.
- Perioperative administration of erythropoiesis-stimulating agents to patients undergoing cardiac or gastrointestinal cancer surgery.

Grade 2B recommendations

We suggest:
- Preoperative autologous blood donation in patients undergoing surgery for colorectal, prostatic or hepatic cancer resection, generally with adjuvant treatment with erythropoiesis-stimulating agents, as well as in cardiac procedures with cardiopulmonary bypass.
- Thromboelastography-guided fibrinogen concentrates to patients undergoing cardiac, aortic aneurysm repair, or radical cystectomy surgical procedures, as well as in obstetric haemorrhage.
- Preoperative oral iron administration in patients undergoing orthopaedic or colorectal cancer surgery.
- Perioperative intravenous iron administration to anaemic patients scheduled for orthopaedic, gynaecological or gastrointestinal surgery.
- The administration of intravenous iron, without erythropoiesis-stimulating agents, for treating radiotherapy- or chemotherapy-induced anaemia in cancer patients.
- Fluid resuscitation in patients with severe blood losses.

Grade 2C recommendations

We suggest:
- Perioperative cell salvage in patients undergoing hepatic or urological cancer surgery, abdominal trauma, Caesarean section, or ruptured ectopic pregnancy.
- Thromboelastography-guided administration of prothrombin complex concentrates to patients not on vitamin K antagonists and presenting with bleeding trauma, perioperative haemorrhage or acute liver failure.
- The administration of prothrombin complex concentrates, instead of fresh-frozen plasma, to patients on vitamin K antagonists who need immediate reversal of anticoagulation.
- The administration of recombinant activated factor VII to patients presenting with severe or refractory haemorrhage, including intracranial haemorrhage and postoperative haemorrhage after cardiac or liver surgery.
- Postoperative intravenous iron administration for treating postoperative anaemia after cardiac, obstetrics and gynaecological or orthopaedic surgical procedures.

Grade 0 recommendation

We cannot make any evidence-based recommendation on the use of perfluorocarbon- and haemoglobin-based oxygen carriers as alternatives to allogeneic blood transfusion.

1. Background and objectives

The Spanish Consensus Statement on Alternatives to Allogeneic Blood Transfusion (AABT), so-called the Seville Document (SD), was first published in 2006[1]. The original purpose of the SD was to generate recommendations based on the best available evidence on AABT indications, in order to assist all professionals involved in the administration of both allogeneic blood transfusions (ABT) and AABT. The present SD update pursues an identical goal. Also, as in the original SD, the SD update defines AABT as any measure aimed at reducing transfusion requirements and, therefore, the transfusion of red blood cells, preserving the patient's safety at all times. For a detailed analysis, the measures were divided into pharmacological and non-pharmacological AABT.

Why did the SD 2006 consensus document need an update? There are several reasons that justify this SD update: (i) the persistent variability in the clinical use of AABT; (ii) the withdrawal of drugs for which there was a high degree of evidence in the original SD (e.g., aprotinin); (iii) new indications for drugs or devices, not covered by the original SD (e.g., prothrombin complex, fibrinogen and viscoelastic tests); (iv) warning alerts generated by government agencies regarding the adverse effects of some drugs (e.g., erythropoiesis-stimulating agents); (v) the limitations of Delphi methodology used in the first SD edition, as this methodology directly links the level of evidence to grade of recommendation, resulting in recommendations always being formulated positively, sometimes leading to confusion among the readers; and (vi) the incorporation of the Spanish Society of Hospital Pharmacy as a new, active member of the consensus.

The recommendations of the updated SD are aimed at surgical, trauma or critically ill patients with blood loss who may require the use of pharmacological or non-pharmacological AABT. As in the original SD, the updated SD only contemplates the alternatives to transfusion of packed red blood cell concentrate (PRBC). For the purpose of this document, we define the transfusion rate as the number of transfused PRBC units or the percentage of transfused patients. The main question that arises in each item is formulated, positively or negatively, as: *"the AABT in question reduces/does not reduce the transfusion rate"*. Recommendations on the use of a particular AABT to reduce transfusion

rates were graded according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology[2-4].

2. Methodology

2.1. Scientific Societies and expert panel

This updated SD was produced by a panel of 40 professionals convened by six Spanish Scientific Societies involved in health care: Spanish Society of Anaesthesiology and Reanimation (SEDAR), Spanish Society of Hospital Pharmacy (SEFH), Spanish Society of Haematology and Haemotherapy (SEHH), Spanish Society of Critical Care Medicine SEMICYUC), Spanish Society of Thrombosis and Haemostasis (SETH) and Spanish Society of Blood Transfusion and Cellular Therapy (SETS). There were one general coordinator, one general vice-coordinator, nine topic coordinators (including the general coordinator), 25 collaborators, and six observers (the Presidents of the different Societies). With the exception of the members convened by SEFH, the panel composition for this updated SD did not differ substantially from that of the original SD[1]. All six Societies endorsed the recommendations formulated in the SD update.

2.2. GRADE methodology

The available evidence on the efficacy and safety of AABT was analysed according to GRADE methodology. We chose GRADE methodology because it has a number of advantages over other methodologies, such as the Delphi methodology, including: clear separation between quality of evidence and strength of recommendation; explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings; transparent process of moving from evidence to recommendations; explicit acknowledgement of values and preferences; and clear, pragmatic interpretation of strong *versus* weak recommendations for clinicians, patients, and policy makers, as well as for guidelines development.

Strong recommendations (Grade 1) may be A, B or C depending on the quality of evidence (high, moderate, low or very low). In all cases of strong recommendation, benefits clearly outweigh risks and burden (a positive recommendation), or vice versa (a negative recommendation). However, the implications are different. A Grade 1A or 1B recommendation may be applied to most patients, in most circumstances and without reservation, whereas a grade 1C recommendation may change when evidence of higher quality become available. *Weak recommendations* (Grade 2) may also be A, B or C depending of the quality of evidence. Grade 2A and 2B recommendations mean that benefits are closely balanced with risks and burden and that the best action may differ depending on circumstances or patients' or societal values. In contrast, a Grade 2C recommendation means that there is uncertainty in the risk to benefit balance and that other alternatives may be equally reasonable.

These differences in strength are reflected by the wording of the recommendations. Thus, when making a strong recommendation, we use the terminology, *"We recommend..."* or *"We do not recommend..."*. However, when making a weak recommendation, we used a less definitive wording, such as, *"We suggest..."*[4]. For each particular AABT, the target patient population is defined, details on implementation and doses are given, when appropriate, and a safety statement is always included[4]. Finally, it should be borne in mind that for some AABT and/or patient populations no evidence-based recommendation could be given (Grade 0).

3. Non-pharmacological alternatives to allogeneic blood transfusion

The non-pharmacological AABT include restrictive transfusion therapy, preoperative autologous blood donation, acute normovolaemic haemodilution, perioperative red cell salvage and assessment of haemostasis by thromboelastography.

3.1. Restrictive transfusion therapy in non-bleeding patients

Allogeneic blood is an increasingly scarce and expensive resource; there is a lack of evidence regarding the efficacy of ABT to increase tissue oxygen consumption or reduce tissue oxygen debt in selected patients; and, more importantly, ABT is not risk-free, as there is an association between ABT and increased morbidity and mortality. All these have prompted several Scientific Societies to recommend a restrictive approach when using ABT. Thus, the level of haemoglobin (Hb) below which a PRBC unit is transfused (i.e. the "transfusion trigger") should be intimately related to the patient's ability to tolerate normovolaemic anaemia and, consequently, to his/her cardiopulmonary reserve.

3.1.1. Critically ill, trauma and/or surgical patients, without cardiac and/or central nervous system dysfunction

We recommend the use of restrictive transfusion therapy, maintaining haemoglobin concentrations between 70 g/L and 90 g/L, to reduce the transfusion rate. ***Grade 1A***.

Randomised controlled trials (RCT) in euvolaemic, critically ill adults[5] and paediatric patients[6], as well as in patients undergoing vascular[7] or orthopaedic[8] surgery and in those presenting with acute upper

gastrointestinal bleeding[9], have documented that the majority of such patients can tolerate haemoglobin concentrations as low as 70. Nevertheless, patients' tolerance of normovolaemic anaemia depends on their cardiopulmonary reserve, the volume and speed of blood loss, and the acute or chronic onset of anaemia.

3.1.2. Critically ill, trauma and/or surgical patients, with cardiac and/or central nervous system dysfunction

We recommend the use of restrictive transfusion therapy, maintaining haemoglobin concentrations between 80 g/L and 100 g/L, to reduce the transfusion rate. ***Grade 1A***.

It has been documented that patients who present with ischaemic heart disease and/or have undergone cardiac surgery, have a poor tolerance of anaemia[10]. Anaemic patients with symptomatic ischaemic heart disease and/or brain dysfunction may require higher haemoglobin levels. In elderly anaemic patients (haematocrit <33%) with myocardial infarction, the correction of anaemia with PRBC transfusion improves the clinical outcome[11]. The efficacy of PRBC is linked to the severity of anaemia and myocardial ischaemia. In anaemic patients (Hb <120 g/L) with ST elevation, PRBC transfusion improves the clinical outcome[12]. Conversely, in patients with mild anaemia, as well as in those with ischaemia but without ST elevation, PRBC transfusion may worsen the clinical outcome[10]. It has been shown that patients who undergo cardiac surgery and have no signs of perioperative ischaemia tolerate haemoglobin levels of 80 g/L without increased postoperative morbidity or mortality[10,13,14]. A recent RCT[15] documented that in elderly patients, who had either a history of or risk factors for cardiovascular disease and had undergone surgery for hip fracture, restrictive transfusion therapy (transfusions given for symptoms of anaemia or at the physician's discretion for a Hb level <80 g/L), as compared with a liberal strategy (transfusions given below a Hb threshold of 100 g/L), did not increase rates of postoperative morbidity or mortality.

Given its high metabolic rate, the brain has little tolerance of anaemia, requiring a continuous and abundant supply of oxygen. As haemoglobin-bound oxygen is the main component of oxygen transport, anaemia may adversely affect brain function in patients with traumatic brain injury, subarachnoid haemorrhage or stroke. It is likely, although not definitely documented, that anaemic patients with severe brain dysfunction may require higher haemoglobin levels than those without it[16,17].

3.1.3. Safety

In euvolaemic surgical patients, almost all RCT conducted to date have shown that the use of restrictive transfusion therapy does not increase the rates of postoperative morbidity or mortality or the length of hospital stay, while it does reduce both the percentage of transfused patients and the volume of allogeneic blood administered. Critically ill patients, especially those with acute brain and/or cardiac dysfunction, may have worse outcomes if they are exposed to severe anaemia. However, although anaemia may increase morbidity and mortality, PRBC transfusion does not necessarily revert the deleterious effects of anaemia.

3.1.4. Summary

The majority of trauma, critically ill and/or surgical patients can tolerate haemoglobin levels of 70 g/L. However, for those presenting with acute cardiac and/or central nervous system dysfunction, a haemoglobin level of at least 80 g/L may be required. In any case, transfusion decisions should be individualised according to patient's co-morbidity, symptoms and haemoglobin concentration.

3.2. Preoperative autologous blood donation

Preoperative autologous blood donation (PABD) is a modality of autotransfusion consisting in the withdrawal of one or several units of the patient's own blood, in the days or weeks prior to the intervention. These units undergo serological screening and storage, and may be reinfused into the patient during the procedure or in the immediate postoperative period.

3.2.1. Major orthopaedic surgery

We do not recommend the routine use of preoperative autologous blood donation to reduce transfusion rates in procedures usually requiring two or fewer units of packed red blood cells per patient. ***Grade 1B***.

In adult patients undergoing major orthopaedic surgery (knee, hip or spine), data from RCT and observational studies showed a 20% reduction of the transfusion rate. However, in most of these studies transfusion criteria were not established. In addition, 60-70% of patients undergoing PABD received some type of transfusion, autologous or allogeneic, and 40% of the deposited units were not used[18-22]. Preoperative administration of recombinant human erythropoietin(rHuEPO)[23] or perioperioperative red cells salvage (PRCS)[24] is at least as effective as PABD in reducing ABT requirements.

We recommend the use of preoperative autologous blood donation to reduce transfusion rates in procedures usually requiring three or more units of packed red cells per patient, preferably with adjuvant treatment with iron and/or recombinant human erythropoietin. ***Grade 1C***.

Observational studies in patients undergoing orthopaedic procedures associated with major bleeding, such as revision of total hip arthroplasty and correction

of scoliosis, have shown that PABD significantly reduces the transfusion rate, although up to 30% of PABD units were not used[25,26]. In small studies of lower limb prosthetic surgery, the use of rHuEPO as an adjuvant to PABD further reduced the use of ABT, although this strategy was not cost-effective[1]. In addition, in patients undergoing scoliosis or complex spinal surgery, PABD with adjuvant treatment with rHuEPO facilitated the donation of the requested autologous units and resulted in a significantly decreased exposure to ABT when compared with PABD alone[27,28]. Furthermore, the concomitant intravenous (IV) administration of iron may enhance the bone marrow response to rHuEPO, reducing the dose of the rHuEPO required and, thereby, improving cost-effectiveness[29].

3.2.2. Elective cardiac surgery

We suggest the use of preoperative autologous blood donation to reduce transfusion rates in elective cardiac surgical procedures with cardiopulmonary bypass. ***Grade 2B***.

Data from two large observational studies indicate that preoperative donation of two autologous units was the most effective strategy to prevent ABT with lower incremental costs[22,30]. In some studies, adjuvant treatment with rHuEPO improved the efficacy of PABD in cardiac surgery procedures, both in adults and children[1].

3.2.3. Oncological surgery

We suggest the use of preoperative autologous blood donation to reduce transfusion rates in surgical procedures for solid cancer resection. ***Grade 2B***.

The results of various RCT and observational studies suggested that PABD may reduce ABT requirements by as much as 30% in colo-rectal cancer surgery[31], radical prostatectomy[32], and hepatic resections[33]. Once again, adjuvant rHuEPO treatment enhanced the efficacy of PABD in reducing ABT rates[31-33].

3.2.4. Safety

The use of PABD is contraindicated permanently in seropositive patients and patients with serious cardiovascular disease, and temporarily in those with active bacterial infection, a haemoglobin level <100 g/L or body weight <10 kg[34]. The results of a meta-analysis[18] indicated that the use of PABD reduced transfusion rates without increasing postoperative morbidity or mortality. However, it should be borne in mind that the incidence of adverse effects during PABD is higher than that observed for altruistic blood donation and that PABD increases the risk of receiving any type of transfusion. It is mandatory by law to discard unused units as well as seropositive units and to communicate any adverse event of PABD transfusion to the national haemovigilance system[35].

3.2.5. Summary

The use of PABD would be indicated in patients undergoing elective surgical procedures in which the risk of transfusion is greater than 30-50% (usually with a preoperative Hb <145 g/L), patients for whom compatible ABT is difficult to find, and those who refuse to receive ABT. The risk of receiving ABT is reduced further in PABD patients receiving adjuvant rHuEPO plus iron and undergoing surgical procedures that require the predeposit of three or more autologous units. Finally, it must be remembered that the PABD programme should only be implemented in those centres in which a scheduled surgery date is guaranteed.

3.3. Acute normovolaemic haemodilution

Acute normovolaemic haemodilution (ANH) consists of the extraction and anticoagulation of a predicted volume of blood from the patient and its simultaneous exchange for a cell-free crystalloid and/or colloid solution to maintain normovolaemia. Even though extreme ANH and other types of haemodilution have been used, moderate ANH (final haematocrit 25-30%) is the preferred technique. It is used in patients undergoing major surgical procedures with moderate-to-severe blood loss, and is usually performed after the induction of anaesthesia, before the intraoperative phase of bleeding.

3.3.1. Major surgical procedures

We do not recommend the routine use of acute normovolaemic haemodilution, as a single blood-sparing technique, given its low effectiveness at reducing the transfusion rate. ***Grade 1B***.

The results of two meta-analyses of 42 RCT showed that the use of ANH resulted in a small, significant reduction in transfusion rate[18,36]. However, the effectiveness of ANH was virtually eliminated in studies in which a transfusion protocol was applied and when partnered or compared with other AABT (e.g., PABD, tranexamic acid)[18,36,37].

3.3.2. Safety

This AABT should only be used in those institutions that can implement logistics for blood removal and volume replacement without detracting from patient care, and following the recommendations of published guidelines[38]. Bags of blood can be kept in the operating theatre at room temperature for a maximum of 6 hours and reinfused in reverse order of their removal. Although in two meta-analyses ANH was not associated with increased risks of morbidity and mortality, the quality of the evidence in this regard is moderate to low[36,37]. In adult patients undergoing cardiac surgery, ANH has been associated with increased rates of kidney failure[39] and disorders of psychomotor development in children[40]. In

contrast, the use of ANH was associated with reduced rates of postoperative infection in people undergoing orthopaedic surgery[41].

3.3.3. Summary

Most of the studies did not show a significant reduction of transfusion rate, although ANH has contributed to the concept of tolerance to low haemoglobin levels in low-risk patients. Therefore, despite its low cost, ANH should only be used in association with other AABT in selected patients, except in those centres in which no other AABT can be implemented. The available evidence on other modalities of haemodilution, such as moderate hypervolaemic haemodilution or augmented acute haemodilution, is insufficient to be able to make any recommendation[1].

3.4. Perioperative red cell salvage

Perioperative red cell salvage (PRCS) is defined as the collection of the patient's blood in surgical procedures in which blood loss is significant. During surgery, intraoperative cell salvage is performed using devices that aspirate, anticoagulate, wash and concentrate the blood shed from the surgical field, which is returned to patients as PRBC in saline. After surgery, postoperative cell salvage consists of the collection and reinfusion of blood lost through the wound drains. When intraoperative cell salvage is not indicated, postoperative cell salvage is usually performed using devices that collect and return unwashed filtered shed blood.

3.4.1. Major orthopaedic surgery

a) Total knee or hip arthroplasty

We recommend the use of perioperative red cell salvage, reinfusing filtered and/or washed salvaged blood, to reduce the transfusion rate. ***Grade 1B***.

In patients undergoing surgery for primary total knee arthroplasty[42,43] or total hip arthroplasty[44,45], postoperative recovery and reinfusion of washed or filtered shed blood reduced the absolute risk of receiving ABT by 20% (11% *versus* 30%), but not the number of ABT units per transfused patient. Postoperative cell salvage with washed blood was also effective in reducing the transfusion rate in revisions of total hip arthroplasties, especially if it was associated with other AABT[46].

b) Spine surgery

We recommend the use of perioperative red cell salvage, within a multimodal blood management programme, for reducing the transfusion rate in patients undergoing surgery for scoliosis or complex degenerative spine pathology. ***Grade 1C***.

In instrumental lumbar or lumbo-sacral spine surgery, with or without iliac crest bone autografting, postoperative cell salvage significantly reduced the volume of ABT, but not the percentage of patients who underwent ABT[47]. In surgery for correction of scoliosis, in which up to 90% of the patient's estimated blood volume can be lost, PRCS alone or associated with other AABT, significantly reduces transfusion rate[48,49].

3.4.2. Cardiac surgery

We recommend the use of perioperative red cell salvage to reduce transfusion rates in elective cardiac surgical procedures with cardiopulmonary bypass. ***Grade 1B***.

In cardiac surgery with cardiopulmonary bypass (CPB), salvage, washing and reinfusion of blood from the surgical field, the cardiotomy reservoir and the postoperative chest drainage reduced the percentage of patients exposed to ABT when compared to a control group, but not the number of ABT units infused per patient[50]. However, PRCS was not effective if it was limited to processing pericardial suction[51] or used in cardiac surgery without CPB[52].

3.4.3. Major vascular surgery

We recommend the use of perioperative red cell salvage to reduce transfusion rates in vascular surgical procedures for abdominal aorta aneurysm repair. ***Grade 1B***.

Several studies on elective surgery for repair of an abdominal aorta aneurysm showed that intraoperative cell salvage reduced, by 40%, the absolute risk of exposure to ABT and the ABT volume when compared to control management[53]. It has been estimated that intraoperative cell salvage is cost effective when blood loss exceeds 800 mL. In surgery to repair a ruptured abdominal aorta aneurysm, intraoperative cell salvage reduced ABT requirements by three units per patient[53,54]. In elective and ruptured abdominal aorta aneurysm, the use of an endovascular prosthesis reduced bleeding and transfusion requirements in comparison with open surgery, although the role of intraoperative cell salvage in this setting has not been sufficiently studied.

3.4.4. Other surgical procedures

We suggest the use of perioperative red cell salvage, with washing and filtering and/or irradiation of salvaged blood, for reducing transfusion rates in surgical resection of hepatic or urological cancers, Caesarean section or ruptured ectopic pregnancy. ***Grade 2C***.

Several RCT and observational studies suggest that PRCS may reduce transfusion rates in patients undergoing liver transplantation for hepatocellular

carcinoma or cirrhosis[55], radical prostatectomy[56], Caesarean section[57], rupture of ectopic pregnancy[58], or abdominal trauma[59].

3.4.5. Safety

Data from clinical studies conducted in different types of urgent or elective surgery clearly showed that PRCS did not increase either the risk of postoperative morbidity or mortality or the length of hospital stay. However, some serious adverse effects have been reported, especially coagulopathy, when large volumes of recovered and processed blood are transfused. As for orthopaedic surgery, although serious adverse effects have been barely detected, more than 1,000 mL of unwashed filtered blood should not be reinfused[60]. In contrast, the results of a systematic review indicate that reinfusion of salvaged unwashed filtered blood after cardiac procedures is not recommended[18]. The indication for PRCS in cancer surgery and Caesarean section is controversial. In cancer surgery, the results of a recent meta-analysis showed that PRCS did not increase the incidence of metastasis or cancer recurrence[61].

3.4.6. Summary

Intraoperative cell salvage would be indicated in patients undergoing elective surgery in which a blood loss of more than 1,500 mL is expected and at least the equivalent of 1.5-2 units of PRBC can be recovered. On the other hand, the use of postoperative salvage and reinfusion of unwashed filtered blood would be restricted to patients with haemoglobin <14 g/dL undergoing elective prosthetic surgery in which a postoperative blood loss volume between 500 mL and 1,000 mL is expected, and at least the equivalent of 1 unit of PRBC can be recovered[1]. It must be stressed that the recommendations given in this section are limited by the poor methodological quality of many of the studies analysed, which generally involved a small number of patients (less than 60 per arm). In addition, as the trials were not blinded and lacked adequate concealment of treatment allocation, transfusion practices may have been influenced by knowledge of the patient's treatment status, thus biasing the results in favour of PRCS. Finally, it is worthy noting that the contribution of PRCS to ABT reduction decreased when a transfusion protocol was implemented.

3.5 Point-of-care coagulation testing: thromboelastography

Thromboelastrography (TEG) provides a global evaluation of the viscoelastic properties of a clot (cellular model of blood coagulation), displays the results graphically and enables the analysis of clot formation and lyses in less than 10 minutes at the point-of-care (e.g. at the bedside). Thus, TEG has significant advantages compared to conventional coagulation tests; namely, rapid results to guide haemostatic therapy, leading to early clinical decisions, and overall evaluation of coagulation in whole blood[62,63]. Up to 35% of the bleeding trauma patients present with abnormal coagulation tests upon hospital admission. The so-called "acute traumatic coagulopathy"[64] is an independent predictor of poor outcome and, if present, needs to be treated early and aggressively. On the other hand, surgical patients may also develop different coagulation disorders, which should be managed on an individual basis. TEG enables individualised administration of blood components (plasma and platelet concentrates) and clotting factor concentrates (fibrinogen and prothrombin complex).

3.5.1. Bleeding in patients with severe trauma

We recommend the use of thromboelastography to guide the replacement of blood clotting factors and reduce the transfusion rate. ***Grade 1C****.*

Patients with bleeding injuries may develop early clotting alterations (within 30 minutes following trauma), including hypocoagulability, hypercoagulability or hyperfibrinolysis[62,63]. At least 20 studies have documented that the use of TEG enables more efficient management of coagulation and may reduce transfusion rate[62,64].

3.5.2. Bleeding in surgical patients

We recommend the use of thromboelastrography to guide the replacement of blood clotting factors and reduce the transfusion rate. ***Grade 1C.***

A retrospective study that included more than 3,000 patients undergoing cardiovascular surgery documented that TEG significantly decreased the rates of transfusion and thromboembolic events[65]. Retrospective studies involving small numbers of patients undergoing vascular, liver or obstetric surgery concluded that TEG reduced transfusion rates and enabled early treatment of coagulation disorders[66,67].

3.5.3. Safety

The use of TEG carries no risks for the patient. However, as TEG does not evaluate platelet function, patients with platelet dysfunction should be assessed with other technologies[63].

3.5.4. Summary

TEG is a useful technique for the early assessment of coagulation disorders and facilitates selective administration of blood components and clotting factors. Although its use is associated with a significant decrease in ABT, it does not diminish the high mortality rate of patients with severe bleeding[67].

4. Pharmacological alternatives to allogeneic blood transfusion

Pharmacological AABT include measures to decrease bleeding, stimulate erythropoiesis and improve oxygen transport.

Pharmacological alternatives to decrease bleeding

The reduction of perioperative blood loss is essential to decrease a patient's exposure to ABT. This reduction may be achieved through proper management of platelet anti-aggregant and anticoagulation therapy, maintenance of normothermia, use of controlled, induced or permissive hypotension, meticulous surgical haemostasis and, when possible, minimally invasive surgical techniques and the use of low-vacuum drains. Finally, the administration of drugs that promote clot formation, ensure clot stability and/or delay clot lysis should be evaluated.

4.1. Prothrombin complex concentrates

Prothrombin complex concentrates (PCC) are plasma derivatives that contain varying amounts of clotting factors II, IX and X ("three-factor PCC", marketed in the USA) or clotting factors II, VII, IX and X ("four-factor PCC", marketed in Europe). The three "four-factor PCC" sold in Spain have similar efficacy, but they differ slightly in composition. To prevent thrombin formation, PCC contain protein C, protein S, antithrombin III and/or heparin[68].

4.1.1. Patients being treated with vitamin K antagonists and presenting with active bleeding or requiring urgent or emergent surgery

We suggest the administration of prothrombin complex concentrate to reduce bleeding and/or transfusion rate. ***Grade 2A***.

Within 10 to 30 minutes after administration of a PCC, virtually all patients achieve normalisation of their International Normalised Ratio (INR) values[69-71]. When PCC administration was aimed to prevent bleeding in patients who were to undergo surgery or invasive procedures or to decrease bleeding in patients with active haemorrhage, most of the studies documented its efficacy in achieving these goals[72]. Clinical guidelines suggest the use of four-factor PCC in bleeding patients treated with vitamin K antagonists (VKA), regardless of INR value[73]. In surgical patients, PCC may be preferable to rFVIIa and/or fresh-frozen plasma (FFP)[74]. However, the small number of studies, the retrospective nature of most of them, the low numbers of patients included, the concomitant treatment with FFP or other pro-haemostatic drugs, the absence of control groups, and methodological differences do not allow solid conclusions to be drawn.

4.1.2. Patients being treated with vitamin K antagonists and presenting with intracranial haemorrhage

We recommend the administration of prothrombin complex concentrate to reduce bleeding. ***Grade 1C***.

Intracranial haemorrhage is the most serious event associated with anticoagulation with VKA. The risk of intracranial haemorrhage doubles for every point increase in INR. The rates of haematoma expansion, neurological sequelae and mortality are higher in VKA-associated intracranial haemorrhage than in intracranial haemorrhage of other aetiologies[75-78]. The mortality rate within the first 24 hours can reach 33%[79,80]. The INR is corrected and bleeding controlled more effectively in patients treated with PCC than in those treated with FFP[81,82]. However, the rates of mortality and sequelae remain consistently high, regardless of the treatment chosen[79,80].

4.1.3. Patients not being treated with vitamin K antagonists and presenting with coagulopathy in the setting of trauma, perioperative haemorrhage or acute liver failure

We suggest the administration of prothrombin complex concentrate to reduce bleeding and/or transfusion rate. ***Grade 2C***.

Bleeding in trauma patients. Generally patients with massive haemorrhage receive more PRBC units than FFP units (ratio 3:1 or higher). Although controversial, data from trauma patients with critical bleeding in the military context have documented that mortality improved when patients received similar amounts of PRBC, FFP and platelet concentrates (i.e. a 1:1:1 ratio), thus suggesting the need to provide large amounts of clotting factors from the onset of bleeding[83,84]. As a PCC quickly delivers large amounts of clotting factors, early PCC administration may reduce transfusion requirements[85].

Bleeding in surgical patients. PCC administration is associated with decreased transfusion requirements in the perioperative period[86], especially in patients undergoing cardiac surgery[65].

Acute liver failure. One observational study suggests that PCC could be useful in the prophylaxis or treatment of bleeding in patients with deficiency of liver-dependent clotting factors secondary to acute liver failure[87].

4.1.4. Patients being treated with vitamin K antagonists and requiring immediate reversal of anticoagulation: prothrombin complex concentrate versus *fresh-frozen plasma or recombinant activated factor VII*

We suggest that prothrombin complex concentrate is superior to fresh-frozen plasma or recombinant activated factor VII for reducing bleeding and/or transfusion rate. ***Grade 2C***.

FFP contains varying amounts of all coagulation factors. Although the optimal FFP dose has not been established, a dose of 15 mL/kg is usually recommended. However, doses as high as 30 mL/kg may be needed to provide optimal amounts of clotting factors[88,89]. Compared with FFP, PCC has several advantages: (i) greater content of liver-dependent clotting factors, but lacks fibrinogen and factor XIII; (ii) no need for group matching (whereas this is necessary for FFP); (iii) faster administration (FFP must be thawed, delaying its administration); (iv) it corrects the INR more quickly and effectively does than FFP (less than 30 minutes with PCC); and (v) smaller volumes necessary (at the suggested dose, at least 1,000 mL of FFP are needed for a 70 kg patient, which may lead to transfusion-associated cardiovascular overload [TACO] and transfusion-related acute lung injury [TRALI])[69-71]. Most guidelines[73,74] and observational studies[81,82] suggest that PCC is superior to FFP in controlling VKA-induced haemorrhagic events. In mice with VKA-induced intracranial haemorrhage, PCC or FFP was more effective than rFVIIa at halting expansion of the haematoma[90]. Although the administration of rFVIIa reduced the size of the haematoma in patients with intracranial haemorrhage, mortality remained invariably high. In addition, the high rate of thromboembolic events has discouraged the routine use of rFVIIa in VKA-treated patients with critical haemorrhage[91].

4.1.5. Dosage

In patients with intracranial haemorrhage, the administration of 25-50 IU/kg of PCC slows the expansion of the haematoma, corrects the INR in less than 30 minutes and enables surgical control of the haematoma[80]. In general, either fixed or individualised doses can be used. A recent study found no advantage from using individualised doses, recommending a single fixed dose of 1,000 IU PCC for all situations[92]. However, most authors recommend individualised doses (based on the patient's weight and current and target INR), which vary between 15-50 IU/kg. In all cases, administration of PCC should be supplemented with 5-10 mg of vitamin K, IV. Generally, the PCC dosage is based on the percentage of plasma clotting factors, so the INR must be converted to this percentage (Table I). The dose is then calculated using the equation:

units of factors of PCCP =
(target level of factors [%] – current level of factors [%])
× body weight [kg].

For example, for a man weighing 80 kg with a current INR of 7.5 (5% of plasma clotting factors) and a target INR of 1.5 (40% of plasma clotting factors), the PCC dose would be (40–5)×80=2,800 IU [93].

Table I - Conversion of INR values to % of plasma clotting factors.

	INR	% plasma clotting factors
Supra-therapeutic range	>5	5
	4-4.9	10
Therapeutic range	2.6-3.2	15
	2.2-2.5	20
	1.9-2.1	25
Infra-therapeutic range	1.7-1.8	30
	1.4-1.6	40
	1.0-1.4	100

4.1.6. Safety

Variable, but low rates of thrombo-embolic events, especially in arterial territories (stroke, myocardial infarction, pulmonary embolism) have been reported in patients treated with PCC[65,70,94]. However, in the majority of cases, a cause-effect relationship between PCC administration and increased rates of clinically relevant thromboembolic phenomena has not been documented. Most Authors consider PCC as a safe drug[94].

4.1.7. Summary

As in other recent clinical practice guidelines, we suggest the administration of PCC for patients being treated with VKA who present with bleeding or require invasive procedures, although this is a weak recommendation based on data from retrospective studies involving few patients (Grade 2C). However, a strong recommendation is to administer PCC to VKA-treated patients with intracranial haemorrahge (Grade 1C), since several retrospective studies and at least two prospective studies have documented that administration of PCC in this context resulted in a decreased rate of haematoma expansion. Finally, PCC could potentially be useful in bleeding patients not being treated with VKA (Grade 2C).

4.2. Fibrinogen

Adequate levels of fibrinogen (1.5-4.5 g/L) are critical to achieve effective haemostasis. Fibrinogen facilitates platelet aggregation and, when activated by thrombin, gives rise to fibrin polymers, which are the basis of clot formation[66]. Severe haemorrhage involves the loss of coagulation factors, including fibrinogen. Intensive resuscitation with crystalloid solutions further dilutes existing clotting factors. In addition, colloids may interfere with the formation of an effective clot, by altering its firmness and stability. Both mechanisms (loss and dilution of clotting factors) lead to coagulopathy. The presence of coagulopathy is an independent risk factor for poor clinical outcome[62-66]. In addition, pre-operative fibrinogen levels are predictive of perioperative bleeding[66,95,96].

Fibrinogen seems to be the coagulation factor that first reaches a critically low level (<1 g/L) drung active bleeding. There are three ways to replace fibrinogen: FFP, cryoprecipitate and fibrinogen concentrate. The compound most commonly used in Spain is fibrinogen concentrate, which is also a plasma derivative, but unlike FFP and cryoprecipitate, does not require cross-matching and is administered quickly (up to 6 g can be given in less than 3 minutes)[97,98].

4.2.1. Patients with traumatic bleeding

We recommend the administration of fibrinogen concentrates to reduce bleeding and/or transfusion rate. ***Grade 1C****.*

European guidelines on traumatic bleeding recommend the administration of fibrinogen in all cases of severe bleeding, in which TEG shows a fibrinogen deficiency or plasma fibrinogen is below 2 g/L[99]. Recent reviews of retrospective studies of patients with bleeding trauma conclude that TEG-guided fibrinogen administration, with or without PCC, reduces the transfusion rate and may improve clinical outcome[62-67,95,96,100,101].

4.2.2. Bleeding in surgical patients

We suggest the administration of fibrinogen concentrates to reduce bleeding and/or transfusion rate. ***Grade 2B****.*

In patients undergoing surgery to repair a ruptured abdominal aortic aneurysm, administration of massive amounts of FFP significantly reduced mortality rate from 39% to 15%, suggesting that early administration of clotting factors may improve the clinical outcome[102]. In addition, preoperative and postoperative infusion of high doses of fibrinogen (6 g in 2 minutes) increased clot firmness and reduced bleeding and transfusion requirements[102]. In a retrospective study of more than 3,000 patients undergoing cardiac surgery, TEG-guided administration of fibrinogen and PCC reduced the rates of transfusion and thromboembolic events[65]. A recent RCT documented that haemostasis is more effectively restored with fibrinogen and FFP than with FFP alone[103]. One RCT involving 20 patients undergoing radical cystectomy documented a significantly lower transfusion rate in the group treated with fibrinogen[104]. A series of six cases shown that combined administration of fibrinogen and other blood products may control bleeding in patients with obstetric haemorrhage[105].

4.2.3. Dosage

Fresh-frozen plasma contains approximately 2 g/L of fibrinogen; therefore, large volumes of FFP (2 L) are required to increase fibrinogen levels by 1 g/L. The concentration of fibrinogen is higher in cryoprecipitate than in FFP[66,95]. There is no agreement on a standard fibrinogen dose. Prophylactic doses of 2 g are given before surgery and doses of 6 g have been given in ongoing severe bleeding[97,101], although the most usual dosage is 2-4 g.

The fibrinogen dose can be calculated using the following formula[66]:

$$\text{doses of fibrinogen} = \text{target fibrinogen increment (g/L)} \times \text{plasma volume (L)}.$$

The plasma volume can be estimated to be 0.04 L/Kg. As an example, 5.6 g of fibrinogen are required to raise the plasma fibrinogen concentration from 1 g/L to 3 g/L in a 70 kg bleeding patient ($2 \times 0.04 \times 70 = 5.6$).

4.2.4. Safety

Fibrinogen is considered a safe drug[96]. However, its use has been associated with increased risks of coronary ischemia[66] and arterial and venous thromboembolic events when high doses are administered (up to 12 g)[106]. Despite being a plasma derivative, transmission of blood-borne infections have not been described with fibrinogen.

4.2.5. Summary

The level of fibrinogen is critical to achieve effective haemostasis, since it is the coagulation factor that first reaches a critically low level (<1 g/L) during severe bleeding. Observational studies and case series suggest that early administration of fibrinogen can be effective in reducing the transfusion rate. Fibrinogen is often administered together with FFP and PCC, which prevents a proper assessment of its effectiveness. Administration of fibrinogen should ideally be guided by bed-side TEG rather than by conventional laboratory tests[107]. However, large RCT are needed before recommending its generalised use for the treatment of acquired fibrinogen deficiency in critical bleeding[108].

4.3. Synthetic antifibrinolytic agents

Within this pharmacological group, we will discuss the efficacy and safety of tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA). We will not consider the use of aprotinin, as it has been withdrawn from the market. TXA and EACA are synthetic lysine analogues that competitively inhibit the binding of plasminogen to lysine residues on the fibrin surface, thus preventing its conversion into active plasmin. TXA is 10 times more potent than EACA.

4.3.1. Major orthopaedic surgery

We suggest the administration of tranexamic acid to reduce perioperative blood loss and/or transfusion rate. ***Grade 2A****.*

In several studies, with explicit transfusion protocols, in patients undergoing total hip arthroplasty[109] or total knee arthroplasty[110], IV administration of TXA reduced the volume of perioperative blood loss and the requirements for ABT by as much as 25%. Topical TXA, as irrigation or intra-joint injection, also reduced postoperative bleeding, but its effect on transfusion rate was less evident[111]. In spine surgery, primarily scoliosis, TXA administration, in combination with other AABT, resulted in a dose-dependent reduction of bleeding volume and ABT volume, but generally did not affect the percentage of patients who received ABT[112-114].

We do not recommend the administration of ε-aminocaproic acid for reducing perioperative blood loss and/or transfusion rate. ***Grade 1B.***

Results of a meta-analysis did not show that EACA has a beneficial effect on reducing the transfusion rate in patients undergoing orthopaedic surgery (RR: 0.73; 95% CI 0.20-1.73)[115].

4.3.2. Cardiac surgery

We recommend the administration of tranexamic acid to reduce perioperative blood loss and/or transfusion rate. ***Grade 1A***.

Compared with placebo, TXA reduced transfusion rate and the risk of reoperation for persistent or recurrent bleeding in patients undergoing cardiac surgery with CPB[116]. In myocardial revascularisation surgery without CPB, TXA administration reduced the risk of receiving ABT[117]. Topical administration of TXA reduced postoperative bleeding, but not ABT requirements[118].

We recommend the administration of ε-aminocaproic acid for reducing perioperative blood loss and/or transfusion rate. ***Grade 1B***.

In cardiac surgery with CPB, EACA administration reduced ABT requirements and the rate of re-exploration for bleeding[116]. On the other hand, in the BART study, EACA and TXA showed similar efficacy in reducing bleeding and ABT requirements[119], and the blood-saving effects of both agents were observed even in patients treated with aspirin[120].

4.3.3. Hepatic surgery

We recommend the administration of tranexamic acid to reduce perioperative blood loss and/or transfusion rate. ***Grade 1B***.

In liver transplantation, the administration of high doses of TXA reduced ABT requirements, while the continuous infusion of low doses of TXA reduced fibrinolysis but not ABT requirements[121]. A RCT of 214 patients undergoing liver resection showed that TXA administration reduced intraoperative bleeding and surgery time and abolished the need for ABT[122].

4.3.4. Miscellaneous surgery

We suggest the administration of tranexamic acid to reduce perioperative blood loss and/or transfusion rate in patients undergoing gynaecological or urological surgery. ***Grade 2A***.

In elective Caesarean section, one RCT including 660 patients showed that TXA administration reduced the volume of blood loss, the percentage of women with a blood loss of more than 1,000 mL and the need for uterotonics[123]. In radical retropubic prostatectomy, one RCT involving 200 patients showed that administration of TXA reduced intraoperative blood loss and transfusion rate[124].

4.3.5. Trauma patients with severe bleeding

We recommend the administration of tranexamic acid to reduce blood loss and/or mortality rate. ***Grade 1B***.

The results from the CRASH-2 study, a RCT involving more than 20,000 patients from 274 hospitals in 40 countries, showed that administration of TXA within 8 hours of injury significantly reduced mortality from all causes (14.5% *vs* 16%), including mortality due to bleeding (4.9% *vs* 5.7%)[125]. More recently, a retrospective study of 896 military patients wounded in combat showed an association between the administration of TXA and lower rates of coagulopathy and mortality, especially among those who needed massive transfusion[126].

4.3.6. Gastrointestinal haemorrhage

We suggest the administration of tranexamic acid to reduce blood loss and improving clinical outcome. ***Grade 2A***.

In a meta-analysis of RCTs, including 1,267 patients with gastrointestinal haemorrhage due to ulcer or mucosal erosion, the administration of TXA reduced by 20-30% the rate of re-bleeding, avoided surgery in 40% of patients, and decreased mortality rate by 40%. Despite these good results, TXA is not frequently used in gastrointestinal haemorrhage, mostly because of the efficacy of other compounds and the use of endoscopic procedures to arrest bleeding[127].

4.3.7. Dosage

The doses of TXA used most frequently in the studies reviewed were:

- Total hip or knee arthroplasty: an initial dose of 10-15 mg/kg before surgery, followed or not by infusion of 1 mg/kg/h for 4-6 h or the repetition of the initial dose in the postoperative period.
- Spinal surgery: an initial dose of 20-100 mg/kg, followed by an infusion of 10 mg/kg/h for 4-6 h.
- Cardiac surgery with CPB and liver transplantation: an initial dose of 30 mg/kg followed by an infusion

of 16 mg/kg/h until the end of the surgery (plus 2 mg/kg in the CPB circuit).
- Cardiac surgery without CPB: an initial dose of 1 g, followed by an infusion of 200-400 mg/h until the end of the surgery.
- Topical use in cardiac and orthopaedic surgery: 1-3 g.
- Caesarean section: 1 g preoperatively.
- Prostatectomy: an initial dose of 500 mg/20 min followed by an infusion of 250 mg/h until the end of the surgery.
- Bleeding trauma: 1 g in 10 min within the first 8 hours after the trauma, followed by an infusion of 1 g in 8 hours.
- Gastrointestinal bleeding: 3-6 g/day IV for 3 days.

Epsilon-amino-caproic acid seems to be of use only in cardiac surgery. A starting dose of 10 g followed by an infusion of 2 g/h until the end of surgery was used in the BART study (no medication was added to the CPB circuit)[119].

4.3.8. Safety

The studies analysed did not show that synthetic antifibrinolytic agents increased the risks of either thromboembolic events (including myocardial infarction, stroke, venous thrombosis or pulmonary embolism) or mortality. However, an increased rate of postoperative seizures has been described in patients undergoing cardiac surgery who received high doses of TXA, especially those with a history of renal dysfunction[128,129].

4.3.9. Summary

TXA and EACA are used in a wide range of haemorrhagic conditions and in patients at haemorrhagic risk. Their effectiveness in reducing blood loss, transfusion requirements and number of re-operations for bleeding has been demonstrated in surgery and trauma. With the exception of cardiac surgery, TXA seems to be more effective than EACA. In these clinical settings, randomised studies have not shown that synthetic antifibrinolytic agents increase the risks of thrombotic events or mortality. However, the use of synthetic antifibrinolytic agents in orthopaedic surgery is an "off-label" indication, and more safety studies are needed before drawing a definitive recommendation in this setting.

4.4. Desmopressin

Desmopressin (DDAVP) is a synthetic vasopressin analogue which has some haemostatic effects deriving from its ability to increase platelet adhesion (by increasing the expression of platelet receptor GPIb) and plasma levels of factor VIII and von Willebrand factor (by increasing their release from hepatic sinusoidal endothelial cells).

4.4.1. Patients undergoing elective surgery

We do not recommend the use of desmopressin to reduce blood loss and/or transfusion rate in elective surgical procedures in patients without von Willebrand's disease ***Grade 1A***.

A meta-analysis performed on 18 studies with a total of 1,295 patients showed that administration of DDAVP did not reduce blood loss or transfusion rate[130].

4.4.2. Dosage

A 3- to 4-fold increase in plasma levels of von Willebrand factor occurs within 30-60 minutes of the administration of 0.3 mg/kg DDVAP. This increment is independent of the route of administration and lasts for 5-10 hours. However, it must be borne in mind that DDVAP produces tachyphylaxis (i.e., repeated doses cause depletion of endothelial reserves of von Willebrand factor), leading to loss of effectiveness in 24 h[1].

4.4.3. Safety

Patients receiving DDVAP did not experience an increase in the rate of postoperative nonfatal acute myocardial infarction, reoperation for bleeding or mortality when compared with those from a control group.

4.4.4. Summary

Desmopressin administration increases platelet adhesiveness and plasma levels of factor VIII and von Willebrand factor. This compound is useful in the prevention and control of haemorrhage in patients suffering from mild or moderate von Willebrand's disease. However, there is not convincing evidence supporting a role for DDAVP in reducing perioperative blood loss or transfusion rate in patients without inherited haemorrhagic disorders, and its use in these populations of patients is not recommended.

4.5. Recombinant activated factor VII

Recombinant activated factor VII is a biological agent with procoagulant properties, which was developed initially for the treatment of bleeding in haemophilic patients with inhibitors against factors VIII and IX, and in patients with acquired haemophilia. In Europe, the authorisation of its use has been extended to patients with selective deficiency of factor VII and Glanzmann's thrombasthenia.

4.5.1. Patients with intractable bleeding refractory to conventional haemostatic interventions

We suggest the use of activated factor VII for the treatment of severe refractory haemorrhage. ***Grade 2C***.

Recombinant activated factor VII has been used in patients with critical bleeding in the context of different surgical and non-surgical procedures, such as trauma,

cardiac and hepatic surgery and postpartum haemorrhage. Although it exerted a variable effect on morbidity and transfusion requirements, a beneficial effect on mortality has not been observed and a clear indication for it use is lacking[99,131-133]. A study in patients with trauma and active bleeding was prematurely discontinued when similar rates of mortality between rFVIIa-treated and placebo groups were recorded (12% *versus* 11%)[134]. Similarly, no benefit of rFVIIa administration was observed in patients with intracranial haemorrhage or haemorrhage secondary to oesophageal varices[135,136].

A systematic review evaluating the use of rFVIIa in five different clinical settings (intracranial haemorrhage, cardiac surgery, trauma, liver transplantation and prostatectomy) concluded that there was no evidence of a reduction of mortality rates with rFVIIa, whereas the clotting factor increased the risk of thromboembolism in some clinical settings[137].

4.5.2. Dosage

Although rFVIIa doses varied between studies (9-100 μg/kg), for patients with refractory critical haemorrhage requiring massive transfusion, doses of 90 μg/kg seem to be reasonable.

4.5.3. Safety

Important rFVIIa-associated side effects, especially thromboembolic complications, have been reported[138,139]. In a recent meta-analysis of 35 studies of over 4,000 randomised subjects the incidence of arterial thrombotic events (5.5%) and coronary events (2.9%) among patients receiving rFVIIa was significantly higher than that among those receiving placebo. These differences were more pronounced in patients older than 65 years (9% *versus* 4.1%, P =0.02)[139].

4.5.4. Summary

There is insufficient good quality evidence to support the indiscriminate use of rFVIIa in severe haemorrhage to halt bleeding or reduce transfusion requirements. The design of most available studies is complex and the number of patients too small to detect a clear benefit. Exceptionally, the use of this clotting factor may be considered in patients with life-threatening haemorrhage after implementing conventional haemostatic measures. Given the paucity of evidence and the poor risk-to-benefit balance, administration of rFVIIa should only be considered for intractable bleeding of medical or surgical aetiology. Recombinant activated factor VII should, therefore, be administered on an individual basis, according to the clinical scenario, the characteristics of the patient and the medical judgement of the risk-to-benefit ratio in each case.

Pharmacological alternatives to stimulate erythropoiesis

4.6. Iron

It is well known that the preoperative haemoglobin level is the main independent risk factor for receiving ABT. Normal erythropoiesis needs a healthy bone marrow with an adequate supply of various nutrients (iron, vitamins C, B1, B6, B12 and folic acid), and hormones (erythropoietin, thyroid hormones and steroids). In the absence of information on other haematinics, only the possible benefit of oral and IV iron administration to reduce transfusion rate will be discussed. *The intramuscular route for iron administration is not recommended.*

4.6.1. Preoperative oral iron therapy

We suggest preoperative administration of oral iron to improve preoperative haemoglobin levels and/or reduce transfusion rate. ***Grade 2B****.*

Colon cancer surgery. In anaemic patients, the administration of ferrous salts, starting 14 to 30 days prior surgery, improved the level of haemoglobin and decreased transfusion rate[140,141].

Orthopaedic surgery. In patients scheduled for total knee or hip arthroplasty, the administration of oral iron, together with a restrictive transfusion protocol, improved haemoglobin levels, reduced transfusion rates and, in some cases, the length of hospital stay[142,143].

4.6.2. Postoperative oral iron therapy

We do not recommend postoperative administration of oral iron to improve postoperative haemoglobin levels and/or reduce transfusion rate. ***Grade 1B****.*

Surgical patients. The results of several RCT of patients undergoing surgery for total hip arthroplasty, total knee arthroplasty, hip fracture repair or myocardial revascularisation showed that administration of oral iron did not hasten the correction of postoperative anaemia or reduce the transfusion rate, but was associated with a high rate of adverse effects[144-146].

Critically ill patients. The administration of oral iron decreased the transfusion rate, but only when previously transfused patients were included in data analysis[147].

4.6.3. Preoperative intravenous iron therapy

We suggest preoperative administration of intravenous iron to improve preoperative haemoglobin levels and/or reduce transfusion rate. ***Grade 2B****.*

Surgical patients. In anaemic patients scheduled for orthopaedic, gynaecological or digestive tract surgery, preoperative administration of IV iron sucrose or ferric carboxymaltose corrected anaemia and reduced the transfusion rate[148]. In a study of 437 patients with

colorectal cancer, early multidisciplinary assessment and treatment of anaemia (74% with IV iron) improved preoperative haemoglobin levels and reduced the transfusion rate[149]. However, in a RCT of colon cancer patients, preoperative IV iron sucrose did not increase haemoglobin levels, although there was a trend to lower transfusion rates[150].

4.6.4. Perioperative intravenous iron therapy

We suggest perioperative administration of intravenous iron to surgical patients expected to develop severe postoperative anaemia in order to reduce transfusion rate. ***Grade 2B***.

Orthopaedic surgery. In hip fracture patients, perioperative administration of IV iron plus restrictive transfusion therapy decreased the transfusion rate and postoperative morbidity, especially in non-anaemic patients and in those with subcapital hip fracture[151-153]. In anaemic hip fracture patients, administration of IV iron plus rHuEPO (1×40,000 IU) was more effective than IV iron alone at reducing the transfusion rate[154,155]. Similarly, in patients undergoing total knee arthroplasty, the administration of IV iron (plus 1×40,000 IU rHuEPO if Hb <130 g/L) significantly reduced the transfusion rate[156].

4.6.5. Postoperative intravenous iron therapy

We suggest postoperative administration of intravenous iron to improve haemoglobin levels and/or reduce transfusion rate. ***Grade 2C***.

Cardiac surgery. The administration of IV iron, with or without rHuEPO, neither improved haemoglobin levels nor reduced the transfusion rate, although it did increase ferritin levels and reticulocyte counts[157].

Orthopaedic surgery. In lower limb arthroplasty[158] and correction of scoliosis[159], postoperative IV iron improved haemoglobin levels and/or reduced transfusion rates.

Gynaecological surgery. Postoperative IV iron significantly improved haemoglobin levels[160,161].

4.6.6. Intravenous iron therapy for moderate-to-severe post-partum anaemia

We recommend intravenous iron administration to correct anaemia and reduce transfusion rate. ***Grade 1B***.

Administration of IV iron sucrose[162,163] or ferric carboxymaltose[164,165] improved anaemia, ferritin levels and quality of life, and reduced transfusion rate.

4.6.7. Intravenous iron therapy in inflammatory bowel disease

We recommend intravenous iron administration to correct iron deficiency and anaemia and reduce transfusion rate. ***Grade 1B***.

Compared with oral iron, IV iron sucrose[166,167] and ferric carboxymaltose[168] were more effective at correcting the anaemia and replenishing iron deposits, and had a lower rate of side effects. Treatment with IV ferric carboxymaltose was shown to be superior to that with IV iron sucrose[169].

4.6.8. Intravenous iron therapy in cancer-associated anaemia

We suggest the administration of intravenous iron, without erythropoiesis- stimulating agents, to prevent chemotherapy/radiotherapy-induced decreases in haemoglobin and to reduce transfusion rate. ***Grade 2B***.

Data from two studies involving 134 patients with gynaecological cancer receiving adjuvant chemotherapy and/or radiotherapy showed that IV iron administration improved haemoglobin levels and reduced transfusion rate[170,171].

We recommend the administration of intravenous iron, as an adjuvant to erythropoiesis-stimulating agents, to correct chemotherapy-induced anaemia and reduce transfusion rate. ***Grade 1A***.

A meta-analysis[172] documented that the administration of IV iron plus erythropoiesis-stimulating agents corrected anaemia and improved transfusion rate, without increasing the rate of adverse effects. In addition, because IV iron allows doses of erythropoiesis-stimulating agents to be reduced, IV iron adjuvant therapy can be cost-effective[173].

4.6.9. Dosage

Oral iron. There is huge variability in the content of elemental iron among different oral iron formulations. For the treatment of preoperative anaemia, we recommend a dose of 100 mg of elemental iron/day for 2-6 weeks, depending on the time available before surgery. One RCT in critically ill patients used ferrous sulphate 325 mg/day (65 mg elemental iron)[147].

IV iron. The amount of IV iron required to replenish total iron deficiency can be estimated using Ganzoni's formula:

Total iron deficiency =
[target Hb – current Hb] × weight × 0.24 + 500.

In addition, 200 mg IV iron per 500 mL of blood loss should be administered. The administration schedule will depend on the IV iron formulation used:

- Iron sucrose: up to 3 mg/kg/session, maximum 200 mg/session, maximum 600 mg/week.
- Ferric carboxymaltose: up to 20 mg/kg/session, maximum 1,000 mg/session, maximum 1,000 mg/week.
- Iron isomaltoside 1000: up to 20 mg/kg/session, maximum 2,000 mg/session.
- Low molecular weight iron dextran: up to 20 mg/kg/session.

4.6.10. Safety

Although no serious IV iron-related adverse effects have been described, the number of surgical patients enrolled in the studies analysed is insufficient to draw definitive conclusions. The frequency of severe adverse effects with non-dextran IV iron formulations is extremely low[174] and significantly lower than the frequency with ABT[175]. A small proportion of patients treated with iron dextran have had anaphylactic reactions and, to a greater extent, anaphylactoid reactions. With regards to the risk of infection, a study of 32,566 haemodialysis patients showed no correlation between the administration of IV iron and increased rates of infection or mortality[176]. In contrast, in patients undergoing major surgery, low preoperative ferritin levels were associated with increased rates of postoperative infections[177,178]. However, administration of IV iron should be avoided in patients with pre-treatment ferritin values >300-500 ng/mL and transferrin saturation >50%. Moreover, despite the absence of definitive clinical data, it seems reasonable to avoid IV iron administration in the setting of acute infection.

4.6.11. Summary

Iron deficiency and iron-deficiency anaemia are frequent among medical, surgical and critically ill patients. Iron supplementation may, therefore, contribute significantly to the correction of anaemia and/or reduction of the transfusion rate. Whenever there is enough time and no contraindications, iron supplementation should be given in the oral formulation (e.g., ferrous sulphate), because of its low cost, easy administration, and acceptable tolerance. However, if there is poor absorption or poor tolerance, or an accelerated response to treatment is required, it would be fully justified to use IV iron, which allows a more rapid and complete bone marrow response and iron store replenishment. With the exception of high molecular weight iron dextran, IV iron formulations have a favourable benefit-risk profile in the treatment of iron-deficiency anaemia in different acute and chronic conditions.

4.7. Recombinant human erythropoietin

Recombinant human erythropoietin, obtained by genetic engineering, was initially authorised to treat the anaemia associated with chronic renal failure. After IV or subcutaneous administration, it mimics the effects of endogenous erythropoietin, stimulating erythropoiesis, inhibiting apoptosis of erythroid precursors and promoting their proliferation and maturation to erythrocytes. Its indications have now been expanded to the correction of anaemia and avoidance of ABT in patients receiving chemotherapy for non-myeloid malignancies, as well as in patients included in a PABD programme or scheduled for elective orthopaedic surgery.

4.7.1. Elective orthopaedic surgery

We recommend preoperative administration of recombinant human erythropoietin to reduce transfusion rate in patients with moderate anaemia (haemoglobin between 100 and 130 g/L) who are expected to have moderate blood losses. ***Grade 1A***.

In a meta-analysis on three randomised trials involving 684 patients with moderate anaemia who were scheduled for lower limb prosthetic surgery, preoperative administration of rHuEPO significantly reduced the risk of receiving ABT[179]. Subsequently, two RCT (896 patients)[180,181] and a case-control study (770 patients)[182] documented a similar reduction in transfusion rate.

4.7.2. Other major surgical procedures

We suggest the administration of recombinant human erythropoietin to reduce transfusion rate in anaemic patients undergoing major surgery. ***Grade 2A***.

Cardiac surgery. In a meta-analysis of RCT, preoperative administration of rHuEPO reduced the transfusion rate in patients undergoing cardiac surgery with CPB[183]. More recently, three RCT demonstrated the utility of a single dose of rHuEPO in the immediate preoperative period to reduce transfusion requirements in procedures with or without CPB[184-186]. However, there is no evidence that postoperative rHuEPO hastens the recovery from postoperative anaemia[157].

Gastrointestinal cancer. Several RCT, mainly in patients with colorectal cancer, have shown an increase in haemoglobin levels and a decrease in ABT requirements, but rHuEPO doses and treatment duration varied between studies. However, it could be verified that IV iron improved the efficacy of rHuEPO[187-189].

4.7.3. Critically ill patients

We do not recommend the use of recombinant human erythropoietin to treat anaemia and reduce the transfusion rate in patients who do not have a previous indication, with the possible exception of trauma patients, particularly those with severe traumatic brain injury. ***Grade 1A***.

It has been documented that, when a restrictive transfusion protocol was implemented, administration of rHuEPO decreased transfusion requirements discretely, but without reducing mortality[190]. In addition, a net increase in haemoglobin was only observed in one study in which adjuvant therapy with IV iron was administered[191]. However, for critically ill patients who were younger (<55 years) or presented with initially less severe illness (APACHE score <20) or with trauma as their admission diagnosis, rHuEPO administration improved survival rates[192]. Similar findings were observed in a population of patients with severe traumatic brain injury[193].

4.7.4. Dosage

Orthopaedic surgery. Two different protocols of rHuEPO administration have been adopted: 4 doses of 600 IU/Kg/week subcutaneously, beginning 3 weeks before surgery, or 15 doses of 300 IU/Kg/day, beginning 10 days prior to surgery and continuing 4 days after it. Similar protocols have been used in *cardiac and oncological surgery*. Although the effectiveness of these two protocols has been fully proven, the minimum effective dose of rHuEPO to reduce the transfusion rate in these patients is unknown, as similar results have been obtained using lower doses and shorter periods of administration, especially with adjuvant IV iron therapy[156,180,183-185,194,195].

4.7.5. Safety

Various government agencies (US Food and Drug Administration, European Medicines Agency, and the Spanish Agency of Medicines and Sanitary Products) have issued alerts on the association between the use of rHuEPO and an increased risk of thromboembolic events and mortality in patients receiving long-term treatment for anaemia associated with chronic renal failure or cancer chemotherapy, as well as in patients undergoing orthopaedic surgery without thromboembolic prophylaxis[196]. The RCT analysed documented that administration of rHuEPO in surgical and critically ill patients did not result in significantly higher rates of deep venous thrombosis or other clinically relevant thrombotic events when compared with a control group, provided that patients received pharmacological thromboembolic prophylaxis. However, it should be remembered that, except for patients scheduled for elective orthopaedic procedures or included in a PABD programme, the use of rHuEPO in surgical patients is "off-label". The available data do, therefore, suggest that it would be necessary to adjust the rHuEPO dose (administering adjuvant iron, preferably IV), as well as to pay special attention to thromboembolic prophylaxis (administering anti-thrombotic and, perhaps, platelet antiaggregant drugs)[191,197,198].

4.7.6. Summary

The administration of rHuEPO is indicated to correct anaemia and reduce the transfusion rate in patients undergoing elective orthopaedic surgery, and to facilitate the implementation of PABD programmes requiring three or more units of blood. The efficacy of rHuEPO in reducing the rate of ABT is maximal in patients with preoperative haemoglobin levels between 100 and 130 g/L and the product does not apparently increase the incidence of thrombotic complications. However, it must be borne in mind that these are low incidence adverse effects, and that the majority of studies with rHuEPO have been performed in patients without cardiovascular disease. It would, therefore, be advisable to adjust rHuEPO dose individually, ensure iron supply to the bone marrow and provide adequate thomboembolic prophylaxis. In addition, rHuEPO could be administered to treat anaemia in non-orthopaedic surgical patients ("off-label" use), but it is not recommended for critically ill patients who do not have a prior indication for this drug, with the possible exception of trauma patients, particularly those with severe traumatic brain injury.

Pharmacological alternatives to improve oxygen transport

4.8 Crystalloids and colloids solutions

The correction of haemorrhage-associated hypovolaemia, administering IV crystalloid and/or colloid solutions, is a priority measure and, in itself, the first AABT to be considered in the event of any acute or subacute haemorrhage, as hypovolaemia is tolerated less well than anaemia. Isotonic 0.9% saline, Ringer's solution and other balanced salt solutions, such as Hartmann's solution (Ringer lactate), are among the most commonly used crystalloid solutions. They are inexpensive, do not alter haemostasis or renal function, and there is large accumulated experience with their use. Usually, only 25% of infused crystalloid volume is retained within the intravascular compartment. Hypertonic crystalloid solutions (1.8-7.2% NaCl) would have the theoretical advantages of a more rapid correction of hypovolaemia and reduction of cerebral oedema. However, there are no conclusive evidence of their efficacy and they may lead to hypernatremia. The most commonly used colloids are hydroxyethyl starch (HES), gelatine and human albumin solutions. Infusion of 5% albumin produces a plasma expansion equal to 75% of the volume infused. Gelatines, given their low molecular weight, have a short intravascular half life (2-3 hours) and their plasma expansion capacity is limited (70-80%). The 6% HES solutions have a longer intravascular half-life (6-8 hours) and larger plasma expansion capacity (80-120%), and are the most widely used colloids for volume expansion nowadays. Nevertheless, the discussion regarding selection of crystalloids or colloids for fluid resuscitation is as old as it is controversial[199].

4.8.1. Patients with mild or moderate blood loss

We recommend initial volume replacement with crystalloids or colloids to decrease the transfusion rate. ***Grade 1C****.*

Patients with mild or moderate haemorrhage (<30% of volaemia or <1,300 mL), without data on additional bleeding, can be managed with a crystalloid[200,201]. Adequate replenishment of the circulating volume and,

therefore, of the cardiac output, allows the maintenance of oxygen supply to tissues. Colloids may be reserved for patients who are haemodynamically unstable despite the infusion of crystalloids[202,203].

4.8.2. Patients with severe blood loss

We recommend initial volume replacement with crystalloids or colloids to decrease the transfusion rate. ***Grade 1C***.

Patients with severe haemorrhage (30-40% of volaemia) can be initially managed with crystalloids[200,201]. It has been recommended to infuse small volumes of Ringer lactate, containing only the lactate L isomer, to maintain a systolic blood pressure of 80-90 mmHg (controlled or permissive hypotension)[204]. However, it seems justified to add colloids or vasoactive drugs, after initial resuscitation with moderate amounts of crystalloids. Once volaemia is restored, the need for ABT should be assessed on the basis of laboratory tests and estimated blood losses. A pooled analysis of RCT comparing various HES solutions in major surgery concluded that the administration of HES 130/0.4 may significantly reduce transfusion needs[205].

4.8.3. Patients with critical bleeding

We suggest initial fluid resuscitation with crystalloids or colloids, followed by transfusion of blood components and plasma derivatives, to decrease the transfusion rate. ***Grade 2B***.

Immediate transfusion of blood products is recommended for patients with critical bleeding (>40% of volaemia), who do not respond to the initial infusion of 2 litres of fluids, have severe bleeding with haemodynamic instability or a blood loss ≥50 mL/minute[206]. Patients presenting with coagulopathy, acidosis and hypothermia have significantly worse outcome[64]. Classically, it was thought that the coagulopathy had a delayed onset and was due to bleeding-associated loss of coagulation factors, which were diluted further by the infusion of large amount of fluids. This justified the transfusion of blood products with low ratios of PRBC:FFP (6:1) and PRBC:platelet concentrate (10:1).

However, recent studies have documented the very early onset of coagulopathy, which is present upon admission in up to a third of the patients, before fluid resuscitation[64]. It has been suggested that early administration of blood products in a 1:1:1 ratio (i.e., the same amounts of PRBC, FFP and platelet concentrate; the so-called "massive transfusion protocol"), rather than large amounts of fluids, increases survival[64,83]. However, it should be remembered that this practice is based on retrospective analysis, subject to a number of limitations and biases. Thus, some observational studies have demonstrated an association between early initiation of a massive transfusion protocol and improved clinical outcome, including decreased transfusion rates and increased survival[64,83,207], although others have not[84,208,209]. Secondly, the design of the massive transfusion protocol for traumatic bleeding was based on data from the military context, which is often very different from the civilian context. Finally, it has not been conclusively demonstrated that the massive transfusion protocol decreases morbidity or improves survival in civilian patients with haemorrhagic trauma[84,208,210,211]. In a recent systematic review on this topic, the authors concluded that there is not sufficient evidence to indicate the use of the 1:1:1 massive transfusion protocol in these populations of patients[210]. Similarly, the European Guidelines on Massive Transfusion[99] and recent updates of clinical practice guidelines[84,208,210,211] do not provide specific recommendations on the 1:1:1 massive transfusion protocol. Therefore, until new evidence is available, the traditional approach, based on volume replacement, monitoring of haemostasis and transfusion of the appropriate blood products, can be considered valid for the vast majority of bleeding patients.

4.8.4. Dosage

Crystalloids. An initial dose of 3 mL of crystalloids (preferably Ringer lactate) per mL of blood loss, at an infusion rate of 60-80 mL/kg/hour, while achieving bleeding control, is recommended. The objective should be to maintain a systolic blood pressure of 80-90 mmHg (permissive hypotension)[204]. Patients with traumatic brain injury may require the infusion of larger amounts of fluid to maintain systolic blood pressure. Hypertonic saline solutions carry the potential risk of hypernatraemia, and only a single dose can be administered. The dose of the 7.2% NaCl solution, with or without HES, is 4 mL/kg, although this treatment is not widely used.

Colloids. An initial dose of 1 mL of colloids per mL of blood loss is recommended. The maximal dose of HES is 20 mL/kg/day for HES 200/0.5 and 50 mL/kg/day for HES 130/0.4. As gelatines do not accumulate in the body, a maximal daily dose has not been described, but it is recommended that the dose of 20 mL/kg/day is not exceeded[200,204].

4.8.5. Safety

The infusion of large amounts of crystalloids (generally saline isotonic solution) is associated with an increased incidence of nausea, vomiting, generalised oedema, pulmonary dysfunction and hyperchloraemic metabolic acidosis[204]. Under normal conditions, the lactate of Ringer's lactate is quickly metabolised to bicarbonate, but some clinical and experimental observations indicate reduced lactate

clearance in haemorrhagic shock, probably due to poor liver perfusion, leading to metabolic acidosis. Under ideal conditions, 25% of infused crystalloid volume remains within the vascular compartment, whereas the remaining 75% leaks into the extravascular compartment. Increased capillary permeability may reduce intravascular crystalloid retention, resulting in an increase of interstitial oedema.

Adverse effects of colloids include anaphylactoid reactions, pruritus, coagulopathy and haemorrhagic events, with varied incidences depending on the type of colloid. While gelatines are more frequently associated with anaphylactoid reactions, HES solutions are linked to itching and coagulopathy. High molecular weight HES may worsen kidney function in patients with pre-existing kidney disease, especially those with sepsis. Although HES solutions may alter the results of tests of haemostasis and decrease clot firmness, the administration of low molecular weight HES rarely results in clinically relevant coagulopathy leading to bleeding complications. The administration of HES might produce a dose-dependent reduction of factor VII activity, mild platelet dysfunction, and prolonged activated partial thromboplastin time. Most of these changes have a dilutional aetiology, and may lead to increased blood loss, especially in patients undergoing cardiac surgery. Given its lower molecular weight and degree of substitution, pentastarch causes less haemostatic derangements than hetastarch. A recent Cochrane Database review of 63 RCT concluded that there are no data demonstrating that resuscitation with colloids, rather than with crystalloids, reduces mortality risk in patients with trauma, burns or surgery[212]. In addition, septic patients resuscitated with colloids, rather than crystalloids, had higher rates of mortality and renal failure[213]. In another study of patients admitted to an Intensive Care Unit, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy[214].

4.8.6. Summary

Crystalloid solutions are inexpensive, do not alter haemostasis or produce renal damage, and there is large experience with their use. Their main disadvantage in that only 25% of infused volume is retained within the intravascular compartment. Isotonic saline is the most widely and safely used crystalloid solution. The available evidence indicates that crystalloids are the solutions of choice for the initial treatment of hypovolaemic acute anaemia due to moderate to severe bleeding. Another recommended management for severe bleeding is the infusion of small volumes of Ringer's lactate (60-80 mL/kg/h) containing only the L isomer of lactate to maintain a systolic blood pressure of 80-90 mmHg (controlled or permissive hypotension). There is no evidence indicating that colloid solutions are superior to crystalloid solutions as an AABT. Colloids are used in the event of severe haemorrhage and haemodynamic instability, usually in association with crystalloids. Among colloids, HES are most widely used as an AABT, flowed by gelatines; the use of albumin as a plasma expander is not recommended.

4.9. Perfluorocarbon- and haemoglobin-based oxygen carriers

Perfluorocarbon-based oxygen carriers (PFCOC) are linear, cyclic or polycyclic hydrocarbon compounds in which hydrogen atoms have been replaced by fluorine atoms. They are characterised by having a high capacity to dissolve gases (O_2, CO_2, N and NO), and do not contain biological products. The amount of oxygen dissolved in perfluorocarbon emulsions is directly proportional to the patient's inspiratory O_2 fraction.

Haemoglobin-based oxygen carriers (HBOC) are compounds derived from human, animal or recombinant haemoglobin and are free from cellular elements.

4.9.1. Administration of perfluorocarbon-based oxygen carriers to patients who are bleeding and/or require blood transfusion

We cannot make any recommendation regarding the use of perfluorocarbon-based oxygen carriers as an alternative to the transfusion of red blood cell concentrates. ***Grade 0****.*

Very few studies on the use of PFCOC as AABT have been published, and most of them have showed an increased rate of adverse effects[215-217]. No PFCOC is currently approved in the European Union for use as an AABT. Perftoran has been approved for use in Russia, Ukraine and Mexico. A RCT of 30 cardiac surgery patients conducted in Mexico concluded that the use of Perftoran did not result in a significant reduction of transfusion rate with respect to the rate in a control group[218].

4.9.2. Administration of haemoglobin-based oxygen carriers to patients who are bleeding and/or require blood transfusion

We cannot make any recommendation regarding the use of haemoglobin-based oxygen carriers as an alternative to the transfusion of red blood cell concentrates. ***Grade 0****.*

A RCT of 688 orthopaedic surgery patients documented a decrease in ABT rate and an increase of

adverse events in the group that received Hemopure[219]. Similarly, although there are case-reports showing that PolyHeme administration may improve survival in extreme circumstances[220], a recent clinical trial demonstrated that PolyHeme use did not provide any advantage in terms of survival or blood saving, and resulted in an even higher rate of adverse events[221]. A randomised, single-blind, dose escalation safety trial of Hemospan administered to orthopaedic surgery patients did not detect serious adverse events associated with the use of this HBOC[222]. No HBOC is currently approved as an AABT in the European Union.

4.9.3. Dosage

It is not possible to make recommendations regarding the doses of PFCOC or HBOC.

4.9.4. Safety

Initially, HBOC had very short intravascular half-lives and caused significant adverse effects, including abdominal pain, hypertension and nephrotoxicity. Currently available products, which have been obtained using techniques of stabilising the haemoglobin molecule, have longer intravascular half-lives and lower rates of adverse effects, although notifications of HBOC-associated hypertension and acute renal failure still persist[1,223]. In general, PFCOC-related toxicity includes thrombocytopenia, complement activation and cytokine release, reticulo-endothelial system blockade, flu-like symptoms and central nervous system effects.

4.9.5. Summary

Based on the available scientific evidence, the current role of artificial oxygen carriers as AABT is uncertain and limited in practice to specific situations in which human blood components were not available. However, should the ongoing research lines be fruitful, new oxygen carriers with improved safety profile could be available in the near future.

Scientific Society of affiliation and Conflict of Interest disclosure of topic coordinators

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Appendix A
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José Aurelio Gómez-Luque
Mónica Izuel
Víctor Jiménez-Yuste
Santiago Ramón Leal-Noval
Eduardo López-Briz
María Fernanda López-Fernández
Juan Vicente Llau
José Antonio Martín-Conde
Bruno Montoro-Ronsano
Victoria Moral
Manuel Muñoz
Carmen Paniagua
José Antonio Páramo
Manuel Quintana
José Antonio Romero-Garrido
Juan Carlos Ruiz
Ramón Salinas-Argente
Calixto Sánchez
Pau Torrabadella

Appendix B
Acronyms (in alphabetical order):

AABT	Alternatives to allogeneic blood transfusion
ABT	Allogeneic blood transfusion
ANH	Acute normovolaemic haemodilution
CPB	Cardiopulmonary bypass
DDAVP	Desmopressin
EACA	Epsilon aminocaproic acid
FFP	Fresh-frozen plasma
GRADE	Grades of Recommendation Assessment, Development and Evaluation
Hb	Haemoglobin
HBOC	Haemoglobin-based oxygen carriers
HES	Hydroxy ethyl-starches
INR	International Normalised Ratio
IV	Intravenous
PABD	Preoperative autologous blood donation
PCC	Prothrombin complex concentrate
PFCOC	Perfluorocarbon-based oxygen carriers
PRBC	Packed red blood cells
PRCS	Perioperative red cell salvage
RCT	Randomised controlled trials
rFVIIa	Recombinant activated factor VII
rHuEPO	Recombinant human erythropoietin
SD	Seville Document, 2006 version
TACO	Transfusion-associated cardiovascular overload
TEG	Thromboelastography
TRALI	Transfusion-related acute lung injury
TXA	Tranexamic acid
VKA	Vitamin K antagonists