SPECIAL ARTICLE

Forum for debate: Safety of allogeneic blood transfusion alternatives in the surgical/critically ill patient

M. Muñoz Gómez\textsuperscript{a,*}, E. Bisbe Vives\textsuperscript{b}, M. Basora Macaya\textsuperscript{c}, J.A. García Erce\textsuperscript{d}, A. Gómez Luque\textsuperscript{e}, S.R. Leal-Naval\textsuperscript{f}, M.J. Cololina\textsuperscript{g}, J. Comin Colet\textsuperscript{h}, E. Contreras Barbeta\textsuperscript{i}, J. Cuenca Espiérrez\textsuperscript{j}, A. Garcia de Lorenzo y Mateos\textsuperscript{k}, F. Gomollón García\textsuperscript{l}, M. Izuel Ramí\textsuperscript{m}, M.V. Moral García\textsuperscript{n}, J.B. Montoro Ronsano\textsuperscript{o}, J.A. Páramo Fernández\textsuperscript{p}, A. Pereira Saavedra\textsuperscript{q}, M. Quintana Díaz\textsuperscript{k}, Á. Remacha Sevilla\textsuperscript{r}, R. Salinas Argente\textsuperscript{s}, C. Sánchez Pérez\textsuperscript{t}, G. Tirado Anglés\textsuperscript{u}, P. Torrabadella de Reinoso\textsuperscript{v}

\textsuperscript{a} Medicina Transfusional Perioperatoria, Facultad de Medicina, Universidad de Málaga, Málaga, Spain
\textsuperscript{b} Servicio de Anestesiología y Reanimación, Hospital Universitario del Mar, Barcelona, Spain
\textsuperscript{c} Servicio de Anestesiología y Reanimación, Hospital Clinic, Barcelona, Spain
\textsuperscript{d} Servicio de Transfusión, Hospital San Jorge, Huesca, Spain
\textsuperscript{e} Servicio de Anestesiología y Reanimación, Hospital Universitario Virgen de la Victoria, Málaga, Spain
\textsuperscript{f} Servicio de Cuidados Críticos y Urgencias, Hospital Virgen del Rocío, Sevilla, Spain
\textsuperscript{g} Servicio de Anestesiología y Reanimación, Hospital Universitario Vall d’Hebron, Barcelona, Spain
\textsuperscript{h} Servicio de Cardiología, Hospital Universitario del Mar, Barcelona, Spain
\textsuperscript{i} Banc de Sang i Teixits, Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain
\textsuperscript{j} Servicio de Cirugía Ortopédica y Traumatología, Hospital Universitario Miguel Servet, Zaragoza, Spain
\textsuperscript{k} Servicio de Medicina Intensiva, Hospital Universitario La Paz, Madrid, Spain
\textsuperscript{l} Servicio de Gastroenterología, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
\textsuperscript{m} Servicio de Farmacia, Hospital Miguel Servet, Zaragoza, Spain
\textsuperscript{n} Servicio de Anestesiología, Reanimación y Tratamiento del Dolor, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
\textsuperscript{o} Servicio de Farmacia, Hospital Universitario Vall d’Hebron, Barcelona, Spain
\textsuperscript{p} Servicio de Hematología, Clínica Universidad de Navarra, Pamplona, Spain
\textsuperscript{q} Servicio de Hemoterapia y Hemostasia, Hospital Clínic de Barcelona, Barcelona, Spain

\textsuperscript{*} Corresponding author.
\textit{E-mail address: mmunoz@uma.es} (M. Muñoz Gómez).

\begin{itemize}
\item 2173-5727/© 2015 Elsevier España, S.L.U. and SEMICYUC. All rights reserved.
\end{itemize}
Safety of allogeneic blood transfusion alternatives

Servicio de Laboratorio de Hematología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Territorial Banc de Sang i Teixits Catalunya Central, Barcelona, Spain
Servicio de Anestesiología y Reanimación, Hospital General Universitario de Elda, Elda, Alicante, Spain
Unidad de Cuidados Intensivos, Hospital Royo Villanova, Zaragoza, Spain
Unidad de Cuidados Intensivos, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain

Received 6 February 2015; accepted 22 May 2015
Available online 25 November 2015

KEYWORDS
Allogeneic transfusion; Erythropoiesis; Procoagulants; Hydroxyethyl starch; Restrictive transfusion criteria; Safety

Abstract In recent years, several safety alerts have questioned or restricted the use of some pharmacological alternatives to allogeneic blood transfusion in established indications. In contrast, there seems to be a promotion of other alternatives, based on blood products and/or antifibrinolytic drugs, which lack a solid scientific basis.

The Multidisciplinary Autotransfusion Study Group and the Anemia Working Group España convened a multidisciplinary panel of 23 experts belonging to different healthcare areas in a forum for debate to: (1) analyze the different safety alerts referred to certain transfusion alternatives; (2) study the background leading to such alternatives, the evidence supporting them, and their consequences for everyday clinical practice, and (3) issue a weighted statement on the safety of each questioned transfusion alternative, according to its clinical use.

The members of the forum maintained telematics contact for the exchange of information and the distribution of tasks, and a joint meeting was held where the conclusions on each of the items examined were presented and discussed. A first version of the document was drafted, and subjected to 4 rounds of review and updating until consensus was reached (unanimously in most cases). We present the final version of the document, approved by all panel members, and hope it will be useful for our colleagues.

© 2015 Elsevier España, S.L.U. and SEMICYUC. All rights reserved.

PALABRAS CLAVE
Transfusión alogénica; Eritropoyesis; Procoagulantes; Coloídes; Criterios restrictivos de transfusión; Seguridad

Foro de debate: seguridad de las alternativas a la transfusión alogénica en el paciente quirúrgico y/o crítico

Resumen En los últimos años han aparecido alertas de seguridad, no siempre bien sustentadas, que cuestionan el uso de algunas alternativas farmacológicas a la transfusión de sangre alogénica y/o lo restringen en indicaciones establecidas. Asimismo también a la preconización de otras alternativas, incluyendo productos hemáticos y fármacos antifibrinolíticos, sin que haya una base científica sólida que lo justifique.

Por iniciativa del Grupo de Estudios Multidisciplinares sobre Autotransfusión y del Anemia Working Group España se reunió a un panel multidisciplinar de 23 expertos del área de cuidados de la salud en un foro de debate para: 1) analizar las diferentes alertas de seguridad en torno a ciertas alternativas a la transfusión; 2) estudiar los antecedentes que las han propiciado, la evidencia que las sustenta y las consecuencias que conllevan para la práctica clínica, y 3) emitir una valoración argumentada de la seguridad de cada alternativa a la transfusión cuestionada, según el uso clínico de la misma.

Los integrantes del foro mantuvieron contactos por vía telemática y una reunión presencial en la que presentaron y discutieron las conclusiones sobre cada uno de los elementos examinados. Se elaboró un primer documento que fue sometido a 4 rondas de revisión y actualización hasta alcanzar un consenso, unánime en la mayoría de los casos. Presentamos la versión final del documento, aprobada por todos los miembros del panel, esperando sea de utilidad para nuestros colegas.

© 2015 Elsevier España, S.L.U. y SEMICYUC. Todos los derechos reservados.
Introduction

In recent years there have been many safety alerts from official organisms such as the European Medicines Agency (EMA) or the Spanish Medicines Agency (Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]), as well as in editorials and articles published in widely read international journals. Many of these alerts, not always based on sound evidence, question the safety of certain allogecic blood transfusion alternatives (ABTAs), fundamentally of a pharmacological nature, and/or expand the restrictions of their indications in different clinical scenarios where their use appeared to have been consolidated. On the other hand, the use of other alternatives is also being suggested, particularly those destined to reduce perioperative bleeding, based on the utilization of blood products and/or synthetic antifibrinolytic agents, though solid scientific justification of such use is lacking.

The Multidisciplinary Autotransfusion Study Group and the Anemia Working Group España decided to convene a forum for debate with the purpose of analyzing and assessing these safety alerts, and of addressing the resulting controversies regarding ABTAs.

Methodology

Upon initiative from the Multidisciplinary Autotransfusion Study Group and the Anemia Working Group España, a multidisciplinary panel was created, comprising 23 experts from different health care areas, including Anesthesia and Resuscitation, Cardiology, Traumatology and Orthopedic Surgery, Intensive Care, Hematology and Hemotherapy, Gastroenterology, Hospital Pharmacy, Transfusion Medicine and Emergency Care, with extensive and documented experience in the field of ABTA. Most of these experts had participated in the drafting of the Update on the Seville Document 2013 (DS2013), endorsed by 6 Spanish scientific societies, though on this occasion they intervened on a personal basis and not in representation of their respective societies.

The members of the forum maintained telematics contact, with the distribution of tasks and the exchange of updated scientific information (based on Medline searching and Dropbox downloading of the relevant documents). A physical meeting was also held, with working sessions in which the members of the panel were distributed into four groups according to their experience with certain ABTAs (management of anemia, reduction of bleeding, colloid fluid therapy and restrictive transfusion criteria). Following these working sessions in small groups, a joint session was held with all the forum members.

The group sessions addressed the following tasks: (1) analysis of the different safety alerts referred to certain transfusion alternatives used in clinical practice issued by the United States Food and Drug Administration (FDA), the EMA or the AEMPS, such as those published in recent issues of widely read journals; (2) study of the background leading to such alternatives, the evidence supporting them, and their consequences for everyday clinical practice; and (3) issuing of a weighted statement on the safety of each questioned transfusion alternative, according to the clinical scenario in which it is used.

The joint session served to present and discuss the conclusions of the working groups referred to each of the examined items. The contents of the presentations were in turn used to draft a first version of the document, which was subjected to four rounds of review and updating until consensus was reached (unanimously in most cases). The final version of the document and the summary of conclusions (Appendix A of the additional material available in the electronic version) were approved by all the panel members.

Management of anemia

Intravenous iron

Background

The administration of intravenous iron (IVF) is indicated for the management of iron deficiency and ferropenic anemia in those cases where iron supplementing via the oral route is not possible or is ineffective. With the formulations available for clinical use in Spain, the benefits of IVF clearly outweigh the risks, provided adequate measures are taken to minimize possible allergic reactions. Both the DS2013 and the European guide for the management of severe surgical bleeding (ESA guide) recommend the use of IVF in surgical patients in order to improve anemia and replenish the iron deposits. Intravenous iron formulations that allow the rapid administration of high doses (e.g., iron isomaltose-1000 and iron carboxymaltose) facilitate the implementation of these recommendations.

However, two documents have been published on the risk of adverse effects of IVF: an alert referred to the risk of hypersensitivity, which led to revision of these drugs by the Committee for Medicinal Products for Human Use of the EMA and a metaanalysis alerting to an increased risk of infection in patients treated with these products.

Safety of intravenous iron

Regarding the risk of hypersensitivity, the EMA and AEMPS consider that there is a clear association between the administration of IVF and hypersensitivity reactions. While the incidence of such reactions is very low, they can prove fatal. Nevertheless, the agencies underscore that the information supplied by the industry and the national pharmacovigilance centers affords very low quality evidence and is not valid for detecting safety differences among the different IVF formulations. They therefore recommend annual reviews of the reports on allergic reactions and prospective studies. The agencies have also drafted recommendations in relation to the administration and contraindications of IVF. A consensus document has recently been published on the management of hypersensitivity reactions.

With regard to the increase in the risk of infection, a metaanalysis of 72 clinical trials (comprising about 10,000 patients) concluded that these formulations improve the hemoglobin (Hb) levels and reduce the allogeneic blood transfusion (ABT) rates, but increase the relative risk of infections (RR: 1.33; 95%CI: 1.10–1.64). Different experts have criticized this latter conclusion, however, since: (1) in most the included studies infection was not a predefined
target variable; (2) there was great heterogeneity regarding the dose and duration of treatment, the types of iron, study populations, etc.; (3) no dose–effect relationship was observed between the administration of IVF and an increased incidence of infections or mortality, and (4) the studies that did include definition criteria for this variable recorded no increase in infection rate in the patients treated with IVF. Furthermore, a later metaanalysis involving a larger number of studies (n = 103; over 19,000 patients) identified no increase in the risk of infection in the patients that received IVF. It should be remembered that the risk of infection is increased in situations of iron overload, but also in cases of ferropenia, and that the administration of IVF in nonferropenic patients might increase the risk of infections. A correct diagnosis is therefore essential in order to guarantee the efficacy and safety of treatment with IVF.

**Erythropoiesis stimulators**

**Background**

The alerts regarding the adverse effects of erythropoiesis stimulators, such as an increased risk of thromboembolic events (TEEs) and mortality in different clinical contexts, are not new. However, they have led to changes in the indications of these stimulators and in the treatment schemes in renal and cancer patients. In the surgical context, recombinant human erythropoietin (epoetin-alpha, rHuEPO) is only indicated in patients undergoing elective orthopedic surgery with hemoglobin or for facilitating preoperative autogenous donation—though it has also been used in traumatologic, heart and cancer surgery. In relation to the approved indication, two studies in vertebral surgery have reported an increase in venous thrombosis in patients treated with rHuEPO and who had not received thromboprophylactic measures. In view of these data, the FDA required the Summary of Product Characteristics of these products to include a mention referring to “consideration of the use of deep venous thrombosis preventive measures during use of the product”. In Spain this recommendation was already included in the Summary of Product Characteristics of rHuEPO.

**Safety of recombinant human erythropoietin**

In the context of elective orthopedic surgery, a recent metaanalysis has confirmed the efficacy of rHuEPO in reducing ABT, without increasing the risk of TEE versus placebo—though the authors underscore that most of the patients received thromboprophylaxis and had a low cardiovascular and thromboembolic risk. Furthermore, it may be argued that this indication involves a series of factors that do not predispense to increased TEE risk: (1) treatment is relatively brief (3–4 weeks); (2) the rHuEPO dose tends to be adjusted to obtain a target hemoglobin concentration of 13–14 g/dl (except in special patients such as Jehovah witnesses, or patients undergoing more bleeding-prone operations or revision surgery); (3) coadjuvant IVF is usually provided, which improves the erythropoietic effect and significantly lowers the platelet counts; and (4) most patients are exposed to these hemoglobin levels for less than 15 days, since persurgical bleeding causes them to quickly drop to 10 g/dl or even lower.

Regarding the off-label use of human erythropoietin in other scenarios, the administration of rHuEPO in coronary or heart valve surgery with or without IVF has been shown to reduce ABT, lessen morbidity-mortality, and shorten hospital stay, without adverse effects in any of the published studies. In contrast, the available data reveal no benefit of administration in application in anemia and/or in reducing ABT in heart failure, colorectal cancer surgery, or in critical patients—with no approved indication for this drug before admission to intensive care. Indeed, treatment may even increase the incidence of complications or mortality in some cases.

Therefore, until further efficacy and safety information becomes available, rHuEPO should only be used in the context of its approved indications, and following the national and international recommendations and guidelines.

**Drug measures for reducing bleeding**

**Antifibrinolytic agents**

**Background**

Within this drug category, an analysis is made of the efficacy and safety of tranexamic acid (TXA), particularly in orthopedic surgery, and the reintroduction on the market of aprotinin (APT).

Total knee arthroplasty (TKA) or total hip arthroplasty (THA) is associated to significant perioperative blood loss and an ABT rate of 20–30%, with an average of two transfusion units per patient. The efficacy and very low cost of TXA (1000 mg = 1 €) have caused it to be increasingly used in TKA and THA, despite the fact that orthopedic surgery nominally is not included among the specific indications stated in the Summary of Product Characteristics of the drug. In addition to the above, the strong impact of the CRASH-2 study must be taken into account, as it has led many professionals to consider that the effects of TXA in patients with early coagulopathy and secondary hyperfibrinolysis, associated to bleeding trauma, are extrapolatable to patients undergoing elective orthopedic surgery—the clinical context of which is very different. Hence, the administration of TXA in orthopedic surgery patients generates uncertainties regarding safety.

**Safety of tranexamic acid**

Different large observational studies, randomized controlled trials and metaanalyses appear to confirm the efficacy of TXA in reducing perioperative or traumatic bleeding, as well as the need for ABT, in different clinical scenarios, with a high degree of recommendation by both the DS2013 and the ESA guide—though there is some uncertainty regarding the increased risk of TEE, seizures and mortality in some of them.

In orthopedic surgery, both documents only recommend the administration of TXA in TKA, THA and vertebral surgery for reducing perioperative bleeding and the need for ABT (grade 2A recommendation). The ESA guide moreover adds that TXA can contribute to a hypercoagulability state in some patients (with a history of TEE, hip fracture surgery, and...
cancer, age < 60 years, female sex). Therefore, an individualized risk/benefit analysis is advised instead of routine use of the drug in this clinical context (grade 2A recommendation). Furthermore, the guide points out that further studies are needed to clarify the neurological risk, the appropriate indications, and the dosing characteristics of TXA.11,37

Thus, the intravenous administration of TXA has demonstrated its efficacy in reducing blood losses and transfusion needs in orthopedic surgery, though with variable results.30 On the other hand, its impact upon perioperative TEE and mortality has not been adequately evaluated and remains unclear. This may be particularly relevant for the use of TXA in THA and TKA, where postoperative hypercoagulability has been demonstrated.38

A review of the published metaanalyses showed TXA to reduce perioperative blood loss and the proportion of patients requiring ABT, though with significant heterogeneity that points to the need for careful interpretation of the effect of the drug in this scenario.29 Since ABT is also a risk factor for hypercoagulability in patients subjected to TKA and THA, and considering that TXA significantly reduces the ABT rate, a lesser incidence of TEE should be expected. Since this decrease has not been confirmed,29 the alternative hypothesis is that the administration of TXA in TKA and THA would induce an increase in the risk of TEE, as has been evidenced in hip fracture surgery,29 and this could be compensated by the benefit derived from the lessened exposure to ABT. Thus, the existing evidence appears to advise caution rather than complacency when using TXA in TKA and THA.

In order to confirm the safety of TXA in this context, it would be necessary to design studies including an adequate number of transfused and non-transfused patients treated or not treated with the drug (approximately 5000 patients per arm), with a careful analysis of the incidence of TEE (deep venous thrombosis, pulmonary embolism, stroke and myocardial infarction) and mortality. In the meantime, we should abide with the specifications of Article 13 of Chapter III of Spanish Royal Decree (RD) 1015/2009, on “Requirements for access to medicines under conditions different from those authorized in Spain”. In this regard, although such drug use is not subject to case-by-case authorization by the AEMPS, the latter may issue recommendations that will have to be taken into account in developing treatment-care protocols in healthcare centers.40

### Safety of aprotinin

In relation to heart surgery, a metaanalysis published in 2009 showed the use of aprotinin (APT) to be associated to an increase in mortality compared with TXA,41 though two recent metaanalyses have cast doubts on the purported greater toxicity of APT in comparison with the lysine analogs.42,43 Lastly, a fourth metaanalysis of randomized and observational studies found that in comparison with the lysine analogs, APT may be associated to increased mortality risk in low- and intermediate-risk heart surgery, but does not appear to have an impact upon mortality in high-risk heart surgery.44 On the basis of these data, the EMA recommends lifting suspension on the use of APT in the European Union, though restricting its administration to adult patients programmed for isolated myocardial revascularization with extracorporeal circulation and a high bleeding risk. The EMA moreover insists on maintaining adequate anticoagulation with heparin in these patients.4 We remain in wait of new data on the use of APT in relation to this revised indication.

### Clotting factor concentrates

#### Background

The safety of prothrombin complex concentrate (PCC) and fibrinogen concentrate (FBNC) used as ABTA for hemostatic control in surgical or traumatic bleeding is subject to controversy, since there are doubts regarding the reporting of TEE to the pharmacovigilance system (under-reporting problems).

The three PCC formulations marketed in Spain contain coagulation factors II, VII, IX and X ("four factors” PCC), with some differences in other components. Prothrombin complex concentrate is indicated in substitution of fresh frozen plasma (FFP) in patients receiving vitamin K antagonists and who suffer severe or critical bleeding (referred to amount or location—particularly in the intracranial hemorrhage [grade 1C]), or who need urgent or emergent surgery (grade 2A).10 However, its off-label utilization is increasingly common in bleeding patients not treated with vitamin K antagonists, as reflected in DS2013 (grade 2C),36 the ESA guide (grade B)13 and the European trauma guides (grade C).45

Fibrinogen levels are critical for effective hemostasis, and FBNC is indicated for the treatment of congenital fibrinogen deficiencies. Based on observational studies, the guides support the usefulness of the early administration of FBNC in patients with critical bleeding and hypofibrinogenemia (plasma fibrinogen < 1.5 g/l [Clauss method] and/or ROTEM FIBTEM < 7 mm) (grade 1C),10,11,45 though the indication is not universally accepted.46

### Safety of clotting factor concentrates

A review has been made of the TEE rates associated to the administration of PCC and/or FBNC, documented by a series of recent studies involving a large number of patients and in different clinical scenarios. The TEE rate associated to the use of PCC and/or FBNC varies between 1% and 4%, depending on the type of study, the clinical scenario and the drug administered, and in most cases no causal relationship has been established.

Furthermore, some studies have jointly administered PCC and FBNC, in addition to plasma, red cell concentrates and/or TXA, which further complicates evaluation of the safety of these products. There have been no reports of infectious disease transmission47–50 (Appendix A of the additional material available in the electronic version).

According to the Cochrane Library,51 the analysis of this information shows the quality of the existing evidence on the safety of these drugs to be low. We therefore need controlled studies specifically designed to assess efficacy and safety with respect to conventional therapy in the management of coagulopathy in patients with critical bleeding. Nevertheless, it is conceivable that early administration at adequate doses and in the context of an algorithm for the management of hemostasis, guided by point of care determinations (thromboelastography/thromboelastometry)
instead of conventional laboratory tests, might improve the efficacy and safety of such products in this clinical setting.

Lastly, it should be remembered that patients treated with these drugs are at a high risk of suffering TEE as a consequence of their background disease process and/or to concomitant treatments (red cells, plasma, platelets, TXA, etc.), and not necessarily due to the administration of clotting factor concentrates.

Volume replacement

Background

Volume replacement or fluid resuscitation through the intravenous administration of crystalloids (0.9% saline solution, Ringer, Ringer lactate) and/or colloids (hydroxyethyl starch [HES], gelatins, human albumin) is a priority measure and represents the first ABTA in the event of significant volume loss due to bleeding or loss of plasma, fluids and electrolytes (usually in the gastrointestinal tract), or internal depletion (redistribution in sepsis). All these solutions can have known or potential adverse effects, depending on the dose and the clinical scenario in which they are used.

The potential risks associated to the administration of HES were considered by a Pharmacovigilance Working Party in September 2008, fundamental on the results of a number of studies. In the VISEP study, the administration of HES 200/0.5 at a concentration of 10% in patients with severe sepsis was associated to an increase in the incidence of acute renal failure and in the need for dialysis versus the group treated with Ringer lactate, and such toxicity was moreover dose dependent.

Two more recent studies have shown that critical patients treated with HES 130/0.4 required dialysis more often than those administered saline solution or Ringer lactate, while mortality after 90 days increased in septic patients and did not change in critical patients. On the basis of the publication of these studies, the EMA started an investigation on the safety problems with HES (November 2012), and called upon a group of experts (April 2013). Drawing upon the conclusions of this group, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended the avoidance of HES in septic patients (May 2013), and subsequently advised its withdrawal from the market (June 2013). In October 2013, the PRAC completed its review of HES solutions, including data from new studies, results of the post hoc analysis of earlier studies, and information supplied by the manufacturers. The PRAC confirmed that HES should not be used for the treatment of septic patients, burn cases or critical patients, due to the increased risk of renal failure and mortality in such individuals.

Safety of colloids

This decision of the PRAC has led to a decrease in the use of HES and of colloids in general, and to the generalized use of crystalloids (see the recommendations of the ESICM, NICE and ESA; Appendix A of the additional material available in the electronic version).

What is the level of evidence supporting limitation of the use of HES solutions? The evidence is fundamentally based on large and randomized trials. However, the administration of colloids in these studies was carried out under clinical trial conditions, which are not applicable to routine practice. Following a critical review of these studies, three editorials came to the same conclusion: following the administration of a wrong fluid, at an inadequate dose, at an inappropriate time and in the wrong patient, it is not surprising to observe adverse effects and complications. The results of the CRISTAL study, comparing the use of colloids (n = 1414) versus crystalloids (n = 1443) in critical patients during the early phase of treatment for hypovolemic shock (without including the administration of maintenance fluids during admission to the ICU), appear to support these opinions: the use of colloids did not modify mortality after 28 days, lowered the risk of mortality after 90 days, and did not increase the risk of needing renal replacement therapy. This finding should be regarded as exploratory, however, and further studies are needed focused on the correction of acute hypovolemia in the early stages of hemodynamic stabilization, which is the strict indication of HES.

Considering the above data, the alert of the EMA on the use of HES, while supported scientifically, may be somewhat precipitated. Rather than closing the issue, which remains the subject of discussion among experts throughout the world, the EMA should have focused on its role as an observer until the scientific community reaches an agreement.

On the other hand, since the benefit of the use of colloids in restoring volemia appears to be unquestionable, the EMA has allowed HES solutions to continue to be used in surgical patients or cases of bleeding critical trauma, considering that the benefit/risk ratio is positive. However, such use is conditioned to the adoption of adequate measures to reduce the potential risks (e.g., evaluating renal function during the three months after the operation), and to the conduction of additional safety studies.

In the meantime, a clinical management algorithm has been recommended for the use of HES in relation to this indication, contemplating the following aspects: (1) strict identification of patients with hypovolemia; (2) restriction of the administration of HES to the initial phase of volume replacement, limiting its administration to an interval of generally less than 6 h from the start of hypovolemia and no longer than 24 h; (3) administration of HES exclusively in patients without pre-existing renal failure or acute renal failure (except if oliguria is due to hypovolemia); and (4) adherence to the authorized maximum dose of each product (for example, ≤30 ml/kg/day in the case of HES 130/0.3), including the volume administered in the operating room.

On the other hand, there are no safety assessments referred to the use of gelatin solutions, despite the fact that they have been employed for many years as volume replacement measure in trauma, surgical and critical patients, and in the emergency care setting. Further studies are therefore needed in this regard.

In relation to human albumin solutions, a recent metaanalysis of randomized studies has not found their administration as part of volume replacement therapy in adult critical patients with sepsis (with or without background hypoalbuminemia) to consistently reduce mortality
versus crystalloid use. This consequently does not support recommendation of the use of such solutions.\textsuperscript{71}

**Safety of crystalloids**

The growing shift from colloids toward crystalloids has led to reconsideration of the safety of the latter. A structured review of the available evidence\textsuperscript{15} has revealed an increased incidence of hyperchloremic acidosis with the use of 0.9\% saline solution and an increase in lactate levels when large volumes of Ringer lactate are administered. Although the available data are limited, in high risk patients the administration of 0.9\% saline solution appears to be associated to increased bleeding and red cell transfusion compared with Ringer lactate. Furthermore, 0.9\% saline solution may also favor the appearance of kidney damage.\textsuperscript{73} The NICE therefore recommends avoiding 0.9\% saline solution when crystalloids are employed, except in specific circumstances.\textsuperscript{64}

**Application of “restrictive” transfusion criteria**

**Background**

In almost all recent randomized, observational and retrospective studies and metaanalyses (come involving hundreds of thousands of patients), ABT has shown an independent association to increased incidences of infection, TEE, myocardial infarction, in-hospital mortality and mortality after 30 days, longer hospital stay, and even an increased risk of cancer relapse.\textsuperscript{74-76}

These disadvantages of ABT have led to proposals to apply restrictive transfusion criteria, versus more permissive or liberal criteria. In this context, the AABB has developed a series of recommendations\textsuperscript{77} of help in deciding “when to consider the need for transfusion”, while the recommendations of the DS2013\textsuperscript{10} which perfectly complement those of the AABB, provide orientation as to “when to transfuse” (Appendix A of the additional material available in the electronic version). Some of these recommendations have been adopted by the Spanish Society of Hematology and Hemotherapy (Sociedad Española de Hematología y Hemoterapia) and the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias [SEMICYUC]) in the context of their participation in the project: Quality Commitment of the Scientific Societies in Spain (Compromiso por la Calidad de las Sociedades Científicas en España) (http://www.msssi.gob.es/organizacion/sns/planCalidadSNS/cal_sssc.htm).

Specifically, the following recommendations have been adopted: “Do not administer more red cell concentrate units than needed to alleviate the symptoms of anemia or for restoring a safe hemoglobin range (7-8 g/dl in stable non-cardiological patients)” (Sociedad Española de Hematología y Hemoterapia); and “Do not administer red cell concentrates to non-bleeding and hemodynamically stable critical patients, without cardiological and/or central nervous system disorders and with a hemoglobin concentration of over 7 g/dl” (Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias).

However, several randomized\textsuperscript{78-81} and observational studies\textsuperscript{82-86} in different clinical contexts have recorded an increase in morbidity-mortality among patients assigned to restrictive transfusion criteria. Although most of these studies were not designed to evaluate safety and lacked the statistical power needed to do so, they cast doubts on whether the systematic application of a series of predefined transfusion thresholds (in practice almost exclusively based on hemoglobin concentration) might increase the risk of infra transfusion (and of delayed transfusion once the need for transfusion is identified), thereby compromising patient safety.\textsuperscript{7}

**Safety of restrictive transfusion criteria**

Since publication of the work of Hebert et al.\textsuperscript{85} in critical patients, many studies have compared restrictive versus liberal transfusion criteria in normovolemic patients in different clinical contexts, and many of them have been analyzed in the DS2013 and ESA guide.\textsuperscript{10,11,76-81,86-91} Almost all of these studies have demonstrated that in comparison with “liberal” transfusion, the application of a “restrictive” criterion lessens the need for ABT and reduces the incidence of infections.\textsuperscript{92} The measure moreover seems to be safe, since no increase in morbidity-mortality or in the duration of hospital stay is observed as a result. On the other hand, the three-year follow-up of elderly patients with hip fracture and a history of important cardiovascular problems in the FOCUS study likewise revealed no differences in mortality rate.\textsuperscript{93}

Nevertheless, it must be remembered that these studies have a series of limitations that complicate their application to routine practice (Appendix A of the additional material available in the electronic version), and that the adoption of restrictive transfusion criteria—while effective in reducing the need for ABT and its possible complications\textsuperscript{94,95}—is not enough. Recently, it has been seen that despite the application of restrictive criteria, those critical and surgical patients that receive transfusions had a poorer clinical outcome than the non-transfused patients.\textsuperscript{96,97}

In order to resolve these issues, and in accordance with the principles of Patient Blood Management, we must shift toward ABT indication focused on the patient, with a view to satisfying his or her individual needs (i.e., “customized” indication).\textsuperscript{98} This will imply a change in paradigm from “restrictive use” to “optimum or adequate use”, transfusing the minimum amount needed to revert the symptoms and signs of hypoxia, or to restore safe hemoglobin levels based on the clinical characteristics of each patient. In many cases, the administration of a single red cell concentrate unit may be a valid option.\textsuperscript{98}

In addition to the mentioned recommendations, we must consider the dynamics/kinetics of postoperative bleeding, the context of the situation and the environment of the patient (degree of monitoring), and the logistic problems in obtaining red cell concentrates “when they are needed” (response time), since it is the responsibility of the medical
team to detect and satisfy the ABT requirements in a timely manner.  

Conflict of interest


Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medine.2015.05.005.

References


43. Meybohm P, Herrmann E, Nierhoff J, Zacharowski K. Aprotinin may increase mortality in low and intermediate risk but not in high risk cardiac surgical patients compared to tranexamic acid and e-aminocaproic acid – a meta-analysis of randomised and observational trials of over 30,000 patients. PLoS ONE. 2013;8:e58009.


53. Sarode R, Milling TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting...