Prothrombin complex concentrates (PCCs) are purified drug products with hemostatic activity derived from a plasma pool. Today, PCCs contain a given and proportional amount of four non-activated vitamin K-dependent coagulation factors (II, VII, IX, and X), a variable amount of anticoagulant proteins (proteins C and S, and in some antithrombin) and low-dose heparin. In some countries PCC products contained only three clotting factors, II, IX, and X. Dosage recommendations are based on IU of F-IX, so that one IU of F-IX represents the activity of F-IX in 1 mL of plasma. Reversion of the anticoagulant effect of vitamin K antagonists (VKAs) in cases of symptomatic overdose, active bleeding episodes, or need for emergency surgery is the most important indication for PCCs and this effect of PCCs appears to be more complete and rapid than that caused by administration of fresh frozen plasma. They may be considered as safe preparations if they are used for their approved indications at the recommended dosage with adequate precautions for administration, and have been shown to be effective for reversing the effect of VKAs. Their adequate use based on decision algorithms in the perioperative setting allows a rapid normalization of International Normalized Ratio (INR) for performing emergency surgery, minimizing bleeding risk. This review aims to propose two algorithms for to use the PCCs in the perioperative setting, one to calculate the PCCs dose to be administered in a bleeding patient and / or immediately before urgent surgery, based on patient’s clinical status, prior INR and INR target and another for reversing the action of oral anticoagulants depending on urgency of surgery. (Minerva Anestesiol 2011;77:1-2)

Key words: Prothrombin complex concentrates - Blood coagulation factors - Hemorrhage - Algorithms.
been expanded in recent years. This, together with the increased life expectation, has markedly risen the number of patients treated to approximately 700000 in Spain, which represents approximately 1.3% of the total population. The most significant complication derived from chronic anticoagulation is severe hemorrhage, whose incidence is variable, but may range from 0.9 and 1.35/100 patient/year. Among them, it is necessary to highlight the incidence rate of intracranial hemorrhage and fatal bleeding, which range from 0.46 and 0.7/100 patient/year and from 0.25 and 0.3/100 patient/year respectively. Factors related to an increased risk of bleeding include anticoagulation intensity, variability, and duration; age; patient comorbidity; and concomitant treatments. Risk of bleeding significantly increases when INR (international standardized ratio) is 4.5 or greater. PCCs have also been used to correct both congenital and acquired deficiencies of specific factors (particularly II and IX), and their use in perioperative management of massive bleeding is becoming widespread even in non-anticoagulated patients, particularly when availability of FFP is limited. Unfortunately, there are no controlled clinical trials that allow for making recommendations to support use of PCCs for indications not listed in the prescription information, and most of these recommendations are based on retrospective, observational studies, in clinical cases, or in expert recommendations.

This document reviews the different PCCs available in our setting, their established and potential indications, their dosage, adverse effects, and precautions to be considered when used in

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Description</th>
<th>Benefits vs. risk and burdens</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptional strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risk and burden, or vice versa</td>
<td>RCTs with important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate quality evidence</td>
<td>Benefits closely balanced with risk and burden, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptional strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits and burden; benefits, risk and burden may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
the perioperative period. When scientific evidence is available, this will be provided using the GRADE methodology,11 recommending (Grade 1) or suggesting (Grade 2) the use of PCCs based on whether the degree of evidence in the available literature is strong (A), moderate (B) or low (C) (Table I).

Characteristics

PCCs started to be used for clinical purposes in the early 1970s as a source of F-IX for treating patients with type B hemophilia. They were obtained using the Cohn fractionation technique or calcium absorption of plasma. Since they were initially used in 1976 to successfully revert excess anticoagulation secondary to VKAs,12 PCCs have been effectively used for restoring hemostatic competence in patients anticoagulated with these drugs. These agents are enriched in prothrombin and factors VII, IX, and X, and also contain trace amounts of factors VIII, VIIa and IXa. However, the specific content of each clotting factor, particularly FVII, varies by concentrate. The anticoagulant vitamin K-dependent factors protein C and protein S are also present at variable concentrations.13 Over time, both composition and preparation of PCCs have evolved to make them more effective and safe for administration.

Approximately 15 preparations are currently marketed worldwide, but in our setting there are three commercial PCC preparations available (Prothromplex NF-/Baxter SL, Beriplex-CSL Behring, and Octaplex-Octapharma SA). These are very similar but not identical, each having some different characteristics (Table II). Clinical use of all of them is practically superimposable, and there is no evidence of superiority of one over another. The Summaries of Product Characteristics of the PCCs available in Spain may be consulted at the website of the Spanish Agency for Medicinal Products and Medical Devices (www.emps.es).

Today, PCCs contain a given and proportional amount of four non-activated vitamin K-dependent coagulation factors (II, VII, IX, and X), a variable amount of anticoagulant proteins (proteins C and S, and in some antithrombin) and low-dose heparin (Table II).13 Dosage recommendations are based on IU of F-IX, so that one IU of F-IX represents the activity of F-IX in 1 mL of plasma.

All four factors provided by PCCs are essential for the hemostatic process. Thus, the tissue factor/factor VIIa complex that activates factors IX and X is produced during the starting phase of the coagulation process. The formed F-Xa generates a small amount of thrombin (by activation

### Table II.— Contents in coagulation and anticoagulant factors of fresh frozen plasma and prothrombin complex concentrates marketed in Spain (data in IU/mL).

<table>
<thead>
<tr>
<th>Factor</th>
<th>FFP (*) (IU/mL)</th>
<th>PROTHROMPLEX INF (IU/mL)</th>
<th>BERIPLEX (IU/mL)</th>
<th>OCTAPLEX (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-II</td>
<td>1</td>
<td>30</td>
<td>20-48</td>
<td>11-38</td>
</tr>
<tr>
<td>F-VII</td>
<td>1</td>
<td>25</td>
<td>10-25</td>
<td>9-24</td>
</tr>
<tr>
<td>F-IX</td>
<td>1</td>
<td>30</td>
<td>20-31</td>
<td>25</td>
</tr>
<tr>
<td>F-X</td>
<td>1</td>
<td>30</td>
<td>22-60</td>
<td>18-30</td>
</tr>
<tr>
<td>Protein C</td>
<td>1</td>
<td>&gt;20</td>
<td>15-45</td>
<td>7-31</td>
</tr>
<tr>
<td>Protein S</td>
<td>1</td>
<td>14-16</td>
<td>13-26</td>
<td>7-32</td>
</tr>
<tr>
<td>AT</td>
<td>1</td>
<td>0.75-1.5</td>
<td>9.2-1.5</td>
<td>-</td>
</tr>
<tr>
<td>Heparin</td>
<td>-</td>
<td>15.5</td>
<td>0.4-2.0</td>
<td>5-12.5</td>
</tr>
<tr>
<td>Viral inactivation/elimination</td>
<td>MB</td>
<td>Steam treatment</td>
<td>Pasteurization</td>
<td>Solvent-detergent</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Nanofiltration</td>
<td>Nanofiltration</td>
<td>Nanofiltration</td>
</tr>
</tbody>
</table>

FFP: fresh frozen plasma; MB: Methylene blue; AT: Antithrombin.
(* By definition, FFP consists of 1 IU/mL of each of the stable and labile coagulation factors (+/-25%), except for fibrinogen.
(Prothrombin complex concentrate data based on manufacturer information and on the labels of the different products available at www.agemed.es)
of prothrombin) that amplifies and propagates the procoagulant signal until the so-called prothrombinase complex (Xa and Va, phospholipids and calcium) is formed. This complex induces quick and effective formation of large amounts of thrombin and, subsequently, fibrinogen at the endothelial lesion site.14, 15

Following administration, a rapid (within 30 minutes) and sustained correction occurs of hemostatic changes secondary to deficiency of vitamin K-dependent coagulation factors, leading to normalization (≤1.3) of the international standardized ratio (INR) of prothrombin time if an adequate dose has been given.16, 17 INR stands for International Normalized Ratio and it’s really just the standard unit used to report the result of a PT test. In the 1980s the World Health Organization determined that patients may be at risk because the results of a PT test would vary from one laboratory to another. In order to standardize the results between labs, the INR was created. The INR, unlike PT, takes into consideration the sensitivity of the thromboplastin reagent and has accepted therapeutic limits for different anticoagulation indications.

The INR is calculated from the following formula: INR = (Patient PT/Normal PT)ISI

Normal PT is obtained by averaging the PTs of a group of healthy individuals not taking medications. The International Sensitivity Index (ISI) is provided by the manufacturer of the thromboplastin and is lot specific and somewhat instrument dependent. On normal conditions of coagulation, the INR is around 1 and the INR range will vary from person to person depending on a variety of factors. The most common INR target range for someone on warfarin is somewhere between 2.0 and 4.0. INRs of 5 or more typically are avoided because the risk of bleeding increases significantly at INRs above 5.18

This reversing effect of PCCs appears to be more complete and rapid than that caused by administration of FFP. It should be noted that the reversing action of FFP on INR is dose-dependent but not linear: standard doses of FFP (15-20 mL/kg) achieve a significant INR reduction, but the normal range19 is not usually achieved. However, complete normalization of these values would require provision of a greater volume of FFP (close to 30 mL/kg), which represents in practice a plasma volume replacement.20, 21 Although there are various factors influencing this effect, one of the most important is variability in the concentration of coagulation factors present in FFP, which may experience a loss of factors close to 25% during the inactivation process. Loss of factors related to storage at -30ºC, particularly in the long term, should also be considered.22 One unit of PCC usually has a concentration of coagulation factors per volume unit approximately 25-30 times greater than FFP (Table II), which means that a 600 IU vial of PCC is equivalent to approximately 600 mL of freshly drawn, unmanipulated plasma. Differences between PCCs and FFP may be summarized by saying that PCCs provide a more complete reversing effect, allow for immediate availability (they do not require blood typing or thawing as FFP), are safer because they do not induce transfusion-related acute lung injury (TRALI) and are administered faster (their volume is much smaller than their FFP equivalent).

This last feature is very useful in pediatric and neonatal patients who have a limited total blood volume and high risk of overload, although in the prescription information appears there is no experience in children (Beriplex®) or they has not been used in cerebral hemorrhage in neonates with deficiency of vitamin K (Octaplex®). In general, in the children the experience of use is insufficient, but it’s true that the specific factors should be used in cases of selective deficits, if they are available (Table III).21-23

### Indications

**Accepted indications**

Administration of PCCs is indicated for:

1) prophylaxis and treatment for bleeding in patients with congenital deficiencies of factors of the prothrombin complex (factors II, VII, IX, and X) in the absence of specific factors (recommendation 1B);

2) prophylaxis and treatment of bleeding in patients with acquired deficiencies of factors of the prothrombin complex (overall recommendation in this indication 1B).
Reversion of the anticoagulant effect of VKAs in cases of symptomatic overdose, active bleeding episodes, or need for emergency surgery is the most important indication for PCCs.\textsuperscript{1,2,24-27} Leissinger \textit{et al.}\textsuperscript{28} conducted a systematic review of 14 studies. Half of these were retrospective in nature, and only one enrolled more than 100 patients. In most of them, PCCs were administered for major bleeding in patients under treatment with VKAs (three studies for intracranial hemorrhage) or for urgent reversion of the anticoagulant effect. The following conclusions could be drawn:

- Administration of PCCs to patients treated with VKAs rapidly reversed (within 30 min) the anticoagulant action to achieve an INR less than 1.3 in most patients, decreasing or stopping bleeding, hematoma volume in intracranial hemorrhage, and transfusion rate. We therefore recommend use of PCCs for this indication (1B).

- The reversing effect of PCCs was faster and more complete than that achieved with FFP, because doses close to 25-30 mL/kg of FFP are required to cause an effect similar to PCCs, and such doses may cause complications related to volume overload. We therefore recommend administration of PCCs instead of FFP when immediate reversion of the effect of VKAs is required (1B).

- A comparison of PCCs to vitamin K again confirmed the faster action of PCCs for reversing the anticoagulant effect. However, use of PCCs without concomitant vitamin K administration is associated to a decreased plasma activity of dependent factors from 6-8 h post-administration. This is because both warfarin and acenocoumarol have a longer half-life than factors present in PCCs. We therefore recommend concomitant administration of PCCs with vitamin K for reversing VKAs (1B).

- A 500-600 IU dose of PCC (approximately 10 IU/kg) may be effective for reversing an INR <5, but individualization of the dose based on weight and initial INR is recommend in all patients (1B).

### Potential indications

#### Unavailability of FFP

When fresh plasma is indicated but not available, use of PCCs is recommended (1B). In patients who refuse transfusion of FFP, PCCs may be an alternative.

#### Risk of hypervolemia

As noted above, the dose needed for adequate reversion of the anticoagulant effect of VKAs may require administration of a substantial volume when FFP is used (up to two liters in an average adult patient), which may be associated with complications related to volume overload.\textsuperscript{29} We suggest use of PCCs in patients who require a supply of factors and have a risk of volume overload (2C).

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### Table III.—Differences between fresh frozen plasma and prothrombin complex concentrates.

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>PPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume to be administered</td>
<td>Large (approximately 30-fold greater)</td>
<td>Small</td>
</tr>
<tr>
<td>Availability</td>
<td>Minimum 30 min</td>
<td>Immediate</td>
</tr>
<tr>
<td>Administration rate</td>
<td>Slow</td>
<td>Fast (*)</td>
</tr>
<tr>
<td>Viral inactivation</td>
<td>Methylene blue</td>
<td>Two steps</td>
</tr>
<tr>
<td>Specific blood group</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of TRALI</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypocalcemia by citrate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thrombogenicity risk</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor content</td>
<td>All</td>
<td>II, VII, IX, X</td>
</tr>
</tbody>
</table>

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; TRALI: transfusion-related acute lung injury.

(*) Infusion rate varies for the different PCCs, with accepted rates of 3 mL/min for Octaplex, 5 mL/min for Prothromplex NF, and a maximum of 8.4 mL/min for Beriplex.)
Massive bleeding

PCCs have been used off-label for massive bleeding in patients undergoing prior cardiac, vascular, or other surgery.\textsuperscript{30, 31} Administration of PCCs in patients not responding to infusion of FFP, platelets, and cryoprecipitates allowed for achieving an adequate hemostasis in 78\% of cases, with a concomitant reduction in transfusion needs.\textsuperscript{32} Use of PCCs in multiple trauma patients with massive bleeding has also been proposed, and although use in such conditions is increasing, no randomized studies allowing for advising routine use of PCCs in these patients are available.\textsuperscript{33-35} We therefore suggest use of PCCs in massive bleeding as a complement to FFP (2C).

Management of overdoses of direct anticoagulants (dabigatran, rivaroxaban, apixaban)

Some animal studies have shown that administration of activated PCC (Feiba®-Baxter SL) reverses the anticoagulant effect of direct thrombin inhibitors (DTI) or anti-FX agents.\textsuperscript{36} However, there are currently no specific antidotes for direct antagonists of factors Xa or IIa. The existing recommendations are based on reports from experts or manufacturers themselves advising conservative measures, because of the short life of these compounds. Such measures may include administration of neutralizers (activated charcoal, gastric lavage) in the event of an overdose. Monitoring of thrombin, ecarin, or activated partial thromboplastin times may be used as a guide of the pharmacological effect.\textsuperscript{37} Management of severe hemorrhage related to administration of direct anticoagulants should consist of replacement with adequate blood products. Use of FFP, PCCs, activated PCCs, or FVIIa may be warranted, but there are no specific recommendations in this regard.\textsuperscript{38-40} FEIBA (an acronym for Factor Eight Inhibitor Bypassing Activity) anti-inhibitor coagulant complex (Baxter Bioscience, Vienna, Austria) was the first activated PCCs developed and manipulated \textit{ex vivo} to increase the content of activated clotting factors, especially FVIIa. FEIBA contains factors II, IX and X mainly non-activated and activated factor VII and at present, is the only one product available to control bleeding in hemophilia patients affected by high titre inhibitors to FVIII or FIX. The drug’s mechanism of action is now believed to be dependent on its content of prothrombin and FXa. The vial potency labelling is in arbitrary units of FVIII inhibitor bypassing units, where one unit of FEIBA shortens the activated partial thromboplastin time (aPTT) of high-titre FVIII reference plasma to 50\% of the blank value. Empirically, FEIBA is administered at doses of 50–75 units/kg every 8–12 h, with a recommended maximum daily dose of 200 units/kg.

For this potential indication, we suggest use of PCCs in the context of bleeding related to direct anticoagulants (2C), and recommend that they are not used as antidotes of direct anticoagulants (1C).

Severe liver failure

In patients with severe or fulminant liver failure in whom an invasive procedure is required, we suggest use of PCCs as a complement to other hemostatic drugs (2C).

Conditions for which use of PCCs is not recommended: prior allergic reactions to the compound; pregnancy or puerperium (except in life-threatening situations); patients with high risk of thrombosis. Thrombotic complications, including venous thromboembolic disease (VTD) and disseminated intravascular coagulation (DIC), as well as other microvascular thromboses and acute coronary syndrome (ACS), have been reported to occur in relation to administration of PCCs. Such complications were mainly, but not only, reported with administration of high doses (>200 IU/kg/day) and particularly in patients with severe liver disease (usually associated with antithrombin deficiency). To prevent these complications, current PCC preparations include heparin and antithrombin or protein C in their composition.\textsuperscript{5, 41}

Active or recent acute thrombotic event

Particularly in patients with a recent history (in the three months prior to administration) of any thrombotic event (acute coronary syndrome (ACS), stroke or VTD),\textsuperscript{41}
Disseminated intravascular coagulation

In DIC there is a dreadful combination of thrombotic events and bleeding diathesis. Treatment is based, among other measures, on administration of heparin in patients with clinical signs of thrombosis, and FFP and platelets in the event of bleeding. In these patients, administration of PCCs is not advised due to the procoagulant capacity of the product, except in life-threatening situations and in those where replacement of deficient coagulation factors by FFP is not sufficient or feasible. Under these circumstances, antithrombin and/or heparin should preferably be administered before PCCs.28

Patients with a history of heparin-induced thrombocytopenia

PCC preparations contain very small amounts of heparin that could theoretically trigger HIT. No case has been reported to date.1

Side effects

PCCs are prohemostatic drugs and have therefore a potential to cause thromboembolic events. While their administration for approved indications is considered to be safe in most cases, some thromboembolic events have been reported, including stroke, ACS, DIC, or VTD. Their actual incidence is not well documented and is reported to be approximately 2%, but this data should be analyzed in the context of the high thrombotic risk of patients usually treated with VKAs who require reversion with PCCs.5 The increase in the risk of occurrence of thrombotic episodes would also be related to the dose of PCC administered, and a maximum dose of 30 IU/kg appears to be safe.42 However, in a series where doses greater than 40 IU/kg were used, no thrombotic complications were reported.43

Virus inactivation and/or eradication procedures are used in the manufacturing process of PCCs (Tables II, III). While the possibility of transmission of infectious agents cannot be ruled out completely, PCCs should be considered a safe treatment in this regard.

Dosage

The most adequate dose of PCCs has not been fully elucidated yet. However, as discussed above, PCC dosage should be individualized to maximize effectiveness, safety, and cost-effectiveness, taking into account that hemostatic competence is achieved with a plasma concentration of coagulation factors of approximately between 30-40%.3, 18, 19, 44 The optimal dose should be calculated based on the following factors: clinical status, prior INR, target INR, and weight of the patient. The duration and administration interval of the total calculated dose must be established based on the clinical and laboratory criteria of each individual patient, avoiding overcorrection, which is not necessary for many surgical procedures and may increase thrombotic risk of the patient.

Based on these considerations and data from the literature for this review, we propose two methods, as an algorithm to calculate the dose that we administered (Figure 1) according to target INR, the patient's weight, bleeding risk and the percentage of clotting factors to INR. And the other proposal (Figure 2) is to be applied to patients with VKAs treatments that require different types of surgery and according to severity. The following method, modified from a proposal by Schulman45, with three successive stages (Figure 1), could be used as a guide to calculate the dose to be administered:

1. Define the target INR, which will be determined by the thrombotic-hemorrhagic risk balance in each patient. Thus, in patients with a high thrombotic risk and a moderate hemorrhagic risk, total correction of INR to maintain levels ranging from 1.5-2 may not be required.

2. Conversion of INR in a proportion of coagulation factors (expressed as a percentage of normal plasma). Thus, for instance, an INR ranging from 4 to 4.9 implies a concentration of approximately 10% of normal value.

3. Calculation of total dose of PCC to be administered. The following formula is used to calculate this: (target percentage of factors – prior percentage of factors) x patient body weight (kg) = IU of PCC. Thus, if an 80-kg patient has an initial INR of 4 (10% of factors) and the target
If the surgery is elective or if it is delayed more than 24 hours, prior suspension of anticoagulant therapy (including bridging anticoagulant therapy with low molecular weight heparin) and the administration of vitamin K should be sufficient. Protocol shown in Figure 2 proposes an algorithm for management and use of PCCs when reversion of the effect of VKAs is needed for "elective", "urgent deferrable", or "urgent-emergent" surgery.

In the case of a life-threatening hemorrhage (e.g. intracranial hemorrhage), empiric administration at doses of 25-50 IU/kg should not be delayed waiting for the INR result.\textsuperscript{27}
whom PCCs are indicated to reverse the effect of VKAs, bridging anticoagulation therapy should be started from 24 hours after surgery in the absence of active bleeding, with individualized assessment of thrombotic and hemorrhagic risk in each patient.46

Conclusions

PCCs are medical products containing various coagulation factors. They may be considered as safe preparations if they are used for their approved indications at the recommended dosage with adequate precautions for administration, and have been shown to be effective for reversing the effect of VKAs. Their adequate use based on decision algorithms in the perioperative setting allows a rapid normalization of INR for performing emergency surgery, minimizing bleeding risk. In patients with active bleeding related to treatment with VKAs, their administration effectively controls bleeding. PCCs have also been

Figure 2.—Decision algorithm for reversing the action of oral anticoagulants depending on urgency of surgery.
used in bleeding patients with no VKA administration, in whom improvement on coagulation parameters could be associated with a significant better clinical evolution. In the future, this indication may be added to the current ones, and PCCs may be part of the management and control protocols for bleeding patients, either due to multiple traumas or to any other condition.

References

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Conflicts of interest. None of the authors has any conflict of interest.

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