Rethinking blood components and patients: Patient blood management. Possible ways for development in France

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Introduction

Despite infectious and immunological serious adverse reactions, now better known and prevented, transfusion of blood components, particularly red blood cells (RBC), has a therapeutic index higher than many current medicines [1]. Many patients benefit from transfusion of blood components. However, the development of knowledge of the physiology of anaemia, tissue
oxygenation and compensatory mechanisms in critically ill patients [2], has triggered prospective randomised clinical trials comparing liberal and restrictive modes of transfusion in various clinical conditions [3]. Combined with better awareness of transfusion risks and growing economic constraints, the results of these clinical trials led to review transfusion therapy as part of a patient-centred therapeutic strategy, the so-called patient blood management (PBM). This overarching view aims to optimise the transfusion strategy and to adapt it to each patient [4,5]. Its ongoing development, which also appears as a re-emergence of well-known basic transfusion medicine principles, is inducing a review of the organisation of the transfusion chain, impacting all stakeholders and institutions involved in this chain: patients, donors, physicians, nurses, hospitals, blood establishments, national competent authorities, healthcare providers. The objective of this review is to present updated scientific basis of PBM, its current state of development in Europe, to suggest ways to explore for its development in France, and propose to integrate PBM in a wider and coordinated approach of the blood supply management.

**Scientific basis of PBM**

Scientific basis of PBM first lays on controlled clinical trials comparing clinical outcomes between strategies using a higher (liberal) vs. lower (restrictive) haemoglobin/hematocrit threshold for RBC transfusion in different clinical settings. A recent Cochrane evidence-based meta-analysis summarizing 19 randomised controlled clinical trials involving more than 6000 patients, has compared clinical outcomes between strategies based on higher haemoglobin thresholds (9.0–13.3 g/dL) and lower haemoglobin thresholds (7.0–10.0 g/dL) for red blood cell (RBC) transfusion [3]. A lower haemoglobin threshold for transfusion was associated with reduced RBC transfusion (mean difference: 1.19 units per patient; 95% CI: 1.85 to 0.53), resulting in a haemoglobin concentration significantly less at the end of the studies (mean difference: 1.48 g/dL; 95% CI: 1.92 to 1.03), without any apparent harm to the patients. The relative risk for 30-day all-cause mortality was lower in patients with anemia transfused at lower haemoglobin threshold: 0.85 (95% CI: 0.70 to 1.03), but this difference did not reach statistical significance. A more recent systematic review, with meta-analyses and trial sequential analyses of 31 randomised clinical trials totalling 9813 randomised patients, has confirmed these results [6]. The authors concluded that, compared with liberal strategies, restrictive transfusion strategies were associated with a reduction in the number of red blood cell units transfused and number of patients being transfused, but mortality, overall morbidity, and myocardial infarction seemed to be unaltered. And although this has to be considered with caution, given the high risk of biases because of confounding factors, consistent with clinical trial data, in a large retrospective cohort study, more restrictive transfusion practice did not appear to impact 30-day mortality [7]. However, for cardiac surgery, performed on patients who are vulnerable to ischemic complications, a recent clinical trial [8] have showed that there were more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio: 1.64; 95% CI: 1.00 to 2.67; \( P = 0.045 \)). Overall, available evidence seems to be strong enough to strongly recommend adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients [9]. The initiators of the clinical trials comparing liberal and restrictive transfusion strategies have recently called for adopting a transfusion threshold of 7 g per deciliter as the standard of care in all critically ill patients [10]. In hospitalized patients with preexisting cardiovascular disease, transfusion for patients with symptoms or a haemoglobin level of 8 g/dL or less should be considered [9]. For patients with coronary heart disease, and particularly an acute coronary syndrome, evidence still remains weak [10], and patients might benefit from higher haemoglobin concentrations [4,9]. This approach seems to be compatible with a recent investigation of the underlying evidence of guidelines recommending a more restrictive haemoglobin threshold [11]. The investigators called for guaranteeing methodologic quality in future RBC transfusion guideline development to ensure that the best available evidence is captured when recommending restrictive transfusion strategies.

By contrast, in a retrospective cohort study analyzing data from more than 225,000 patients, preoperative anaemia, even to a mild degree, has been shown independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery [12]. This first calls for detecting and managing preoperative anaemia in patients scheduled for elective surgery. But it also contributes to raise the questions of how low to go in the reductions of RBC use and how to make sure that reducing over transfusion does not go too far and lead to undertransfusion and potential harm [13]. A retrospective survey conducted in France [14] had suggested that morbidity related to delayed or absent blood transfusion might have been responsible for around 100 estimated perioperative deaths in the year 1999 in France. A recent study conducted in one academic medical centre in England during a one-month period [15] reached very different conclusions. No patient identified with low Hb reading (< 6 g/dL) or low platelet count (< 10 \( \times 10^{9} /L \)) could be found as inappropriately
undertransfused. Furthermore, two retrospective cohort studies of patients who declined blood transfusion for religious reasons [16,17] concluded independently that the risk of death was low in patients with postoperative Hb levels of 7 to 8 g/dL, but the odds of death in patients with postoperative Hb levels ≤ 8 g/dL increased 2 to 2.5 times for each gram decrease in Hb and became extremely high below 5 to 6 g/dL. Although integrating the monitoring of undertransfusion and overtransfusion in haemovigilance programmes would help getting a better picture, overall, available evidence tends to indicate that the new proposed standards of care for RBC transfusion threshold [4,9,10] could be considered as safe enough to avoid the risks of undertransfusion. Of note, no test has been found so far to predict which patients will benefit from RBC transfusion and transfusion decisions should continue to rely on evaluation of the individual patient by skilled clinicians at the bedside who use Hb concentration as no more than a helpful guide [2,9].

The large variation of RBC use is another element favouring the implementation of restrictive transfusion policies and PBM. Thus, in 2010, the RBC use per 1000 population varied in Europe from 20 to 60 (figure 1, adapted from ref. [18]). Although implementation of restrictive transfusion policies is inducing a decreasing trend in RBC use in many developed countries [19], more recent data showed persisting wide variations in RBC transfusion use, in Europe (figure 2, ref. [20]) and worldwide [5]. Most probably, differences in clinical conditions could not represent the only factor explaining these wide variations between countries. Comparisons of RBC consumption between prescribers for a given clinical condition have shown important differences [21,22]. And where it has been investigated, overtransfusion has been clearly documented [5].

This basis, strengthened by numerous years of experience in transfusion medicine, have led to develop restrictive transfusion policies and alternatives to transfusion as ways to optimise the treatment of patients needing transfusion, defined in good practices/recommendations for PBM [4,23-26]. They are founded on three pillars:

- optimise the patient’s own blood supplies (blood volume and red cell mass);
- minimise blood loss;
- optimise patient’s tolerance of anaemia [4,27-29].

These three pillars, initially conceived for elective surgery (table I), can be extended and adapted to all other clinical conditions in which transfusion therapy can be indicated. Based on these principles, in patients with blood loss and/or anaemia, a number of methods/procedures should be considered to optimise the management of the patient. The following examples illustrate this wide therapeutic panel:

- detection of anaemia, identification of underlying causes and management of anaemia (e.g. correction of iron deficiency);
- reduction of patient blood sampling;
- surgical haemostasis and “bloodless” surgical procedures;
- intraoperative and postoperative cell salvage;
- monitoring of coagulation abnormality by point-of-care rotational thromboelastography;
- medications to minimize bleeding;
- avoidance of drug interactions which worsen anaemia;
- optimisation of cardiac output, ventilation, oxygenation;
- computerised prescriber order entry for blood products;
- “single unit” transfusion policy for hemodynamically stable non-bleeding patients.

Assessment of structured PBM programmes involving a multidisciplinary approach, education of clinical staff including new protocols relating to the management of anemia/blood loss, and peer review (benchmarking) of practices and clinical outcomes, has shown a significant reduction of blood component
use [29] and consequently significant cost reductions [19]. However, the cost-effectiveness of PBM still needs to be assessed objectively. Such economical studies have been limited so far. One prospective, randomized, controlled trial included 683 patients with a preoperative Hb level between 10 and 13 g/dL undergoing hip and/or knee arthroplasty [30]. Enrolled patients were randomized for erythropoietin or not, and subsequently for autologous reinfusion by cell saver or postoperative drain reinfusion devices or for no blood salvage device. Erythropoietin was found to significantly reduce the number of patients requiring the use of erythrocyte transfusion (19% with erythropoietin and 29% without), but not the amount of erythrocytes transfused. Erythropoietin increased costs by €785 per patient (€7300 per avoided transfusion). Autologous blood salvage devices were not effective in sparing erythrocyte transfusion. These results emphasise the importance of cost-effectiveness assessment before decision-making regarding costly PBM tools.

**PBM in Europe**

A first survey of PBM implementation in Europe has showed considerable variations from country to country [31], but its recent development through nationwide PBM programs [23–26,32], as recommended in a World Health Assembly Resolution [33], most probably explains the remarkable decreasing trend of RBC consumption observed in Europe (and in many developed countries all over the world) since 2012-13. At the European Union (EU) level, two projects on PBM have been launched early 2014. The Austrian Institute of Technology has been awarded a contract to develop “Good Practices in the Field of Blood Transfusion” by the Consumers, Health and Food Executive Agency of the European Commission [34]. This European PBM project gathers leading experts and involved clinicians in five teaching hospitals in the EU (Austria, Croatia, Denmark, Germany, Portugal). They are expected to publish an “EU Guide for Member States on Good Practices for PBM” in 2016. The Patient Blood Management in Europe (PaBloE) project coordinated by the European Blood Alliance gathers experts from teaching hospitals and related blood establishments in seven EU countries (Denmark, Germany, Italy, Malta, the Netherlands, Sweden, United Kingdom). The objectives of the PaBloE project are as follows:
- to derive good practices in PBM on focused indications from experience and expertise in the participating PaBloE teams and ways to develop their implementation in PaBloE participating teaching hospitals;
- to promote a patient centred approach, in shifting focus from blood product to patient needs;
- to conceive action plans easy, quick and cheap to implement, to cope with current financial constraints.

**Figure 2**

Red blood cells, fresh frozen plasma and platelets (units) transfused per 1000 population, by country (from reference [20]). Consumption in France was 36.9 in 2014.
First outcomes from three surveys on PBM topics have been made available in 2015. The survey on top indications for RBC use showed that two-third of RBC transfusions were given for medical indications and haematology accounted for 30% of total RBC transfusions [35]. The survey on PBM organisations and activities showed variable implementation amongst the participating teaching hospitals [36]. The survey on PBM knowledge by involved clinicians showed some need for improvement, mainly for the management of preoperative anaemia [37]. From these results, the PaBloE project is currently focusing respectively on PBM practices in haemat-oncological patients and preoperative anaemia management practices in surgical patients. The experience gained by both projects could certainly be helpful in European countries, including France (and other countries outside the EU as well).

### PBM in France: possible ways to explore

Although most probably many clinicians individually apply some PBM principles, to the best of our knowledge at this time, effective hospital PBM programmes are still rare in France and there is no national PBM programme. One may wonder if this could contribute to explain, at least partly, why RBC use per 1000 population stayed almost steady in the past few years (36.6 in 2010, 36.2 in 2015), while the decrease went to lower rates in countries with active national programme for implementation of transfusion guidelines, covering important aspects of PBM.

#### Table 1

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Optimise the patient’s own blood supplies (blood volume and red cell mass)</th>
<th>Minimise blood loss</th>
<th>Optimise patient’s tolerance of anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detect anaemia, identify underlying causes, manage to correct anaemia (further evaluation if necessary)</td>
<td>Identify and manage bleeding risks</td>
<td>Compare estimated blood loss with patient specific tolerable blood loss</td>
</tr>
<tr>
<td></td>
<td>Consider erythropoiesis stimulating agents (ESA) if nutritional anaemia rules out/treated</td>
<td>Review medications (antiplatelet, anticoagulation therapy)</td>
<td>Assess/optimise physiologic reserve (e.g. cardiac &amp; pulmonary functions)</td>
</tr>
<tr>
<td></td>
<td>Time elective surgery after management of anaemia</td>
<td>Minimise volume and number of blood samples</td>
<td>Formulate patient specific management plan using appropriate blood conservation modalities to manage anaemia</td>
</tr>
</tbody>
</table>

#### Intraoperative

<table>
<thead>
<tr>
<th>Blood conservation measures</th>
<th>Meticulous haemostasis and surgical techniques</th>
<th>Optimise cardiac output, ventilation, oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications to minimise bleeding</td>
<td>Blood-sparing surgical techniques e.g. cell salvage/reinfusion</td>
<td>Blood conservation measures</td>
</tr>
<tr>
<td>Blood conservation anaesthetic strategies e.g. acute normovolemic hemodilution</td>
<td>Restrictive transfusion strategies</td>
<td></td>
</tr>
<tr>
<td>Medications to minimise bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Postoperative

<table>
<thead>
<tr>
<th>Manage nutritional/correctable anaemia (e.g. folate, iron deficiencies)</th>
<th>Monitor and manage bleeding and anticoagulant treatments</th>
<th>Maximise oxygen delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA therapy if appropriate</td>
<td>Maintain normothermia (unless hypothermia indicated)</td>
<td>Minimise oxygen consumption</td>
</tr>
<tr>
<td>Avoid drug interactions which worsen anaemia</td>
<td>Autologous blood salvage</td>
<td>Blood conservation measures</td>
</tr>
<tr>
<td>Medications to minimise bleeding</td>
<td></td>
<td>Avoid/treat infections promptly</td>
</tr>
<tr>
<td>Minimise volume and number of blood samples</td>
<td>Restrictive transfusion strategies</td>
<td></td>
</tr>
</tbody>
</table>
Coordinated approach of the transfusion chain

A patient-centered vision has led to conceive transfusion medicine activities as a blood supply chain, starting with the patients’ needs and ending with the transfusion of blood components needed by the patients. A working group of the European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) of the Council of Europe (CoE) has studied the management of the supply chain, focusing on RBC. It consists of two main areas, hospitals, where the transfusion is prescribed by clinicians and administered to patients, and blood establishments, acting from donor management to the distribution of RBC. The CoE working group defined the supply chain of RBC as a genuine process comprising the following steps [40]:

- assess past hospital RBC use for patients;
- establish a forecast for overall annual supply (BEs) and use (hospitals);
- establish annual blood collection program (BEs);
- weekly balance RBC use and supply in both BEs and hospitals;
- review the patients’ RBC needs and their satisfaction, and regularly adapt transfusion strategies and supply by integrating the evolution of knowledge.

As such, this process was used as a basis to develop a self-assessment questionnaire to evaluate each stage of the RBC supply process in any country. The combined use of the questionnaire with a SWOT analysis (strengths, weaknesses, opportunities, threats) as a self-assessment tool of the state of the supply chain within a given country, enabling to derive improvement measures and evaluate their effectiveness, has been validated by 12 countries (Australia, Estonia, Finland, France, Ireland, New Zealand, Netherlands, Portugal, Romania, South Africa, United Kingdom). The use of these tools has been extensively discussed in a symposium organised by the European Directorate for the Quality of Medicines and HealthCare [41]. The self-assessment questionnaire and method are available at http://www.isbtweb.org/working-parties/blood-supply-management/questionnaire-and-method-to-assess-and-improve-blood-supply-management-bsm/.

The exchange of information between hospitals and BEs has frequently appeared as the weak link in the blood supply chain management. Conversely, an effective national coordination of the blood supply chain could be observed in several countries, whatever their organisations. An information system that covers the entire chain from donor to recipient (“vein to vein”) has proved of great importance to achieve such national coordination [42].

Conclusions

Optimising the use of blood and blood components through patient-centered PBM programs, improving the effectiveness and efficiency of the blood supply chain, improving donor management in adapting it to the needs of the patients, and coordinating these activities will certainly be key challenges for the tomorrow’s transfusion medicine. Developing multidisciplinary PBM programmes both at hospital and national levels should be considered as a way forward to optimise the transfusion therapy for the primary benefit of the patients, and as such should be strongly encouraged.
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