Transfusion Clinique et Biologique 26 (2019) 188–191

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Update article

The best blood product and its best use for each patient: An evolving role for hemovigilance?

Le meilleur produit sanguin et son meilleur usage pour chaque patient : une évolution des missions de l'hémovigilance?

Pierre Tiberghien [a,b]

[a] *Établissement français du sang, 93218 La-Plaine-Saint-Denis, France*
[b] *Université de Franche-Comté, Établissement français du sang et Inserm, UMR 1098,, 25020, Besançon, France*

ARTICLE INFO

Article history:
Available online 15 May 2019

Keywords:
Transfusion
Blood product
Blood donor
Hemovigilance

ABSTRACT

Transfusion efficacy is an important clinical outcome strongly contributing to transfusion safety. Optimal transfusion care will soon require taking into account novel criteria's in relation with donor, blood product and/or recipient characteristics. Hemovigilance may prepare for these evolutions.

Mots clés :
Transfusion
Produit sanguin
Donneur de sang
Hémovigilance

RÉSUMÉ

L'efficacité transfusionnelle est un critère clinique essentiel qui contribue de façon importante à la sécurité transfusionnelle. L'amélioration des pratiques transfusionnelles requerra demain la prise en compte de nouveaux critères en relation avec les caractéristiques des donneurs, des produits sanguins et/ou des receveurs. L'hémovigilance peut se préparer à ces évolutions.

1. Hemovigilance successes

Hemovigilance includes reporting and assessing transfusion adverse events and incidents as well as surveillance activities encompassing the entire transfusion process. As such, hemovigilance is a cornerstone to mitigating risks to transfusion recipients as well as to blood donors [1]. By careful reporting and analysis of adverse events, hemovigilance has contributed to identifying, quantifying and ultimately reducing transfusion risks in various areas such as errors and "near miss" clerical and procedural events [2], transfusion-related errors, transfusion-transmitted infections [3,4] as well as hemodynamic- and/or inflammatory-related side effects[5,6].

A striking success story to which hemovigilance has significantly contributed is the identification of donor-related risk factors (i.e. anti-HLA antibodies in ever pregnant donors) for TRALI (transfusion-related acute lung injury) occurrence and the implementation of mitigation measures in most jurisdictions, effectively reducing the risk associated with this severe pulmonary complication [5–7].

2. Widening the scope of transfusion safety

The overall efficacy of blood products in transfusion recipients, an integral part of patient blood management, has most often not been considered as within the scope of hemovigilance [1,5,6]. However, transfusion inefficacy or toxicity, resulting from an inappropriate transfusion in view of recipient clinical status and/or from specific characteristics of the donor or blood product are undoubtedly contributive to reduced recipient safety.

E-mail address: pierre.tiberghien@efs.sante.fr

https://doi.org/10.1016/j.tracli.2019.04.001
1246-7820/

Recently, a number of studies have highlighted that low/restrictive (vs high/liberal) red blood cells (RBC) transfusion thresholds in most clinical settings are not only not associated with increased morbidity or mortality [8], but may be associated with improved outcome in specific settings such as gastrointestinal bleeding [9]. Despite these findings, insuring adequate hemoglobin thresholds for RBC transfusion through education and reporting deviations to appropriate guidelines is not presently a mainstay of most hemovigilance programs [5,6].

3. Seeking for appropriate transfusion triggers

Hemoglobin (or platelet) thresholds to trigger transfusion are arguably quite crude and often wrongly considered as independent of recipients attributes (such as age [10]). Overall, such thresholds are not satisfying indicators to decide of the appropriateness of transfusion as well as to evaluate transfusion efficacy. At the other end of the spectrum, assessing recipient survival is obviously appropriate *per se*, but is certainly not a sensitive mean to evaluate transfusion efficacy, in addition to being often not informative outside prospective randomized clinical trials. When performed, such trials can deliver important, on occasion counter-intuitive, findings, i.e. the recent finding that a 50,000 platelet/mm3 threshold (vs 25,000/mm^3) for platelets transfusion in neonates was associated with a significantly higher rate of death or major bleeding [11].

4. Assessing *in situ* efficacy

The development of tools to assess oxygen delivery to the tissues [12], as well as hemostasis [13] and overall homeostasis have the potential of being most profitable to guide transfusion needs, and most importantly to evaluate transfusion efficacy. The provision of such tools to assess current blood products safety and efficacy in relation with to donor, product and recipient characteristics will undoubtedly bring hemovigilance a step further. Furthermore, the assessment of "novel again" blood products such as whole blood [14] or platelets stored at 4 degrees Celsius [15] in the setting of acute bleeding would clearly benefit from such tools as well.

5. Differing blood products

The impact of RBC storage duration and/or manufacturing processes on patient outcome, and therefore safety, have drawn considerable attention. Following numerous observational studies suggesting that prolonged RBC storage was associated with a deleterious clinical outcome [16], several recent prospective randomized trials in various clinical settings not only were unable to confirm a deleterious effect of long-term stored RBC (as assessed by recipient survival) [17,18], but to the contrary raise the hypothesis that long-term storage may possibly be preferable to short-term storage [19,20].

Recently, differing methods of whole blood processing have been found to affect the quality of RBC [21], and may possibly influence patient outcome as well [22]. Metabolic changes in stored RBC supernatants impacting the plasma metabolome of healthy transfusion recipients has been reported, with notably oxylipins (associated with negative hemodynamic properties) and plasticizers from end-of-storage RBC accumulating ~ 20 fold in the bloodstream of transfusion recipients [23]. Such accumulations may vary depending on the recipients (i.e. higher plasticizers exposure in transfused neonates [24]) and could therefore warrant specific transfusion strategies in high-risk patients.

6. Differing donors

Donor characteristics obviously differ significantly and may also have a significant impact on transfusion recipient outcome. In fact, the early knowledge regarding the consequences of differing red blood cells groups between donor and recipients brought transfusion medicine to the forefront of personalized (or "precision") medicine [25], way before such a concept was put forward in oncology and elsewhere in medicine [26]. Nevertheless additional donor characteristics have only recently been considered (with the notable exception of measures to mitigate TRALI) [27], without yet questioning the "first in – first out" rule governing the choice of blood products to be transfused.

The RBC from female donors exhibit lower level of hemolysis compared to RBC from age-matched male donors [28]. Such gender bias is also found with gamma irradiation-induced hemolysis. Increased resistance to mechanical and oxidative stress as well as younger population of circulating RBC in premenopausal female blood donor have been put forward as potential mechanisms for such an effect. Interestingly, frequency of blood donations, irrespective of donor gender, may also modulate RBC predisposition to hemolysis [29]. Red blood cells collected from frequent donors with low ferritin have been reported to be associated with altered susceptibility to hemolysis. On the other hand, female gender (and younger age) have been associated with a lower PH in platelets [30]. More recently, novel approaches such as untargeted metabolomics analysis of donors have identified varying metabolic markers of hemolysis in RBC based on gender, age and ethnicity [31]. Furthermore, storage-induced oxidant stress vary significantly from donor to donor, thus establishing that chronological age of a stored unit of blood does not equate to biologic age of the same unit [32].

A number of large-scale observational studies assessing a potential relation between donor age or gender and transfusion outcome have produced rather striking and contradictory results. A first Dutch study in 2011 reported an association between donor gender and mortality in transfusion recipients with increased mortality in male recipients of female blood products when compared to the 3 other combinations [33]. A more recent study from the same group confirmed overall such findings while noting that the observed increased mortality in male recipients was limited to males under 50 years of age and to female donors with previous pregnancies [34]. Such findings, if confirmed, raise the intriguing possibility that immunity against chromosome Y – encoded minor histocompatibility antigens in female donors exposed to male antigens during pregnancy could be contributive [35]. A Canadian study found that recipient mortality was increased after exposure to RBC from female donors and young donors [36]. However, a more recent study using the Scandinavian Donations and Transfusions (SCANDAT) database did not report concordant findings [37]. Methodological considerations, in particular the necessity to model appropriately the association between the number of RBC transfusions and recipient survival may explain these discrepancies [38].

7. A "new deal" for hemovigilance?

Overall, issues surrounding transfusion safety have significantly evolved to now fully encompass transfusion efficacy. Novel means to assess transfusion safety and efficacy need to be developed and implemented. Such means range from methods assessing *in situ* oxygen delivery as well as local and systemic homeostasis to the analysis of large-scale biological and populational databases pertaining to donors and recipients. Furthermore, hemovigilance-driven prospective randomized transfusion clinical trials should

be encouraged. Long after the demonstration of the importance of "personalized/precision" transfusion medicine with regard to immuno-hematology , ongoing investigations may reveal that optimal transfusion care requires taking into account novel criteria's in relation with donor, blood product and/or recipient characteristics. Preparing for these evolutions is both a challenge and an opportunity for hemovigilance.

Disclosure of interest

The author is employed by the French transfusion public service (Etablissement Français du Sang).

References

[1] Wood EM, Ang AL, Bisht A, Bolton-Maggs PH, Bokhorst AG, Flesland O, et al. International haemovigilance: what have we learned and what do we need to do next? Transfus Med 2019, http://dx.doi.org/10.1111/tme.12582 [Epub ahead of print, Review, PubMed PMID: 30729612].

[2] Bolton-Maggs PHB, Wood EM, Wiersum-Osselton JC. Wrong blood in tube – potential for serious outcomes: can it be prevented? Br J Haematol 2015;168:3–13.

[3] Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, et al. West Nile Virus Transmission Investigation Team. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med 2003;349:1236–45 [Epub 2003 Sep 18. PubMed PMID: 14500806].

[4] Harvala H, Hewitt PE, Reynolds C, Pearson C, Haywood B, Tettmar KI, et al. Hepatitis E virus in blood donors in England, 2016 to 2017: from selective to universal screening. Euro Surveill 2019;24, http://dx.doi.org/10.2807/1560-7917.ES.2019.24.10.1800386 [PubMed PMID: 30862338; PubMed Central PMCID: PMC6415500].

[5] P. Bolton-Maggs, & D. Poles, on behalf of the SHOT Steering Group (2018) The 2017 annual SHOT Report. www.shotuk.org.

[6] ANSM, Rapport d'activité Hémovigilance 2017 https://www.ansm.sante.fr/var/ansm_site/storage/original/application/2cb0fbc705d768d0d55e6943aeb43658.pdf.

[7] Andreu G, Boudjedir K, Muller JY, Pouchol E, Ozier Y, Fevre G, et al. Analysis of transfusion-related acute lung injury and possible transfusion-related acute lung injury reported to the French hemovigilance network from 2007 to 2013. Transfus Med Rev 2018;32:16–27, http://dx.doi.org/10.1016/j.tmrv.2017.07.001 [Epub 2017 Jul 15. Review. PubMed PMID: 28864336].

[8] Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016;10:CD002042 [PubMed PMID: 27731885; PubMed Central PMCID: PMC6457993].

[9] Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11–21, http://dx.doi.org/10.1056/NEJMoa1211801 [Erratum in: N Engl J Med. 2013 Jun 13;368(24):2341. PubMed PMID: 23281973].

[10] G.I. Simon, A. Craswell, O. Thom, M.S. Chew, C.M. Anstey and Y.L. Fung. Impacts of Aging on Anemia Tolerance, Transfusion Thresholds and Patient Blood Management, Transfusion. Medicine Reviews, https://doi.org/10.1016/j.tmrv.2019.03.001 [in press, corrected proofs].

[11] Curley A, Stanworth SJ, Willoughby K, Fustolo-Gunnink SF, Venkatesh V, Hudson C, et al. Randomized trial of platelet-transfusion thresholds in neonates. N Engl J Med 2019;380:242–51, http://dx.doi.org/10.1056/NEJMoa1807320 [Epub 2018 Nov 2. PubMed PMID: 30387697].

[12] Vallet B, Robin E, Lebuffe G. Venous oxygen saturation as a physiologic transfusion trigger. Crit Care 2010;14:213, http://dx.doi.org/10.1186/cc8854 [Epub 2010 Mar 9. Review. PubMed PMID: 20236457; PubMed Central PMCID: PMC2887106].

[13] Opheim EN, Apelseth TO, Stanworth SJ, Eide GE, Hervig T. Thromboelastography may predict risk of grade 2 bleeding in thrombocytopenic patients. Vox Sang 2017;112:578–85, http://dx.doi.org/10.1111/vox.12544 [Epub 2017 Jun 22. Erratum in: Vox Sang. 2018 Oct;113(7):707. PubMed PMID: 28639693].

[14] Spinella PC, Cap AP. Whole blood: back to the future. Curr Opin Hematol 2016;23:536–42 [Review. PubMed PMID: 27607444].

[15] Nair PM, Pandya SG, Dallo SF, Reddoch KM, Montgomery RK, Pidcoke HF, et al. Platelets stored at 4(C contribute to superior clot properties compared to current standard-of-care through fibrin-crosslinking. Br J Haematol 2017;178:119–29, http://dx.doi.org/10.1111/bjh.14751 [Epub 2017 Jun 4. PubMed PMID: 28580719; PubMed Central PMCID: PMC5493018].

[16] Wang D, Sun J, Solomon SB, Klein HG, Natanson C. Transfusion of older stored blood and risk of death: a meta-analysis. Transfusion 2012;52:1184–95, http://dx.doi.org/10.1111/j.1537-2995.2011.03466.x [Epub 2011 Dec 21. Review. PubMed PMID:22188419; PubMed Central PMCID: PMC3883449].

[17] Lacroix J, Hébert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, et al. Age of transfused blood in critically ill adults. N Engl J Med 2015;372:1410–8, http://dx.doi.org/10.1056/NEJMoa1500704 [Epub 2015 Mar 17. PubMed PMID: 25853745].

[18] Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med 2015;372:1419–29, http://dx.doi.org/10.1056/NEJMoa1414219 [PubMed PMID: 25853746; PubMed Central PMCID: PMC5442442].

[19] Chai-Adisaksopha C, Alexander PE, Guyatt G, Crowther MA, Heddle NM, Devereaux PJ, et al. Mortality outcomes in patients transfused with fresher versus older red blood cells: a meta-analysis. Vox Sang 2017;112:268–78, http://dx.doi.org/10.1111/vox.12495 [Epub 2017 Feb 20. Review. PubMed PMID: 28220494].

[20] Ning S, Heddle NM, Acker JP. Exploring donor and product factors and their impact on red cell post-transfusion outcomes. Transfus Med Rev 2018;32:28–35, http://dx.doi.org/10.1016/j.tmrv.2017.07.006 [Epub 2017 Jul 31. Review. PubMed PMID: 28988603].

[21] Almizraq RJ, Norris PJ, Inglis H, Menocha S, Wirtz MR, Juffermans N, et al. Blood manufacturing methods affect red blood cell product characteristics and immunomodulatory activity. Blood Adv 2018;2:2296–306, http://dx.doi.org/10.1182/bloodadvances.2018021931 [PubMed PMID: 30217795; PubMed Central PMCID: PMC6156888].

[22] Heddle NM, Arnold DM, Acker JP, Liu Y, Barty RL, Eikelboom JW, et al. Red blood cell processing methods and in-hospital mortality: a transfusion registry cohort study. Lancet Haematol 2016;3:e246–54, http://dx.doi.org/10.1016/S2352-3026(16)00020-X [Epub 2016 Mar 4. PubMed PMID: 27132699].

[23] D'Alessandro A, Reisz JA, Zhang Y, Gehrke S, Alexander K, Kanias T, et al. Effects of aged stored autologous red blood cells on human plasma metabolome. Blood Adv 2019;3:884–96, http://dx.doi.org/10.1182/bloodadvances.2018029629 [PubMed PMID: 30890545;PubMed Central PMCID: PMC6436007].

[24] Sampson J, de Korte D. DEHP-plasticised PVC: relevance to blood services. Transfus Med 2011;21:73–83.

[25] Hendrickson JE, Tormey CA. Red blood cell antibodies in hematology/oncology patients: interpretation of immunohematologic tests and clinical significance of detected antibodies. Hematol Oncol Clin North Am 2016;30:635–51, http://dx.doi.org/10.1016/j.hoc.2016.01.006 [Review. PubMed PMID: 27113001].

[26] Jameson JL, Longo DL. Precision medicine – personalized, problematic, and promising. N Engl J Med 2015;372:2229–34, http://dx.doi.org/10.1056/NEJMsb1503104 [Epub 2015 May 27. PubMed PMID: 26014593].

[27] Otrock ZK, Liu C, Grossman BJ. Transfusion-related acute lung injury risk mitigation: an update. Vox Sang 2017;112:694–703, http://dx.doi.org/10.1111/vox.12573 [Epub 2017 Sep 25. Review. PubMed PMID: 28948604].

[28] Kanias T, Sinchar D, Osei-Hwedieh D, Baust JJ, Jordan A, Zimring JC, et al. Testosterone-dependent sex differences in red blood cell hemolysis in storage, stress, and disease. Transfusion 2016;56:2571–83, http://dx.doi.org/10.1111/trf.13745 [Epub 2016 Aug 9. PubMed PMID: 27507802; PubMed Central PMCID: PMC5065383].

[29] Kanias T, Stone M, Page GP, Guo Y, Endres-Dighe SM, Lanteri MC, et al. Frequent blood donations alter susceptibility of red blood cells to storage- and stress-induced hemolysis. Transfusion 2019;59:67–78, http://dx.doi.org/10.1111/trf.14998 [Epub 2017 Mar 23. PubMed PMID: 28337765].

[30] Germain M, Grégoire Y, Vassallo RR, Acker JP, Cardigan R, de Korte D, et al. Quality control of apheresis platelets: a multicentre study to evaluate factors that can influence pH measurement. Vox Sang 2017;112:318–25, http://dx.doi.org/10.1111/vox.12505 [Epub 2017 Mar 23. PubMed PMID: 28337765].

[31] Kanias T, Lanteri MC, Page GP, Guo Y, Endres SM, Stone M, et al. Ethnicity, sex, and age are determinants of red blood cell storage and stress hemolysis: results of the REDS-III RBC – Omics study. Blood Adv 2017;1:1132–41, http://dx.doi.org/10.1182/bloodadvances.2017004820 [PubMed PMID: 29034365;PubMed Central PMCID: PMC5638435].

[32] D'Alessandro A, Zimring JC, Busch M. Chronological storage age and metabolic age of stored red blood cells: are they the same? Transfusion 2019, http://dx.doi.org/10.1111/trf.15248 [Epub ahead of print. Review. PubMed PMID: 30865302].

[33] Middelburg RA, Briët E, van der Bom JG. Mortality after transfusions, relation to donor sex. Vox Sang 2011;101:221–9, http://dx.doi.org/10.1111/j.1423-0410.2011.01487.x [Epub 2011 Apr 8. PubMed PMID: 21477152].

[34] Caram-Deelder C, Kreuger AL, Evers D, de Vooght KMK, van de Kerkhof D, Visser O, et al. Association of blood transfusion from female donors with and without a history of pregnancy with mortality among male and female transfusion recipients. JAMA 2017;318:1471–8, http://dx.doi.org/10.1001/jama.2017.14825 [Erratum in: JAMA. 2018 Feb 20;319(7):724. PubMed PMID: 29049654; PubMed Central PMCID: PMC5817970].

[35] Nielsen HS, Wu F, Aghai Z, Steffensen R, van Halteren AG, Spierings E, et al. H-Y antibody titers are increased in unexplained secondary recurrent miscarriage patients and associated with low male: female ratio in subsequent live births. Hum Reprod 2010;25:2745–52, http://dx.doi.org/10.1093/humrep/deq242 [Epub 2010 Sep 7. PubMed PMID: 20823116; PubMed Central PMCID: PMC2955557].

[36] Chassé M, Tinmouth A, English SW, Acker JP, Wilson K, Knoll G, et al. Association of blood donor age and sex with recipient survival after red blood cell transfusion. JAMA Intern Med 2016;176:1307–14, http://dx.doi.org/10.1001/jamainternmed.2016.3324 [PubMed PMID: 27398639].
[37] Edgren G, Ullum H, Rostgaard K, Erikstrup C, Sartipy U, Holzmann MJ, et al. Association of donor age and sex with survival of patients receiving transfusions. JAMA Intern Med 2017;177:854–60, http://dx.doi.org/10.1001/jamainternmed.2017.0890 [PubMed PMID: 28437543; PubMed Central PMCID: PMC5540056].
[38] Cable RG, Edgren G. Blood transfusions from previously pregnant women and mortality: interpreting the evidence. JAMA 2017;318:1445–7, http://dx.doi.org/10.1001/jama.2017.15095 [PubMed PMID: 29049638].