Clin. Lab. 2024;70:XXX-XXX

EDITORIAL

Therapeutic Effect of Apheresis and Buffy Coat-Derived Platelet Concentrates

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(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2024.240728)

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KEYWORDS

platelets, platelet function, platelet concentrates, plateletpheresis

LIST OF ABBREVIATIONS

PC(s) - platelet concentrate(s)
PLT(s) - platelet(s)

EDITORIAL

One of the greatest challenges facing clinical medicine is the treatment of malignant diseases and the management of major blood loss. In both fields, the substitution of platelets (PLTs) is one of the regularly required measures to prevent or control life-threatening bleeding. Patients suffering from leukemia, lymphoma or other forms of cancer are at vital risk due to hyporegenerative thrombocytopenia resulting from disease-related and therapy-related restriction of bone marrow function [1]. The fact that the loss and consumption coagulopathy resulting from massive blood loss can be accompanied by significant thrombocytopenia has given rise to studies showing that supplementing red blood cell substitution with PLT transfusions improves the probability of survival [2].

Various preparations are available for a PLT transfusion. Many platelet concentrates (PCs) are obtained by apheresis, in which a large quantity of PLTs (e.g. 3 x 10e11) is obtained as a single therapeutic unit. A further proportion of PCs are generated from whole blood donations by pooling four to six individual concentrates or four to six intermediate stages, e.g. buffy coats. PCs are

Editorial accepted July 16, 2024

marketed as suspensions in human plasma or in additive solutions, and as leukoreduced or non-leukoreduced components. Finally, pathogen inactivation methods can also be part of the manufacturing process. Accordingly, the European "Guide to the preparation, use and quality assurance of blood components" contains no less than thirteen monographs on PLT components [3].

The question of whether qualitative differences between PLT preparations have clinical consequences for the recipients cannot always be answered with the desirable level of certainty due to a lack of sufficient clinical data [4]. In my opinion, however, the therapeutic range of PLT transfusion may be overestimated.

Retinal bleeding with visual impairment and intracranial bleeding is mostly summarized as WHO grade 4 bleeding, i.e. as debilitating blood loss. This is the category of the most serious bleeding events, which to prevent is the primary goal of prophylactic PLT transfusions in patients suffering from hyporegenerative thrombocytopenia. The collective analysis of published studies shows that grade 4 bleeding occurs more frequently when the gold standard of prophylactic administration of PCs in stable patients with hyporegenerative thrombocytopenia is deviated from by introducing dose-reduced components or pathogen reduction technologies or even replacing prophylactic by therapeutic-only PLT administration. Unfortunately, even in the context of studies, the reliable detection of grade 4 bleeding is not standardized [5]. This makes it all the more critical that hemovigilance systems regularly fail to record bleeds in recipients of PCs because they are attributed to the underlying disease and not to the transfusion therapy.

For the reasons mentioned above, surrogate markers are frequently used to obtain information on possible differences in quality between different PLT preparations. PLT function tests are an obvious choice here, and there are a number of them. However, these tests were developed for patient blood samples with normal PLT counts, and are poorly standardized even for this application [6]. Therefore, there is actually only one surrogate marker for assessing the quality of PCs, namely measuring the CCI value, i.e. the increase in PLTs in the recipient's blood count, and assessing this increase by taking into account the recipient's body measurements and the PLT content of the preparations.

Against the background of immense gaps in knowledge, an absurd dispute has developed in Germany over the question of the equivalence of apheresis PCs and pooled PCs. This dispute is not being conducted scientifically but is being fought out in social courts and is making the refinancing of apheresis PCs considerably more difficult because they are somewhat more expensive than pooled PCs. The starting point for this was the hasty conclusion in a later revised version of German guidelines on blood product transfusion that the therapeutic effect of apheresis PCs and pooled PCs is completely identical, which was not scientifically proven upon closer evaluation of the studies used to justify this statement.

After many years of no further data being collected on the question of the therapeutic effect of apheresis PCs and pooled PCs derived from buffy-coats, Wang et al. now present data from China [7]. They investigated the therapeutic effect of both types of PCs in patients with hyporegenerative thrombocytopenia based on the CCI values of PLT transfusions in a total of 218 patients. They found significantly better CCI values in the recipients of apheresis PCs. This is interesting because, unlike the studies discussed above, which were conducted a long time ago, the study by Wang et al. used plateletpheresis devices and procedures that are currently available in many countries.

The study has, however, some weaknesses that need to be addressed. First, Wang et al. did not examine the CCI values one hour after PLT transfusion, but 24 hours thereafter. Often, there are clearer differences one hour after the transfusion. On the other hand, CCI values after 24 hours may reflect the clinically relevant question for how long the number of circulating PLTs remains improved after PC transfusion. Second, according to the methods section, it is doubtful whether the pooled PCs transfused in the study were produced according to a uniform standard that is already well established in other countries. Thirdly, many of the PCs used were not leukoreduced, which has long been standard for all cellular blood components in many countries.

As a result, the comparative study published in this issue once more does not lead to actually significant new insights. In order to clarify the question of whether there are clinically relevant differences between apheresis PCs and whole blood-derived pooled PCs, the number of PLT transfusions would have to be far higher than in all previous studies on this issue. Nevertheless, the study by Wang et al. provides further evidence that apheresis PCs can be described as the "gold standard" for PLT transfusion until proven otherwise.

The recent work of Koepsell et al. highlighted the important insights that sufficiently large, prospective randomized studies can provide [8]. The MiPLATE trial on the clinical effectiveness of conventional versus Mirasol-treated apheresis PCs in participants with hypoproliferative thrombocytopenia showed a 2.79-relative rate (RR) in the Mirasol compared to the control group in number of days with ≥ Grade 2 bleeding. The study demonstrates that the increase in infection safety through pathogen inactivation procedures in the manufacturing process of PCs must be paid for with an increase in the risk of bleeding, which may result in higher transfusion triggers and shorter transfusion intervals.

A crucial difference between apheresis PCs and pooled PCs is the different number of donor exposures per individual concentrate. It is 1 for an apheresis PC, but 4 to 6 for a pooled PC. The associated risk of transmission of previously unknown emerging infectious agents is theoretically different. However, no pathogen has currently been identified for which a different infection transmission risk already had to be confirmed. The second risk

that may principally be influenced by the number of donor exposures is the immunization of PC recipients against HLA or HPA antigens. In this context, the results of a study on immunocompetent cardiac surgery patients are exciting [9]. They showed that leukocyte reduction effectively prevents the formation of new HLA antibodies in previously non-immunized patients. However, this was not the case if recipients were already immunized before. A completely surprising finding was that irradiation of leukoreduced blood components eliminated the protective effect of leukoreduction on immunization probability. It is still completely unclear whether this observation is also clinically relevant for patients with hyporegenerative thrombocytopenia, who particularly often receive leukoreduced and irradiated blood components.

Finally, the supply situation must be addressed. The study by Wang et al. published in this issue was conducted primarily to introduce pooled PCs in addition to apheresis PCs because there are apparently difficulties also in China in meeting the constantly high demand for PCs [7]. On the other hand, clinical medicine cannot do without apheresis PCs and the donors needed to obtain them, because immunized patients require apheresis PCs, which are selected on a case-by-case basis according to the compatibility of the HLA or HPA antigens of the recipients' antibodies.

In summary, one must even nowadays underline the conclusions that the Workgroup Blood at the Robert-Koch-Institute has drawn 2015 in his statement S15 after intensive study of the current state of scientific knowledge on the production and use of PCs. Clinical medicine requires both apheresis PCs and whole blood-derived pooled PCs. However, the two types of preparation are not the same or easily interchangeable. It should therefore be up to the physician to decide which PLT preparation he chooses as the most suitable for his patients. The scientific community is and remains called upon to continue research on the numerous open questions of production and administration of PCs.

Declaration of Interest:

The author declares that he has no conflicts of interest relevant to the manuscript submitted to Clinical Laboratory.

References:

1. Chabner BA, Roberts TG. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer 2005;5:65-72. (PMID: 15630416)

2. McQuilten ZK, Crighton G, Brunskill S, et al. Optimal dose, timing and ratio of blood products in massive transfusion: results from a systematic review. Transfus Med Rev 2018;32:6-15. (PMID: 28803752)

3. European Directorate for the Quality of Medicines & Health Care of the Council of Europe (EDQM). Guide to the preparation, use and quality assurance of blood components, 21st edition, Strasbourg, 2023;pp 239-63.

4. Arbeitskreis Blut des Bundesministeriums für Gesundheit. [Scientific explanations on the statement "Evaluation of apheresis and pool platelet concentrates" of the AK Blut of 31.03.2015] [Article in German]. Bundesgesundheitsbl 2015;58:1129-50.

5. Estcourt LJ, Heddle N, Kaufman R, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. Transfusion 2013;53:1531-43. (PMID: 23305609)

6. Asmis L, Moldenhauer A, Hitzler W, Hellstern P. Comparison of platelet function tests for the in vitro quality assessment of platelet concentrates produced under real-life conditions. Platelets 2019;30:720-7. (PMID: 30204045)

7. Wang Z, Chen X, Zhang Y, Lu H, Ren L. Comparison of therapeutic effect in apheresis platelets and buffy coat-derived platelet concentrates Clin Lab 2024;70 (Epub-ahead-of-print)

8. Koepsell SA, Stolla M, Sedjo RL, et al. Results of clinical effectiveness of conventional versus Mirasol-treated apheresis platelets in patients with hypoproliferative thrombocytopenia (MiPLATE) trial. Transfusion 2024;64:457-65. (PMID: 38314476)

9. Nelson KA, Aldea GS, Warner P, et al. Transfusion-related immunomodulation: gamma irradiation alters the effects of leukoreduction on alloimmunization. Transfusion 2019;59:3396-404. (PMID: 31608454)