Optimization of blood component preparation
Processing and donor influence
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CHAPTER 10

Future prospects
FUTURE PROSPECTS

The aims of the studies described in this thesis were to improve, to optimize and to standardize the quality of red cell and platelet products, prepared routinely or on demand. This was performed by 1) introduction of a new semi-automated separator for centrifuged whole blood (WB) and buffy coat (BC) pools, 2) examining temperature and time limits for WB and red cell concentrate processing during the first 2 days after collection, 3) reducing donor exposure by development of a new product for intrauterine transfusion, and 4) by studying the donor influence on platelet (PLT) storage performance. Standardization is considered of growing importance due to the expected implementation of pharmacological requirements for cellular blood products destined for transfusion.

Blood component preparation may be further improved and standardized by the use of fully automated processors for 4 to 6 units of WB or pooled BC like the Reveos and TACSI devices (Terumo BCT, Lakewood, CO). Once a Reveos is loaded with the bag system and started, bag closures are opened, and the operator does not need to intervene before the blood is centrifuged and components have been prepared. A disadvantage of these devices may be the need for a specific bag system from the same manufacturer, including the storage container for PLTs. However, programming of the Reveos can differentiate between a 2 component procedure for maximal plasma yield and a 3 component procedure for additional preparation of an interim PLT unit. These interim PLT units can be easily manually pooled and filtered, without necessity for a secondary centrifugation step. The Reveos software also generates a PLT yield index which provides an estimation of PLT content in the interim PLT unit, making it possible to standardize and/or increase PLT content of the final PLT concentrate (PC) by selecting the optimal interim PLT units [1-3].

An estimation of the PLT content of a BC or, like in Reveos of the interim PLT unit, will be helpful to standardize PLT numbers in PC, and may diminish discarding of low or high yield PC. In addition, information about the PLT content will be helpful to prepare PCs from 4 instead of 5 BCs, which is already done in some countries like Canada and the United Kingdom. For the Dutch situation, with PLT production based on pooled BCs, use of 4 BC is particularly interesting when the demand for platelets nears or exceeds the demand for red cells. However, when using 4 BCs it may be quite a challenge to prepare PCs that fulfill criteria for PLT numbers (>250x10⁹), and estimation of PLT content of BCs seems to be an important prerequisite. Since donors have rather stable levels of PLT counts [4,5], this can be realized by counting PLTs before or after collection of the WB, and combining BCs with expected low and high PLT...
counts. An additional advantage of 4 BCs is a lower donor exposure, but a disadvantage may be a higher chance to include PLTs with poor storing performance. So, a switch from 5 BC to 4 BC challenges not only standardization of platelet numbers but also PLT storage properties, although effect of poor storing PLTs may be mitigated by the use of PAS-E as storage medium instead plasma or PAS-C.

The switch in 2018 of the Dutch blood bank to PAS-E as universal storage medium for PLTs was not only a step forward in standardization, but is also considered a better starting point for future introduction of a pathogen inactivation method for PLTs. The use of PAS-E instead of plasma showed smaller effects on lactate metabolism and apoptosis -as detected by Annexin A5 binding- when PLTs were pathogen inactivated with the Mirasol system [6]. Further improvement of pathogen inactivated PLTs may be done by focusing on donor related PLT (mitochondrial) quality and storage performance (Chapter 7-8), optimization of PLT yield [7,8] and improvement of PAS formulation. Next generation platelet additive solutions are under development, with the emphasis on further reduction of the amount of residual plasma in PCs, while simultaneously maintaining the same high PLT quality and maximum storage time [9]. It is recommended to add improvement of PLT quality after pathogen inactivation as a third research goal for better PAS formulations.

In future studies, there may be a role for thromboelastography to evaluate PLT functional quality, as used for Mirasol-treated PCs in plasma [10] or PAS [11]. For good comparison of thromboelastographic data of treated and non-treated PLTs, an appropriate assay has to be chosen with similar ratios of (standardized) plasma and colloids (Chapter 6 and 7). Another modern tool with high potential to contribute to improvement of additive solutions for red cells or platelets is metabolomics technology. Unlike several contributions for improvement of the red cell storage lesion, the technique has not yet been applied in the development of PLT additive solutions or pathogen inactivation processes [12], and deserves further attention.

Metabolomics is becoming more and more a high throughput analysis which has potential to become a powerful tool to screen donor health [13]. For instance, metabolic profiles have to be shown to predict the development of diabetes [14]. Donor age and health are current topics of interest [15,16], and are of increased importance, because (European) blood banks have to increase efforts to keep their donor pool at a sufficient level. In the Netherlands, recently, the maximum donor age was increased from 70 to 80 years, while there is also special focus to recruit young donors. The latter is of particular importance, because as observed in the last study (Chapter 9), there is increased risk for poor platelet storage with age, whether or not caused by metabolic syndrome, Type 2 diabetes or other (unknown) diseases.
In general, there is increasing notion that PLTs may be regarded as short-living metabolic mirrors of body health [17,18], and our studies of platelet storage performance in relationship to individual donors reflect this notion. Health, life style, nutrition and medication may influence storage performance of red cells and platelets. Bashir et al [19] showed a negative effect of lipemic plasma on red cell storage due to a higher degree of hemolysis, and recently Sanquin decided to discard not only the lipemic plasmas itself, but also the red cells of the same donation [20]. The higher hemolysis due to lipids may be caused by a different composition of the red cell membrane, causing higher red cell fragility [21]. Effects of lipids on PLT storage performance have also been studied by our department but results are, as yet, not unambiguous, probably because lipids and fatty acids serve many different roles in PLTs, like substrates for oxidation [22], building blocks of the PLT cell membranes [23] and uncouplers of the mitochondrial membrane potential [24,25]. In addition, lipids and fatty acids are a very heterogeneous group of compounds, and their main role in a platelet may well be dependent on, among others, chain length and degree of saturation.

With regard to PLTs, a causal relationship of PLT storage performance and donor health variables could not be established until now, which warrants further studies. A striking example regarding eating and drinking habits and PLT transfusion was reported by Zimring et al [26]. Caffeine, caffeine metabolites and fatty acid concentrations in PC in plasma were negatively correlated with PLT recovery and survival. However, PLT storage properties were not examined in detail during this study, and so no further conclusions can be drawn regarding effects of these compounds on platelet metabolism during storage. Once a causal relationship is established, it has to be noted that RBC and PLT storage performance may not be a (donor related) constant but can change during donor lifetime in either a positive or negative direction. As suggested, and partly demonstrated by our last study (Chapter 9), metabolic properties of blood cells can become worse by aging, by (chronic) diseases or by other unknown factors. Theoretically, the opposite is also possible when donors change their diet and life style, for example by self-treatment for Type 2 diabetes. The complexity of this topic has been shown in a longitudinal study of one individual who suffered from induced T2D after viral infection. The study also demonstrates that even “genetic profile” cannot be considered as a constant during lifetime [27].

As mentioned above, negative effects of poor storing PLTs may be (partially) mitigated by the use of PAS-E instead of plasma, but this has not been investigated in depth yet. Moreover, the use of PAS as a medium possibly has additional advantages for PLT metabolism and function, as well as for the recipients by preventing high concentrations of triglycerides, of
hormones like insulin, and of medicines like metformin (for treatment of diabetes) [28,29], simvastatin (for treatment of high cholesterol) or losartan (for treatment of high blood pressure) [30]. Although effects of these compounds on PLT storage are regarded as either positive or negative in the literature, the effects are generally studied in models using platelet rich plasma or washed platelets, and not in PLT concentrates stored under blood bank conditions. Likewise, the exact mechanisms that determine the rate of glycolysis in stored PLTs in the presence of simultaneous mitochondrial activity, goes beyond textbook knowledge. Further studies are warranted to link donor characteristics with storage performance of blood cells, in order to reach a higher degree of consistency of these important transfusion products.
REFERENCES


Clot of fresh buffy coat-derived platelets suspended in solvent/detergent plasma. Fibrinogen/fibrin was stained with an in house developed anti-fibrinogen antibody (in green). Platelets were stained for their actin cytoskeleton using Phalloidin Texas Red. The image was taken with a Zeiss LSM 510 confocal microscope.