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State of art

The storage lesions: From past to future

Les lésions de stockage : entre peurs rétrospectives et perspectives

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Abstract

Red blood cell (RBC) concentrates are stored in additive solutions at 4 °C for up to 42 days, whereas platelets concentrates (PCs) are stored at 22 °C with continuous agitation for up to 5 to 7 days, according national regulations, and the use or not of pathogen inactivation procedures. Storage induces cellular lesion and alters either RBC or platelet metabolism, and is associated with protein alterations. Some age-related alterations prove reversible, while other changes are irreversible, notably following protein oxidation. It is likely that any irreversible damage affects the blood component quality and thus the transfusion efficiency. Nevertheless, there still exists a debate surrounding the impact of storage lesions, for both RBCs and PCs. Uncertainty is not completely resolved. Several studies show a tendency for poorer outcomes to occur in patients receiving older blood products; however, no clear significant association has yet been demonstrated. The present short review aims to promote a better understanding of the occurrence of storage lesions, with particular emphasis on biochemical modifications opening discussions of the future advancement of blood transfusion processes. The paper is also an advocacy for the implementation of an independent international organization in charge of planning and controlling clinical studies in transfusion medicine, in order to base transfusion medicine practices both on security principles, but also on clinical evidences.

Keywords: Ageing; Blood cells; Microparticles; Platelets; Oxidation; Proteomics; Red blood cells; Storage; Transfusion

Résumé

Les concentrés de globules rouges sont conservés dans des solutions additives à 4 °C, pour une durée allant généralement jusqu'à 42 jours, alors que les concentrés plaquettaires sont conservés à température ambiante, pour des périodes allant jusqu'à 5 ou 7 jours, selon les législations, et suivant l'usage de procédés de réduction des pathogènes. Le stockage induit obligatoirement des lésions cellulaires touchant leur métabolisme ainsi que des altérations protéiques, notamment au niveau oxydatif. Il est probable que les lésions, lorsqu'elles sont irréversibles affectent tant la qualité des produits sanguins transfusés que leur efficacité. Néanmoins, un doute persiste sur l'importance clinique des lésions de stockages, malgré un certain nombre d'études cliniques qui se veulent rassurantes. Cet article a pour but de faire une brève revue synthétique des lésions de stockage et de les mettre en perspective face aux obligations que les services/établissements de transfusion devront assumer vis-à-vis notamment des autorités sanitaires délivrant l'autorisation de mise sur le marché et dans leur participation aux études cliniques. Il est aussi un plaidoyer pour que la recherche clinique soit coordonnée et organisée afin que les pratiques puissent être basées non seulement sur des arguments sécuritaires, mais surtout sur des évidences cliniques solides.

Mots clés : Ageing ; Blood cells ; Microparticles ; Platelets ; Oxidation ; Proteomics ; Red blood cells ; Storage ; Transfusion

1. Introduction

If blood components (BCs) have to be introduced on the market in 2017 as novel therapeutics, who will accept that red

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blood cells (RBCs) can be stored at 4 °C without any proofs of the absence of clinical consequences of conservation of blood outside physiological condition. The same is true when considering platelets, which are stored in really non-physiological conditions. Both RBCs and platelets are generated by nature in order to survive at 37 °C in the presence of plasma and without any anticoagulant. Who can remember, in 2017, that most of the conditions used to prepare and to store blood components were derived from empirical as well as practical approaches established by pioneer's decades before quality controls and validation procedures were put in place and controlled by external organisations such as the ANSM, Swissmedic or the Paul Erlich Institute? Most of our practices in transfusion medicine are based on historical approaches not necessarily scientifically sounded. For example, the reason why platelets cannot be stored at 4 °C without inducing lesions that did not allows re-circulation is quite recent [1–3]. Normal platelets are produced by megakaryoctes in the bone marrow (as well as in the lungs [4,5]): they circulate within blood, at 37 °C, in presence of plasma and many other cells like leukocytes, RBCs and endothelial cells. Therefore, who can admit that they can be stored at room temperatures with constant agitation in the presence of relatively low concentrations of plasma and in the presence of additive solutions? Nevertheless, this practice is considered as normal and is the standard approach [6,7]. If nowadays such an approach would be proposed to the health authorities, it is all but sure that, according to the detected storage lesions that have been identified, authorities will allow placing on the market such BCs. The real world is quite different. The retrospective regard is like a wink on the distance that is clearly apparent between the requirements that are nowadays considered as normal procedures and the historical pragmatism that prevailed in the last century: regardless of the considerations taken into account, BCs are on the market. Nevertheless, both fundamental, translational and clinical studies are needed in the near future to provide better care to our patients and to provide strong evidence to the health authorities that the processes are under control. In this context, this paper puts in perspective the RBC as well as the platelet storage lesions. Many different physiological and biochemical pathways are affected by storage, and stored BC are clearly very different when compared to freshly drown blood. Therefore, most of clinicians are lost in translation because experimental data and clinical data may be interpreted in divergent manners. Finally, the development of "new" products is hampered, due to all validation steps and procedures that are needed even if based on current practices, without consideration of the biology of cells that will be transfused. All these aspects are hot topics in transfusion medicine.

2. The past

The history of storage lesions is parallel to that of transfusion medicine (reviewed in [8]). Early blood transfusion was a surgical act involving the dissection of veins or arteries in both the donor and the recipient. End-to-end anastomosis of blood vessels was commonly performed. Transfusions were thus performed arm-to-arm, meaning that donors had to be present next to the patients. The first direct blood transfusion (arm-to-arm) of World War I (WWI) was performed by a French physician in 1914. Interestingly, the donor and recipient bloods were not cross-matched to ensure their group compatibility. Indeed, the watchword was to accept the risk of blood incompatibility issues rather than let people die from massive haemorrhage. Following the advance of anticoagulation and short-term preservation procedures, blood was bottled and transfused with no necessary contact between the donor and the patient. Blood preservation saw another substantial improvement in 1943: preservative solutions with different sodium citrate/citric acid ratios were tested. Blood storage for four weeks at 3 °C–7 °C and end-storage haemolysis were examined. Several biochemical parameters-such as spontaneous haemolysis, osmotic fragility, pH, glucose, potassium, and formation of methemoglobin were evaluated. These studies lead to the conclusion that acidified citrate-glucose (ACD) preservative solutions were satisfactory for blood storage. ACD blood preservative solutions allowed blood storage for three weeks (based on 24 h post-transfusion survival) and remained in use until the introduction of phosphate, which allowed blood storage for up to four weeks with increased levels of 2,3-DPG in 1957 [9].

In 1952, the utilization of a closed system of plastic bags for blood collection, preservation in ACD, and transfusion was proposed. Compared to glass bottles, the plastic bag system had the obvious advantages of reduced bacterial contamination (no contact with air), lighter weight, shock resistance, and ease of storage in refrigerators. During the war of Korea, the use of plastic bags for blood transfusion was proposed. Blood stored in such bags had lower plasma potassium levels than blood stored in glass bottles, perhaps due to the presence of diethylhexyl-phthalate (DEHP) released from blood bags limiting microvesiculation of RBC membranes [10]. The next improvements of blood storage involved the introduction of adenine as a constituent of preservative solutions. Citrate phosphate dextrose adenine solutions (CPDA-1 and CPDA-2) were licensed for use in the United States during the late 70s/early 80s, although transfusion medicine had already shifted to the use of packed RBC concentrates (RBCCs). The use of whole blood progressively become obsolete. The first additive solution used for storage of packed RBC units was sodium-adenine-glucose (SAG) [11], which was further modified by addition of mannitol (becoming SAGM) to reduce end-storage haemolysis. Other additive solutions were derived from the original SAG and are currently used worldwide, including additive solution (AS)-1, AS-3, and AS-5 in the United States and Canada, and MAP in Japan. The most recent improvement in blood transfusion involves the removal of leukocytes before or during whole blood processing. Leukoreduction is performed by removal of the buffy coat layer after whole blood centrifugation and/or leukofiltration [12].

Platelet concentrates (PCs) are produced either from whole blood or by apheresis (reviewed in [6,7]). However, taken into consideration the various protocols that are used for manufacturing PCs, several hundreds of different types of PCs are one the market, if we combine all possibilities provided by the type of