Red cell storage: when is better not good enough?

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"Blood for transfusion must be safe, effective, available and cheap," the late John Collins said in a meeting of the U.S. National Academy of Sciences' Institute of Medicine in 1973 during efforts to license the 5-week CPDA-1 blood storage solution[1]. These objectives seem clear individually, but it is usually in their interactions that controversy arises and hard decisions must be made. Most of us are familiar with the interactions of blood safety and the cost of new tests or of new restrictions on the donor population and the availability of components. We all struggle to find new voluntary donors with healthy lifestyles and to justify and pay for increasingly sensitive testing.

However, the interactions between blood's effectiveness and its availability or its cost are less well known. In part this is because the whole concept of blood effectiveness is poorly defined. To the extent that red cell effectiveness has measurable meaning, red cells must be intact, circulate, and survive to be effective, so measures of their hemolysis, *in vivo* recovery, and survival have been gold standards for decades. Other measures, such as the red cell 2,3-diphosphoglycerate (DPG) concentration or their nitric oxide content, have less clear physiologic significance and corresponding lower regulatory importance.

In this issue of the journal, Gulliksson and van der Meer present data on the effects of storing whole blood overnight at room temperature in a primary anticoagulant (CPD; citrate, phosphate, dextrose) before it was separated into components and the red cells subsequently stored conventionally for 42 days in one of five different storage bags and additive solution systems[2].

The paper is part of an international effort to gather data on the "warm overnight hold of whole blood" as a technique to collect and manufacture blood components more efficiently[3].

Conventional thinking suggests that blood should be separated into components as quickly as possible[4]. This thinking has been incorporated into regulations saying that blood must be separated into components within 8 hours or cooled to refrigerator temperatures within that time. As most blood, 70% in some countries, is collected on mobile blood drives away from component manufacturing facilities, this has led to most mobile-blood-drive-collected blood being stored on ice with the resulting loss of platelet function. Additional platelets must then be collected by apheresis to make up for this loss.

Two decades ago, Dutch investigators noted that platelets derived from units of whole blood held warm overnight for processing the next morning actually had better platelet yields and better platelet function than those processed immediately after collection. Holding blood warm overnight is also attractive because it allows all the component manufacturing to be performed during the day shift with efficiencies of scale, reduced staff, and better quality control oversight. Finally, the warm hold appears to reduce bacterial overgrowth in the platelets by allowing white blood cells time to remove low-level contamination. The problems with the "warm overnight hold of whole blood" are the increased loss of labile coagulation factors in the plasma, increased time before the white cells are removed leading to increased cytokine secretion, and the rapid consumption of glucose by the warm red cells.

Red cells derive all of their energy from glycolysis. In the closed environment of a blood bag, the breakdown of glucose leads to the production of lactate and protons with a resulting decrease in pH.

Blood Transfus 2009; 7: 172-3 DOI 10.2450/2009.0110-09

The total energy flux through the system is determined by starting and ending pH, the buffer capacity of the proteins and salts in the bag, the metabolism rate, the glucose content and time. The best way to maximize red cell storage is start storage as close to pH 7.2 as possible and to buffer the red cell additive solution and keep the suspension as cold as possible[5]. Blood is drawn at venous pH, about 7.35 and mixed with CPD of pH 5.8 to produce a resulting whole blood suspension with a pH of about 7.05[6]. If the blood is then cooled, the pH will decline by 0.1 in about a week, if kept at room temperature overnight it will fall that much in 16 hours. This difference can be partially offset by adding an alkaline additive solution during component production[7]. Adding a conventional acidic solution will make the pH drop worse. Gulliksson and van der Meer demonstrated this with higher initial pH and better preservation of adenosine 5'-triphosphate (ATP) concentrations with the new alkaline additive solutions.

Maintaining high ATP concentrations is critical for red cell survival. Reduced ATP concentrations lead to the loss of phospholipid pumping with the resulting exposure of phosphotidyl serine, a phagocytosis signal, and membrane loss through calpain-driven microvesicle formation[8]. These factors appear to be critical determinants of 24-hour in vivo recovery and hemolysis levels required for storage system licensure.

So the question remains as to whether the benefits of the new alkaline storage solutions are good enough to offset the losses and changes caused by the addition acid generated by the red cells during warm overnight storage. Only actual measures of recovery will tell, but the authors' data give reasons for cautious optimism. It is an exciting area of blood system-integrating research where better red cell storage systems may lead to better platelet supplies as well.

References

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