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The Effect of Holding Times of Whole Blood and Its Components During Processing on In Vitro and In Vivo Quality

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ABSTRACT

Whole blood is not usually collected close to the processing site, which results in a holding time between collection and processing. In some countries, the holding time is limited to 8 hours, after which the units are cooled, rendering them useless for platelet preparation. Other countries allow a 24-hour ("overnight") ambient hold to allow platelet preparation. The impact of this holding time on subsequent blood components will be reviewed in this article. In addition, there are various "in-process" holding times that further prolong the time before the final blood component is ready. Particularly, these in-process holding times are not well defined and poorly controlled, but can nevertheless affect the biochemical and functional characteristics of blood components. Furthermore, current, non–evidence-based, guidelines have restricted the length of some of these holding times. This article summarizes the evidence and fills gaps where evidence is lacking.

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Blood is a mixture of living cells in a plasma environment, and outside the body—in plastic bags in the blood bank—these cells continue to metabolize nutrients and consume oxygen. Under these artificial circumstances, cells and plasma can lose their functionality, and even to the current day, studies are ongoing that aim to maintain and improve clinical effectiveness of these cells and plasma.

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The changes to the blood constituents commence immediately after collection and continue up to the moment a blood component is administered to the patient. Whole blood and its components are stored for various periods at various temperatures, all which affect the quality of the transfused product.

Although much is known about the changes during storage of the various blood products such as red cells and platelets [1,2], little is known about the changes in the characteristics of the products during the hold time during the various processing steps that precede storage. Many of these holding steps are often not specified and can vary considerably on a day-to-day basis in normal routine blood banking. As an example, at our blood center, if few collections are performed, the holding time of buffy coats will be much shorter before platelet concentrates are prepared than on a busy day, where first the large bulk of whole blood must be processed before platelets can be prepared. To prevent the fluctuations becoming too large, some of the holding steps have found their way into the guidelines, as it seemed good to set limits to some of them, but often without evidence *why* certain limits were set. Sometimes these limits are unnecessarily restrictive and may potentially lead to loss of products.

This review aims to summarize the available literature on the effect of holding times during processing of whole blood into its components, namely, red cells, platelets, and plasma. Also, additional experiments are discussed where we feel that evidence is lacking, but suspect that the holding time may affect the quality of blood components. The effect of holding temperature has been studied extensively with the introduction of overnight hold of whole blood at ambient temperature and will only be discussed briefly.

Effect of Holding Time of Whole Blood Prior to Processing

Historic Perspective

In the early days of transfusion therapy when hospitals collected whole blood for their own patients, there was generally little time between blood collection and subsequent transfusion. Improvements in anticoagulants, by addition of glucose and adenine, and the ensuing development of blood component therapy, allowed longer storage and thus "banking" of blood components. Blood transfusion services began to specialize and conglomerate, resulting in the formation of (regional) blood banks located at a distance from the hospital. Donations were performed more and more outside the hospital and transported to the blood bank for further processing into its various components, introducing a holding time of several hours before whole blood was separated into components. To allow for transportation, it became common practice that there was a lag time of several hours before whole blood was separated into components.

Currently, the allowed holding time of whole blood at ambient temperature before processing varies between 8 and 24 hours, depending on the requirements of regulating agencies and/or guidelines in force. During this hold at ambient temperature, some changes in blood already take place. One of the most notable changes is the decrease in 2,3-diphosphoglycerate (DPG) concentration in the red cells. In a study comparing immediate vs 6-hour delayed processing, where platelet-rich plasma (PRP) was removed from centrifuged fresh whole blood and split in 2 identical portions, the portions that were held for 6 hours at room temperature had a 10% lower 2,3-DPG concentration at onset of storage than the portions that were refrigerated immediately [3]. Also, the portions held for 6 hours before cold storage subsequently showed a more rapid decrease in concentration, although the differences dissipated after day 12 as 2,3-DPG became depleted, irrespective of the initial holding time. However, ATP content was not affected by the 6-hour hold. ^{51}Cr recovery 24 hours after retransfusion of 21-day-old red cells was slightly better for units cooled immediately ($P = .05$), but with the average value above 85%, both values were deemed to be excellent. No effect on the in vitro quality of platelets was found, and all 10 platelet concentrates were negative when cultured at the end of the 72-hour storage period. Factor VIII concentration (factor VIII:C) in plasma was also similar in both units. In the following years, the maximum holding time was extended from 6 to 8 hours at room temperature, based on a study where after removal of PRP and subsequent 35-day storage, red cells in CPDA-1 showed a satisfactory 78.0% ± 8.1% recovery 24 hours after retransfusion [4].

In the early 1980s, blood centers began experiments to extend the hold time beyond 8 hours. Using a modified anticoagulant, CPD-AD, containing 0.4 mM adenine and a 1.5 times higher glucose than in regular CPD, an overnight holding time of 15 hours could be achieved [5]. ATP was similar during a 5-week storage compared with units held for less than 4 hours, but initial 2,3-DPG was less than half of the controls. There was no effect on platelet quality in vitro. Pietersz et al [6] finally extended the holding time to a full 24 hours after collection. They used butane-1,4-diol cooling plates to ensure that all units reached a temperature of approximately 20°C within 2 hours after collection. ATP was maintained during the first 24 hours and dropped to 81% ± 5% of the initial value after 5 weeks of storage. 2,3-DPG was reduced by two-thirds after 24-hour hold at room temperature and declined further during storage, until it was completely depleted by week 2. Platelet yield was 84% ± 6% for overnight-held units and was slightly higher than the 76% ± 18% found in units processed within 3 hours. Factor VIII concentration declined to 80% ± 3% of the initial value after 24-hour hold, but routinely processed units held for 16 to 20 hours showed sufficient factor VIII:C levels.

Routine overnight storage of whole blood at room temperature for up to 24 hours became standard procedure at the Amsterdam blood center in 1987 [7] and is now common practice in many countries. This practice was initially introduced mainly in Europe and has been subsequently incorporated into the internationally recognized Council of Europe Guide for the Preparation, Use and Quality Assurance of Blood Components [8], and later by the Canadian Blood Services [9]. More recently, the Food and Drug Administration allowed 24-hour room temperature hold for apheresis plasma [10], although overnight hold of whole blood with use of all components (red cells, platelets) has not yet been approved.

Overnight hold of whole blood therefore allows ample time to transport units from the donation site to the processing center. Fewer transport runs between the donation and processing sites are needed when the necessity to comply with a short holding time is no longer required. When all units are available for processing in the morning, efficiency increases (rather than waiting for units to come in) as the workload can be distributed more evenly. Working during business hours is not only more economical but less prone to error than night shifts, as night shifts are associated with increased error rates when performing tasks [11,12]. With the buffy coat method, where multiple units are pooled prestorage to make one platelet concentrate, the different blood groups are available around the same time, to facilitate pool formation.

Effect of Holding Time of Whole Blood on the Quality of Red Cells

As indicated above, 2,3-DPG rapidly declines at room temperature hold, but ATP remains almost unaffected. This has consistently been reported in numerous studies [13–18]. Other parameters also remain more or less unaffected by the preprocessing holding time. One study comparing 7- to 8- vs 23- to 24-hour hold showed no effect on hemolysis and supernatant K^+ [19] after the initial holding time, or throughout 42 days of storage. The same group also conducted a radiolabeling study in 2 collaborating laboratories, that each used slightly different radiolabeling techniques to determine the recovery 24 hours after retransfusion. At site A, using a single ^{51}Cr radiolabel, red cells stored for 35 days in AS-1 showed a 79.2% ± 4.3% vs 79.4% ± 3.9% recovery when produced from 8- or 24-hour-held whole blood. Site B reported 79.7% ± 6.5% vs 83.4% ± 7.2% with a dual label ^{51}Cr/^{99m}Tc method, respectively; all differences were not statistically significant. For units stored for 42 days, site A