Joint UKBTS Professional Advisory Committee ([1])

UKBTS General Information 09

Deviations from the specified storage temperature and interruption of agitation of platelets - practical considerations

June 2020

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1. Introduction

Platelets are delicate cells with an important function. The preparation of platelet concentrates and their handling in the supply chain must ensure the platelets are kept in the best condition possible if they are to be effective following transfusion.

Platelets need to be stored at ambient temperature, for reasons outlined below. This means that they remain metabolically active and need fuel and oxygen to survive. The fuel is provided by the suspension medium – this may be donor plasma or a mixture of plasma with platelet additive solution (PAS) – and oxygen is obtained from the air through the special gas-permeable plastic from which platelet bags are made.

This document describes the current state of knowledge in relation to the effects of interruption of agitation or deviations from the normal storage temperature for platelets. For a comprehensive review of the data on which this document is based, refer to Thomas, 2016.[1]

The acceptability of transfusing platelets that have been subjected to temperature excursions or interruptions to agitation should be informed by local risk assessment. Blood services and hospitals may find this information useful as part of that process.

This document was originally published in 2017. Since then there have been occasions where clearer guidance would have helped to enable pragmatic application of guidance and avoid the waste of clinically-acceptable blood components. The literature was re-examined and minor revisions made to the content of this document, which now refers to periods of non-agitation of up to 11 hours, instead of eight hours. The 11 hour period was studied in the key paper on which the guidance was based. The specifications for platelet handling will still specify three periods of eight hours but this guidance will now provide reassurance that short, unplanned over-runs will not necessarily lead to discard of valuable blood components.

2. Manufacture of platelet concentrates

In the United Kingdom there are currently two methods of preparation of platelet concentrates (PC): selective collection of platelets by an apheresis procedure, and pooling of the buffy coat separated from units of whole blood. These methods are used in approximately equal measures, so best practice for handling of platelets should be consistent and applied to both types of component.

3. Current guidelines for platelet storage

The following extract from the 8th edition of the Red Book[2] refers to the key elements of storage bag capacity, and agitation of the platelets.

- *"The storage period depends on a number of factors including the nature of the container, the concentration of platelets and whether an open or closed system is used.*
- *Packs currently in use for this purpose allow for storage at a core temperature of 22 ± 2°C with continuous gentle agitation for up to 5 days in a closed system. Appropriate pack and platelet concentration combinations may allow storage up to 7 days, but due to concerns over bacterial contamination requires either an assay to exclude bacterial contamination prior to transfusion or application of a licensed pathogen inactivation procedure.*
- *Where any manufacturing step involves an open system the platelets should be used as soon as possible after collection. If storage is unavoidable, the component should be stored at a core temperature of 22 ± 2°C with continuous agitation and used within 6 hours.*
- *Platelets should be gently agitated during storage. If agitation is interrupted, for example due to equipment failure or prolonged transportation, the components are suitable for use, retaining the same shelf life, provided the interruption is for no longer than a total of 24 hours and no single interruption lasts for more than eight hours"*

4. Storage bag capacity

From the point of collection or pooling, the volume and concentration of platelets must be within the specification for the bag in which they are held. Bag manufacturers conduct extensive validation of the storage bags, establishing the maximum capacity of the bags in terms of platelet concentration, volume, and maximum shelf life of platelets stored in the bag. These parameters are critical for the quality of platelets, as the surface area to volume ratio is important for gas exchange; sufficient oxygen must be available for the platelets to respire and not enter anaerobic glycolysis that generates acidic conditions leading to poor platelet quality. Manufacturers of platelet storage bags have therefore assigned limits for platelet content and concentration and UKBTS ensure that platelet components are manufactured within these limits.

5. Gas exchange

Platelet storage bags are made from gas permeable plastic and any storage or transportation periods where the PC are wrapped and/or unagitated can be damaging to the quality of the platelets. The objective of platelet agitation is to ensure gas exchange between the storage

medium and the atmosphere.

Although platelets may be 'in motion' during shipping, this has no benefit when they are wrapped in plastic overwraps and packed together in a transport container, and **periods of transportation are therefore regarded as interruptions to platelet agitation**. Gas exchange must be maintained by observing bag capacity limits and by minimising periods of transportation.

There is no strong evidence for or against the resting of platelets by leaving them unagitated on the bench immediately following collection, prior to placing on an agitator. However, platelet concentrates should not be covered in any way during this rest period, for example by placing in additional plastic bags, stacking on top of each other, or placing in transport containers, as this compromises gas exchange. A short rest period of up to one hour may allow the separation of minor aggregates. It is necessary to transport platelet concentrates (e.g. from manufacturing site to hospital) but these periods without gas exchange must be limited to avoid excessive damage to the platelets.

The current Red Book guidelines[2] for the storage of platelet concentrates are based on data from published studies on the effects of interruptions of agitation and of temperature deviations, reviewed in Thomas 2016.[1]

6. Guidelines and advice on interruptions of agitation

The current Red Book guidelines state*: "Platelets should be gently agitated during storage. If agitation is interrupted, for example due to equipment failure or prolonged transportation, the components are suitable for use, retaining the same shelf life, provided the interruption is for no longer than a total of 24 hours and no single interruption lasts for more than eight hours."*

Interruption to agitation refers to any time following collection by apheresis or manufacture from whole blood when the platelet component is not on an agitator. Blood services will routinely need to transport platelets a number of times; for example NHSBT routinely moves apheresis platelets from a donor centre to a stock holding unit, to a manufacturing site, to a stock holding unit and to a hospital (see Appendix 1). Similarly, hospital transfusion laboratories might not unpack a container of platelets as soon as it has been delivered, may need to send platelets to a satellite hospital, and will send platelets to the ward and back more than once. All these instances of non-agitation will have an impact on the quality of the platelets and need to be accounted for when assuring compliance with the guidelines.

Blood services should therefore make available, if requested, details of their usual supply chain and thus the maximum period for which the platelets will have been without agitation at the point of delivery. Hospitals should use this information to inform their usual procedures and ensure that the platelets are not subjected to a total that exceeds the cumulative maximum of 24 hours of non-agitation. It is not expected that each platelet component will have a full transport history, but it is expected that processes will be in place that ensure

compliance with the guidelines. In the example above if each of the four transport runs is validated to take less than four hours then the platelets will always arrive at the hospital with sufficient resilience to withstand a further eight hours of non-agitation. However, if the journey time from the stock holding unit is more than three hours and the delivery is not unpacked for five hours (the maximum reported in a recent survey) then this would be non-compliant. Transfers to other hospital sites (reported to take up to four hours) must also be included in the assessment of cumulative time of non-agitation in routine practice, as must the transfer time to the ward (and return to the transfusion lab if unused).

Should there be a deviation from the validated and agreed transportation or storage conditions outlined above, the impact on platelet quality will need to be assessed in the context of the interruptions of agitation that those particular platelets have already experienced. For example, if an interruption of agitation is slightly over eight hours but the total duration of all interruptions within the blood service is only 16 hours then this is unlikely to affect the platelets, but no further interruptions should be allowed within the blood service, so that hospitals receive platelets with the resilience to withstand a further eight hours of non-agitation. Further, there may be cases when specific platelet units need to be transported long distances (for instance HLA-matched apheresis-derived units for a named patient) and the eight-hour limit might be breached. In these cases, it is important that the guidelines are applied pragmatically. Wagner et al [3] subjected apheresis platelets in plasma to three periods of non-agitation of 11, 11 and eight hours' duration (a total of 30 hours) and found 9 of 12 Amicus-derived units had pH above 6.4 after seven days, as did 11 of 12 Trima units. It would therefore be reasonable to allow clinical use of platelet units that had been subjected to one or even two periods of non-agitation that lasted no more than 11 hours, taking into account the device used to collect the platelets. Buffy coat derived platelets are not subjected to post-collection and pre-validation transportation, and are usually suspended in additive solution, so are likely to be more resilient to interruptions of agitation up to 16 hours long (van der Meer 2007 [4]).

An alternative approach for platelet components that have been subject to periods of non-agitation longer than the current guidance, could be to restrict the shelf life of the affected components (although this can be difficult to achieve in practice). The previous version of the UK guidelines allowed periods of non-agitation longer than eight hours, but were based on published literature that supported a five day shelf life for platelets. Much of the negative impact on platelets is not detectable until later in storage, and with the bacterial screening processes in place in the UK the shelf life is usually seven days, hence the revised guidelines are more restrictive.

7. Deviations from controlled temperature storage

Platelets should be stored at 20 - 24 °C. The minimum temperature limit is based on evidence that colder storage leads to irreversible changes on the platelet membrane that result in rapid phagocytosis of the platelets following transfusion. Three key studies were published between 1969 and 1994 that reported the effect of storage at different

temperatures for varying durations on the in vivo survival of platelets. Various combinations of time and temperature were studied, with the least harsh combination being 17 hours at 16 °C. Post-transfusion survival of these platelets was reduced from 6.5 days in control units to only 3.5 days in the test units.

The temperature limits in the guidelines should be observed from the point of collection of the platelets by apheresis, or the collection of whole blood intended for the manufacture of platelet pools. This applies to conditions at donor sessions, the performance specification of transport containers, manufacturing facilities and stock holding units. If platelets are unexpectedly subjected to temperatures below 20 °C then consideration should be given to the severity and duration of the excursion. For example, exposure to 19 °C for one hour is unlikely to result in long term damage to the platelets. Potential mitigations could also include use of 'chilled' platelets for the therapeutic treatment of bleeding rather than prophylaxis, as current thinking is that the immediate function of chilled platelets is unaffected; it is only their long-term survival that is compromised.

Although platelets are obviously able to function at 37 °C, storage at temperatures above 24 °C may increase platelet metabolism and ageing, and will also encourage the growth of any contaminating bacteria. However, as the majority of platelet components manufactured in the UK are screened for bacterial growth, this risk is mitigated to some extent. Again, if there is a short term and minor deviation in the storage temperature of platelets then an assessment may be made regarding the likelihood of the effect of this deviation on the components, versus the risk of a critical shortage of platelets.

8. Advice on risk assessment when storage temperature or non-agitation limits are breached

The current Red Book guidelines state*: "Platelets should be gently agitated during storage. If agitation is interrupted, for example due to equipment failure or prolonged transportation, the components are suitable for use, retaining the same shelf life, provided the interruption is for no longer than a total of 24 hours and no single interruption lasts for more than eight hours."*

Periods when platelets are stored out with 20 - 24 °C and/or without agitation should be kept to a minimum.

In exceptional circumstances, if deviations from the current guidance have occurred, a risk assessment must be performed to consider the use or discard of the affected components. The following advice may be helpful during this process.

- If unplanned or prolonged periods of non-agitation occur then the total amount of non-agitation should be estimated, taking the whole supply chain into consideration. For example:

  - if one interruption of agitation is between 8 and 11 hours long and the total duration of all interruptions will be less than 24 hours then this is unlikely to affect the platelets

  - however, if the total is in excess of 24 hours then the effect on platelet quality is likely to become more significant, although a total of under 30 hours may be tolerable but would require a clinical risk assessment of the specific circumstances.

- If the temperature fell below 20 °C (but remained above 18 °C) for less than 12 hours, the platelets may be suitable for transfusion, particularly for therapeutic (rather than prophylactic) use.

- If the temperature exceeded 24 °C but remained below 30 °C then platelet function is likely to be acceptable but the risk of bacterial growth must be considered.

References

1. Thomas S. (2016) “Platelets – handle with care”. *Transfusion Medicine*, doi: 10.1111/tme.12327

2. Guidelines for the UK Transfusion Services, 8th Edition 2013, The Stationery Office.

3. Wagner et al (2008) ”Comparison of the in vitro properties of apheresis platelets during 7-day storage after interrupting agitation for one or three periods” *Transfusion*; **48**, 2492-2500.

4. van der Meer et al (2007) “The effect of interruption of agitation on in vitro measures of platelet concentrates in additive solution” *Transfusion*, **47**, 955-959.

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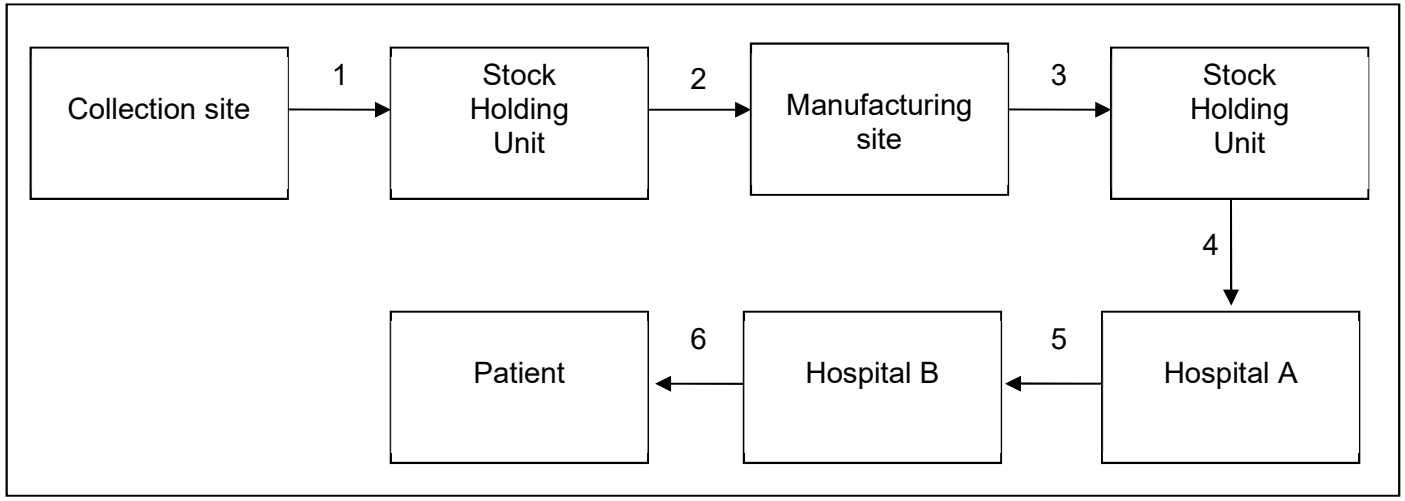
Appendix 1

Diagram showing possible movements of apheresis platelets collected at a donor centre not co-located with a manufacturing centre. Each movement should have a 'usual maximum time' to ensure standard processes that comply with the guidelines on individual and cumulative interruptions of agitation. Blood Services should inform customers of their standard practice. In this example movements 1 to 4 could all be scheduled to take less than four hours, so that upon delivery to the hospital the platelets are still able to cope with a further eight hours of non-agitation during movements 5 and 6. Movement 5 could be a four hour site transfer, and Movement 6 could consist of up to four transfers to ward, with returns in between, if each transfer and return took only 1 hour.



([1]) **J**oint United Kingdom Blood Transfusion and Tissue Transplantation Services **P**rofessional **A**dvisory **C**ommittee (**JPAC**)