

Refrigeration, cryopreservation and pathogen inactivation: an updated perspective on platelet storage conditions

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Running title: Novel storage of platelet components

Word Count: 4510

Sources of support: The Australian governments fund the Australian Red Cross Blood Service to provide blood, blood products and services to the Australian community. This research is supported by an Australian Government Research Training Program Scholarship award.

Conflicts of interest: DC Marks and L Johnson receive funding from MacoPharma for research not related to this study. The other authors have no conflicts of interest to declare.

Abstract

Conventional storage of platelet concentrates limits their shelf life to between 5 and 7 days due to the risk of bacterial proliferation and the development of the platelet storage lesion. Cold storage and cryopreservation of platelets may facilitate extension of the shelf life to weeks and years, and may also provide the benefit of being more haemostatically effective than conventionally stored platelets. Further, treatment of platelet concentrates with pathogen inactivation systems reduces bacterial contamination and provides a safeguard against the risk of emerging and re-emerging pathogens. While each of these alternative storage techniques is gaining traction individually, little work has been done to examine the effect of combining treatments in an effort to further improve product safety and minimise wastage. This review aims to discuss the benefits of alternative storage techniques and how they may be combined to alleviate the problems associated with conventional platelet storage.

Keywords: platelet, storage, cold, cryopreservation, pathogen inactivation

Introduction

Platelets have a primary role in mediating haemostasis, where they are essential to maintain the integrity of the vascular system [1]. Platelet concentrates are primarily transfused prophylactically to prevent the onset of bleeding in patients with thrombocytopenia [2-4]. Additionally, platelets may be transfused therapeutically for the treatment of active bleeding [3, 4]. Conventionally, platelets are stored at room temperature (20-24°C), in gas permeable bags, with constant agitation [5]. This prevents platelets from aggregating and preserves platelet viability by maintaining appropriate gas exchange. Under these conditions, the platelet shelf life is limited to 5-7 days depending on the governing regulator. This limitation is imposed to minimise the deterioration in platelet quality that occurs during storage, as well as the risk of bacterial growth.

The platelet storage lesion

During the storage period, platelets undergo numerous changes, referred to collectively as the platelet storage lesion, which results in deterioration of platelet function and viability [6]. While platelet collection and processing steps required to manufacture platelet concentrates induces a degree of platelet activation, the aim of *ex vivo* storage is to maintain them in a relative resting state (Figure 1). Unfortunately, current strategies result in a progressive activation during storage, demonstrated by upregulated release of alpha granules, altered glycoprotein expression and increased procoagulant activity over the storage period [6-9]. Additionally, glycolysis may be upregulated, leading to increased lactic acid production and a concomitant fall in pH if insufficient buffering capacity is present [10, 11]. Platelet structure and function is altered when the pH falls to 6.8 [5, 12], with a loss of viability below pH 6.0 [5]. Historically, similar changes were once reported when the pH exceeded 7.5 [13].

However, these results were obtained using outdated methods of platelet manufacture, storage containers and agitation techniques and more recent studies do not support an upper limit for the pH [14, 15]. The platelet storage lesion therefore poses a challenge when considering the shelf life of platelet products at the time of transfusion.

The development of the platelet storage lesion can result in undesirable outcomes following transfusion. Notably, the release of soluble platelet mediators during storage increases the risk of certain transfusion reactions, with reports suggesting that up to 30% of patients receiving a platelet transfusion will present with symptoms including fever, chills, cold and discomfort [16]. However, the incidence of more severe transfusion reactions, including anaphylaxis, TACO or TRALI, is rare, occurring in approximately 1% of patients receiving a platelet transfusion [17]. The effectiveness of a platelet concentrate also decreases as the product ages, demonstrating *in vitro* impairment of aggregation responses and weaker clot formation [9, 18, 19]. Consequently, the platelet storage lesion results in platelets with reduced *in vivo* recovery and survival, and lower haemostatic activity [19, 20].

Globally, many blood services face logistic challenges due to the short shelf life of platelets. The day-to-day demand for platelet products is somewhat unpredictable, making it problematic to balance an adequate inventory without incurring excessive wastage. This problem is further compounded by the 'just-in-case' approach, which necessitates the immediate availability of platelet products for medical and surgical procedures, even if only a small proportion is transfused. Furthermore, the short shelf life is particularly challenging when considering the supply of platelet products to remote, rural and military settings [21-23]. The transport of platelet products is further complicated as room temperature stored

platelets also require constant agitation to maintain adequate gas exchange. Combined, it is evident that the development of strategies to overcome the current challenges associated with conventional platelet storage is a pressing issue in the transfusion community. This review will discuss the alternatives that are currently of interest and highlight how, individually or combined, these techniques could alleviate the burdens associated with the currently accepted methods of platelet storage.

Cold Stored Platelets

Cold storage is not a new method of storing platelets, but is undergoing a resurgence of interest. Cold storage involves keeping platelets in a refrigerator (2-6 °C) without agitation and was the convention until the 1970s. It was subsequently shown that platelets stored at room temperature had better *in vivo* survival following transfusion [24, 25]. While circulation time is reduced following cold storage it is becoming evident that storage at low temperatures may provide other benefits.

Cold storage of platelets has the potential to substantially increase the shelf life of platelets, with *in vitro* studies showing that platelets stored out to 21 days maintain functionality [26-28]. The extension of shelf life can be attributed to a decreased metabolic rate, leading to lower glucose consumption, decreased lactic acid production, and better maintenance of pH [26, 29]. Cold storage also has the benefit of significantly inhibiting bacterial growth within platelet products. Storage of platelets at 4 °C retards the growth of many bacterial species, decreasing the probability of transfusion-associated sepsis [30, 31].

When stored in the cold, platelets undergo a number of changes. Firstly, they are found to undergo an irreversible morphological change from their resting discoid shape to a more spherical form [32]. Granule and cytokine release is reduced compared to room temperature stored platelets, while microparticle formation is increased [26, 33]. The expression of surface receptors is also altered when platelets are cold stored. Integrin $\alpha\text{IIb}\beta\text{3}$ undergoes a conformational change to its activated conformation [17, 26, 28]. Furthermore, cold storage induces increased surface expression of P-selectin and externalisation of phosphatidylserine, both markers of platelet activation [28, 34, 35]. While phosphatidylserine is commonly considered a marker of platelet activation, it is also associated with apoptosis [36]. Platelet refrigeration leads to deglycosylation and clustering of GPIb α , resulting in the exposure of N-acetylglucosamine (GlcNAc) and galactose [37, 38]. Recognition of exposed GlcNAc by the $\alpha\text{M}\beta\text{2}$ integrin on macrophages in the liver, leads to rapid removal of platelets from circulation [39]. Furthermore, galactose becomes exposed as the storage progresses, which facilitates platelet clearance by hepatic Ashwell-Morell receptors [40].

While cold stored platelets have a reduced circulation time of between 2 to 4 days as compared to 7 to 9 days for room temperature platelets, they appear to be more haemostatically active [24, 25]. This increase in haemostatic activity is evidenced by improved *in vitro* aggregation responses to agonists including ADP, collagen and epinephrine, as well as increased clot forming potential [29, 34, 41]. Cold platelets also significantly reduce bleeding time in patients taking aspirin [42] and are more efficient at stopping bleeding in thrombocytopenic patients [24]. Additionally, recent analysis of an ongoing study demonstrates a trend towards reduced postoperative bleeding following transfusion of cold stored platelets in patients undergoing cardiothoracic surgery [43]. This improved function

may be beneficial when treating active bleeding, as the shortened lifespan of cold stored platelets would be of little incident as the platelets would be consumed during the progression of haemostasis. The transfusion environment and the understanding of cold stored platelets have shifted significantly since the decision was made to move away from cold storage. As such, further work on cold stored platelets in the context of the contemporary transfusion medicine environment is warranted.

Cryopreserved Platelets

Cryopreservation is also not a new method for storing platelets, being first developed in the 1970s [36]. Despite early investigations yielding positive results, their use was never widely adopted as a conventional method for platelet storage. The currently accepted method of cryopreservation involves the addition of dimethyl sulfoxide (DMSO) to a final concentration of 5-6 %, followed by pre-freeze removal of the DMSO containing supernatant [44-46]. Hyperconcentrated platelet units are then frozen at -80 °C where they have a shelf life of at least two years [46, 47]. In preparation for transfusion, cryopreserved platelets are rapidly thawed and resuspended in a suitable media. Several media have been investigated for their suitability as a reconstitution solution including saline, 100% plasma, 30% plasma/70% SSP+, or 100% platelet additive solution (PAS), such as SSP+ [29, 44, 48-51]. Once thawed and resuspended, cryopreserved platelets typically have a 6 hour shelf life [52].

Cryopreserved platelets differ significantly from conventionally stored platelets. Notably, cryopreserved platelets appear to lose multiple receptors including GPIIb α , GPVI, and integrin α IIb β 3 [40, 44, 48-50, 53]. Cryopreserved platelets are significantly more activated than room temperature stored platelets, as evidenced by increased surface levels of CD62P, along with

phosphatidylserine externalisation and extensive microparticle shedding [39, 44, 48-50, 53]. Further, platelet degranulation is also evident, with increased supernatant concentrations of cytokines including sCD62P, PF4, PDGF-AB, RANTES, TGF- β and EGF present in the platelet supernatant [33, 44, 49, 50, 53].

Despite the altered phenotype, cryopreserved platelets appear to be haemostatically functional. *In vitro* studies have demonstrated that cryopreserved platelets mediate accelerated clot formation and produce greater amounts of thrombin more rapidly than room temperature stored platelets [29, 48, 50, 53, 54]. Importantly, in a randomised controlled trial, cryopreserved platelets were found to reduce nonsurgical blood loss in patients undergoing cardiac surgery [55]. Further, preliminary evidence from the clinical use of cryopreserved platelets in trauma patients indicates their effectiveness [33]. The efficacy and safety of cryopreserved platelets has also been supported by Noorman *et al.*, who have described cryopreserved platelets as being safe and at least as effective as standard blood products in the treatment of active haemorrhage [22]. The renewed clinical interest may pave the way for the development and implementation of cryopreserved platelet products for routine use in more countries.

In preparation for transfusion, cryopreserved platelets are thawed, resuspended, and available for immediate use or can be stored at room temperature. The post thaw shelf life is limited to 6 hours as a risk of bacterial proliferation exists due to the 'open' system that is often used to prepare cryopreserved platelets. This restriction dictates that cryopreserved platelets are basically thawed on demand, immediately prior to transfusion. However, this is not always feasible, or a patient may require fewer transfusions than originally anticipated.

In these situations, the product would be discarded. The ability to extend the shelf life of thawed cryopreserved platelets to 24 hours or beyond, may decrease wastage and improve inventory management as fluctuations in product demand could be better maintained.

Bacterial, viral and emerging pathogens

Bacterial contamination of platelet concentrates remains a major challenge in transfusion medicine, and is the primary motivator for the limitation on shelf life. The storage of platelet concentrates at room temperature increases the risk of bacterial proliferation [56]. Bacteria found in platelet units typically originate from the donor's skin, which may be introduced at the time of donation, despite the best efforts to employ aseptic techniques and skin disinfection [57]. Ideally, any bacteria present will be detected upon screening, limiting the risk of transfusing contaminated units. However, not all countries screen platelet concentrates for the presence of bacteria or do not screen for both aerobic and anaerobic bacterial species [58]. There are also limitations in the bacterial screening systems, resulting in both false positive and negative results [59, 60]. Thus, determining an appropriate balance between the platelet shelf life and allowing sufficient time to culture samples for bacterial testing is a significant challenge. As a result, platelet concentrates may already be transfused before a result is obtained [61]. Bacterial contamination of platelet units is estimated to occur in 1/1000-1/10000 platelet units, depending on the country and method of production [62-65], and a recent study reports that 1/4 contaminated platelet units results in a symptomatic septic transfusion reaction when transfused [66].

In Australia, all blood donors are screened for HIV, Hepatitis B, Hepatitis C, Human T-lymphotropic virus (HTLV-1 and -2), and syphilis at every donation. Despite screening, a

thorough donor questionnaire and deferrals, the safety of the blood supply retains some vulnerability from window period infections and emerging pathogens [67-69]. Each year the list of newly described infectious disease agents grows, but resurgence of known pathogens in certain populations may also occur. There are several well documented pathogens, including West Nile virus [70, 71], dengue virus [72, 73] and chikungunya virus [74, 75] that pose a risk as transfusion transmitted infections and have required the implementation of preventative measures. More recently, the Zika virus has joined the ever-growing list of emerging pathogens [76, 77]. The risk of emerging pathogens therefore highlights significant vulnerabilities for the safe production of blood products globally, demonstrating the need for additional and overarching safeguards to ensure its safety.

Pathogen inactivation

Pathogen inactivation systems are able to inactivate a broad range of pathogens, including bacteria, viruses and parasites. Pathogen inactivation involves exposing platelets to ultraviolet (UV) light, with or without the addition of a photosensitising agent, which damages nucleic acids to inactivate pathogens by impairing protein assembly and cell replication. Additionally, pathogen inactivation treatment also inactivates leukocytes, which negates the need for gamma-irradiation [78]. Globally, many countries, including Belgium, Norway, and Spain have introduced pathogen inactivation technologies into routine practise [58]. Currently, there are three pathogen inactivation systems: INTERCEPT Blood System (Intercept; Cerus, Concord, CA, USA), Mirasol Pathogen Reduction Technology System (Mirasol; Terumo BCT, Lakewood, CO, USA) and the THERAFLEX UV-Platelets System (THERAFLEX; Macopharma, Tourcoing, France). Of these systems, both the INTERCEPT and Mirasol systems have regulatory approval in several countries, while THERAFLEX is currently

undergoing clinical evaluations. While these systems all work to achieve the same end result, the method by which they inactivate pathogens varies in the wavelength of UV light used, photosensitising agent, as well as the mode of action.

The INTERCEPT system functions by exposing pathogens to UVA light (320-400 nm) in combination with a photosensitising agent, amotosalen, which intercalates into DNA and RNA, leading to irreversible covalent crosslinking of nucleic acids with the amotosalen [79]. Following treatment, residual amotosalen and amotosalen photoproducts are removed via adsorption using a compound adsorption device [80].

The Mirasol system functions by exposing pathogens to broad spectrum UVA/UVB light (280-360 nm) in the presence of the photosensitising agent riboflavin (vitamin B2) [81, 82]. Interactions between riboflavin and nucleic acids under UV light leads to oxidation and strand breaks, primarily at guanine residues, preventing subsequent replication or repair [82]. Vitamin B2 is generally considered safe, meaning that removal following treatment is not required [83].

Uniquely, the THERAFLEX UV-Platelets System does not use a photosensitising agent, but rather works by exposing platelets to 200-280 nm (target wavelength 254 nm) UV light while under strong agitation to ensure sufficient light penetration [84, 85]. This treatment causes the formation of cyclobutane pyrimidines and pyrimidine (6-4) pyrimidone dimers, inhibiting nucleic acid elongation during transcription [85-87].

All three systems have been shown to be efficacious against a wide range of pathogens, capable of inactivating a broad spectrum of bacteria, viruses, parasites and leukocytes. The three pathogen inactivation systems effectively inactivate many common species of bacteria, with the exception of bacterial spores [78, 79, 81, 83, 88-90]. Further, these systems are also capable of inactivating a comprehensive range of both DNA and RNA-based viruses, including enveloped, non-enveloped, cell-associated and cell-free viruses [80, 81, 86, 91]. Furthermore, all systems are capable of inactivating an extensive range of parasitic species, including *Trypanosoma cruzi*, *Plasmodium falciparum* and *Babesia microti* [81, 92-94]. However, each system displays limitations in inactivation capacity; with INTERCEPT and Mirasol showing variable effectiveness against parvovirus and hepatitis viruses, while THERFLEX has only a moderate capacity for inactivating HIV [85, 86, 95, 96]. Notably, pathogen inactivation also has the potential to inactivate emerging pathogens that are not routinely included in blood donor screening panels, including dengue virus, chikungunya virus and Ross River virus [77, 97].

Pathogen inactivation treatment of platelets has been shown to exacerbate the platelet storage lesion, causing a myriad of *in vitro* changes. After treatment with the INTERCEPT or Mirasol systems, platelets metabolism is accelerated, resulting in a decrease in pH, increased surface expression of CD62P and phosphatidylserine, as well as increased platelet degranulation [98-104]. However, the extent of these changes appears to be affected by the proportion and type of platelet additive solution used. The *in vitro* functional capacity of platelets also appears affected, with the general consensus being that agonist-induced platelet aggregation is negatively affected by pathogen inactivation [37, 100, 103-106]. Similarly, clot formation is also reduced in pathogen inactivated platelets, with reports

demonstrating a reduction in clot strength, reduced surface coverage and thrombus growth [37, 106]; although evidence to the contrary has also been reported [13, 107, 108]. In addition to the metabolic and activation changes observed by the other systems, THERAFLEX treatment of platelets induces activation of integrin $\alpha\text{IIb}\beta\text{3}$, which may impact platelet aggregation and thrombus formation [85, 109-111]. Although the changes exhibited after pathogen inactivation are indicative of increased activation and acceleration of the platelet storage lesion, pathogen inactivated platelet concentrates still conform to institutional component specifications [112].

While extensive haemovigilance studies have demonstrated that Mirasol and INTERCEPT pathogen inactivated platelets have a similar safety profile to untreated platelets [113, 114], there is conflicting evidence regarding the *in vivo* survival and efficacy of these platelets [98, 115-122]. Further, a recent systematic review has suggested that transfusion of pathogen inactivated platelets increases transfusion requirements and the risk of developing platelet refractoriness [123], although there are also data to the contrary [124, 125]. Several multi-centre studies (PREPAREs, EFFIPAP, MIPLATE) using the INTERCEPT and Mirasol systems are ongoing or recently completed and it is anticipated that this data may assist in clarifying the efficacy of pathogen inactivated platelets [123, 126, 127]. While the THERAFLEX system has not yet received regulatory approval for treatment of platelets, a phase I clinical trial of THERAFLEX-treated platelets in healthy volunteers demonstrated that THERAFLEX-treated platelets were cleared from circulation at a similar rate to untreated platelets, and did not cause any adverse reactions when transfused [128]. A phase III trial is currently underway (EudraCT 2015-001035-20).

Assessment of the potential benefits of combining storage techniques

Pathogen inactivation of platelet concentrates reduces the risk of transfusion transmitted infections. However, it may be possible to extend the shelf life of platelet components by combining pathogen inactivation with other novel storage techniques. As highlighted in Table 1, novel storage modalities offer several advantages over conventional room temperature platelet storage but significant investigation into the feasibility of combining these techniques is still required. The results of such studies will likely vary depending on several parameters including the plasma content of the platelet concentrates, the pathogen inactivation technology applied and the length of storage examined. Based on the outcomes of individual treatments/storage, the final column of Table 1 speculates as to the anticipated results if the indicated treatments were to be combined. It is hypothesised that the refrigerated storage of pathogen inactivated products may provide protection against the accelerated platelet metabolism induced by pathogen inactivation treatment and thus slow the development of the platelet storage lesion. Further, the functionality of cold stored pathogen inactivated platelet components may be enhanced compared to conventional room temperature stored platelets given the improvements observed when these techniques are applied individually [29, 34, 109, 110]. Importantly, while cryopreserved platelets already have a significantly longer shelf life while frozen, the ability to combine this technique with pathogen inactivation may improve product safety and enable an extension of shelf life of the thawed product. Further, the *in vitro* functionality of pathogen inactivated cryopreserved platelets is anticipated to be similar to untreated cryopreserved platelets, although altered compared to conventionally stored platelets [29, 52, 109, 110]. While it is anticipated that combining pathogen inactivation with alternate storage modalities will be safe and efficacious, this cannot be accurately determined without clinical trials.

The possibility of combining cold storage or cryopreservation with pathogen inactivation is a newly emerging area of research. A single study has reported that apheresis platelets treated with the Mirasol system and subsequently cold-stored maintained better platelet counts, metabolism and function over storage than treated controls stored at room temperature [129], demonstrating that combining the two treatments is possible and may in fact be beneficial. Similarly, buffy coat-derived platelets treated with the INTERCEPT system prior to cryopreservation had a similar post thaw recovery and maintained their haemostatic potential when compared to untreated controls [130]. As such, additional investigations combining pathogen inactivation systems with subsequent storage at cold temperatures (refrigeration and cryopreservation) are warranted.

It would be of interest to determine whether the post thaw shelf life of cryopreserved platelets may be extended by storing thawed platelets in the cold (cryo-cold; Table 1). Some of the benefits of cold storage (outlined above) may be translatable to thawed cryopreserved platelets. Cryopreserved platelets experience an accelerated metabolic rate during post-thaw storage [29, 49], which could be reduced if the thawed platelets are stored under refrigerated conditions. Additionally, cryopreserved platelets demonstrate significant granular release [44, 49, 50, 53], which may potentially be mitigated if cryopreserved platelets are stored in the cold once thawed, as is seen with standard cold-stored platelets [33, 34]. Importantly, cold storage significantly inhibits bacterial proliferation [30, 31], the risk of which currently restricts the post-thaw shelf life of cryopreserved platelets. Taken together, these findings support the plausibility of cold storing thawed cryopreserved platelets and hence further investigation may be warranted.

Future directions

The ability to combine pathogen inactivation with cold storage or cryopreservation could potentially alleviate many of the major concerns associated with conventional storage of platelet products. Storing platelets in colder temperatures, whether by refrigeration at 4 °C or cryopreservation at -80 °C, offers the potential of an extended shelf life of several weeks to years, respectively. Whilst refrigerated storage of platelets is simple and appropriate transport and storage conditions are readily available, implementing cold storage may be logistically challenging due to the likely requirement of a dual inventory [131]. Although cryopreserved platelets are more labour intensive and expensive to manufacture, the significant increase in shelf life may be enough to outweigh this initial cost. The implementation of cold storage or cryopreservation as a routine storage option would alleviate the logistical issues surrounding platelet supply to remote, rural and military operations. While these techniques are gaining momentum individually, the possibility of combining these techniques with pathogen inactivation technologies would enable a safeguard against the risk of emerging pathogens and prevent platelet concentrates from being a potential source of infection, and deserve further attention.

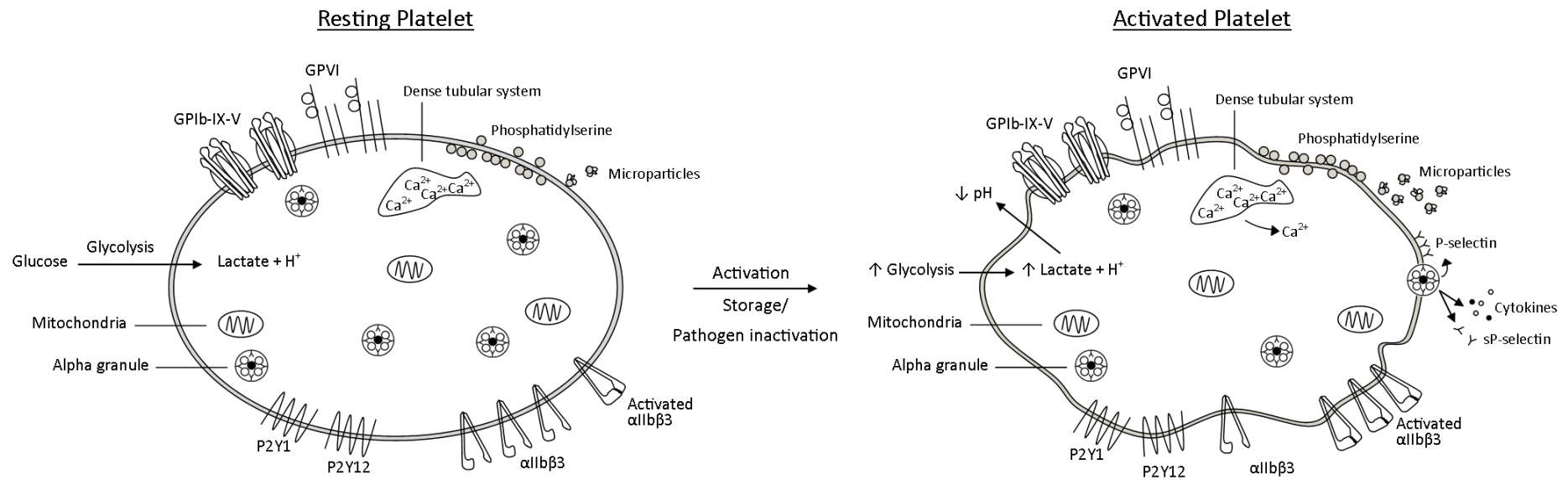


Figure 1. Schematic comparison of resting and activated platelets. The resting platelet is discoid in shape and expresses a multitude of surface receptors. Several receptors including GPIb-IX-V, GPVI, integrin $\alpha\text{IIb}\beta\text{3}$, P2Y1, and P2Y12 are essential for platelet adhesion, activation and aggregation. Additionally, the resting platelet contains alpha granules that are released during platelet activation. Over storage, a degree of platelet activation occurs. As the platelet product ages, platelets release their granular content, causing an increased surface expression of P-selectin (CD62P) and the release of cytokines into the platelet supernatant. Platelet activation also causes a conformational change in certain platelet glycoproteins, including integrin $\alpha\text{IIb}\beta\text{3}$ facilitating fibrinogen binding. The dense tubular system is filled with calcium (Ca^{2+}) which is released during platelet activation and facilitates phosphatidylserine externalisation and microparticle formation, making the platelet product more procoagulant. The rate of glycolysis is also upregulated over storage, increasing the concentration of lactate and lowering the pH. Platelets stored in the cold, cryopreserved or pathogen inactivated share some common characteristics of the activated platelet, although the degree of change is variable.

Table 1. The effects of novel storage modalities on platelet metabolism, activation, function, and product safety compared to room temperature stored platelet components.

Quality Parameter		Cold Storage	Cryopreservation [†]	Pathogen Inactivation (Intercept, Mirasol, or THERAFLEX)	Potential outcomes of combining techniques
Metabolism	Glycolysis	Decreased [26, 29, 34]	Increased [29, 49]	Increased [86, 100, 102, 103, 110, 111, 132] Unchanged [132]	Cold-PI: decreased Cryo-PI: increased Cryo-cold: decreased
	pH*	Decreased [29] Unchanged [26, 34]	Increased [29, 44] Decreased [50] Unchanged [53]	Decreased [84, 86, 100, 102, 103, 106, 110, 111, 132] Unchanged [105, 132]	Cold-PI: unchanged Cryo-PI: unchanged Cryo-cold: unchanged
Activation markers	CD62P	Increased [28, 34] Unchanged [27, 35]	Increased [50, 53, 103]	Increased [86, 100, 101, 103, 111, 132] Unchanged [102, 110, 121, 132]	Cold-PI: increased Cryo-PI: increased Cryo-cold: increased
	Phosphatidylserine	Increased [28, 34, 35]	Increased [44, 48, 50, 53, 103]	Increased [100-102, 110, 111, 132] Unchanged [84, 86, 103, 121]	Cold-PI: increased Cryo-PI: increased Cryo-cold: increased
	Activated integrin α IIb β 3	Increased [26, 28, 35]	Decreased [49, 50, 53]	Increased [105, 110, 132] Unchanged [102, 121]	Cold-PI: increased Cryo-PI: decreased Cryo-cold: decreased
Function	ADP-induced aggregation	Increased [29, 34, 41]	Decreased [29, 44, 49, 50] Increased [53]	Increased [105, 106] Unchanged [100, 103, 110]	Cold-PI: increased Cryo-PI: decreased

					Cryo-cold: decreased
	Collagen-induced aggregation	Increased [29, 34, 41]	Decreased [29, 44, 49, 50, 53]	Increased [86, 106] Decreased [100, 103, 105] Unchanged [84, 110]	Cold-PI: increased Cryo-PI: decreased Cryo-cold: decreased
	Thromboelastography (TEG)	R time: decreased [29, 34, 41] MA: Unchanged [29, 34, 41]	R time: decreased [29, 48, 50, 53] MA: decreased [29, 48, 50, 53]	R time: unchanged [106, 110] MA: decreased [106] MA: unchanged [110]	Cold-PI: R time decreased, MA unchanged Cryo-PI: R time decreased, MA decreased Cryo-cold: R time decreased, MA decreased
Product safety and shelf life	Bacterial proliferation	Decreased [30, 31]	Unknown	Nil or negligible [79-81, 84-86, 89-92]	Cold-PI: nil or negligible Cryo-PI: nil or negligible Cryo-cold: decreased
	May require gamma irradiation	Yes	Yes	No [78]	Cold-PI: no Cryo-PI: no Cryo-cold: yes
	Is the product safe and efficacious?	Yes [24, 42]	Yes [22, 55]	Yes [115, 116, 120, 128]	Cold-PI: undetermined Cryo-PI: undetermined Cryo-cold: undetermined
	Shelf life	At least 2 weeks [26-28]	Frozen: 2 years [46] Thawed: 6 hours [52]	5-7 days [58]	Cold-PI: at least 2 weeks Cryo-PI: at least 24 hours (thawed) Cryo-cold: at least 24 hours (thawed)

The described changes (decreased, increased, unchanged) are compared to conventional room temperature stored platelets on the same days of storage for liquid stored platelets (cold storage or pathogen inactivation) or between pre-freeze and post-thaw samples for cryopreserved platelets.

Abbreviations: Cold-PI = cold storage + pathogen inactivation; cryo-PI = cryopreservation + pathogen inactivation; cryo-cold = cryopreservation + post-thaw cold storage; R time = reaction time; MA = maximum amplitude

*differences due to proportion/type of additive solution

†differences may be due to the type of resuspension media

Acknowledgements

All authors conceived the concept of the paper. LW, MC and LJ drafted the paper. LJ, MP and DCM critically reviewed the manuscript. All authors approved the final version.

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