IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

IMPACT OF PLATELET STORAGE TEMPERATURE ON FUNCTION AND TRANSFUSION OUTCOMES

[1]MRITYUNJOY GHORAI

Email-mrityunjoyghorai123@gmail.com

MSc in Laboratory Technology in immunohematology and blood transfusion (2023-2024), Haldia Institute of Health Sciences

[2]Akash Kumar

MSc in Laboratory Technology in immunohematology and blood transfusion (2023-2024), Haldia Institute of Health Sciences

[3]AHAMMED SAYEED NIZAM

MSc in Laboratory Technology in immunohematology and blood transfusion (2023-2024), Haldia Institute of Health Sciences

[4]Sambit Roy

Assistant Professor (Department of MLT), Haldia Institute of Health Sciences

[5]Biswajit Chakraborty

Associate Professor & HOD (Department of MLT), Haldia Institute of Health Sciences

Abstract

Platelet transfusion constitutes an important part of modern transfusion medicine and serves an important purpose for prophylaxis and treatment of bleeding complications in thrombocytopenic, platelet dysfunction, trauma, surgical, and hematological disorders. The new advances in platelet biology have made cold storage (1–6°C) once again relevant for this purpose. Platelets stored under cold conditions demonstrate lower rate of metabolic decline, improved adhesiveness and aggregation, enhanced thrombin generation, and better ability to form clots. They are especially useful for the treatment of bleeding due to trauma, surgery, and emergency situations. Cold storage, however, promotes faster elimination of platelets after transfusion, making them less suitable for preventive purposes. This review discusses the biological influence of storage temperature on platelet biology (structural, metabolic, activated, and functional). Furthermore, it highlights benefits and disadvantages of storing platelets under ambient or cold conditions, their effect on the clinical outcome, and current problems in the application of platelet transfusions. Lastly,

it outlines modern developments, clinical studies, and research efforts directed to improvement of platelet transfusions through better platelet storage conditions.

Keywords**:** *Cold-stored platelets, Platelet storage, Platelet transfusion, Platelet function, Room-temperature platelets*.

1. Introduction

Platelet transfusion is one of the most significant and important therapeutic methods in current transfusion medicine [1]. Since the first successful platelet transfusion, which occurred in the middle of the last century, progress in the techniques of blood component separation, the storage of platelets, and transfusion practice has greatly refined the management of patients who are at risk of bleeding. Platelets play a vital role in the processes of primary hemostasis, causing adhesion, activation, aggregation and supporting the coagulation process [2]. Therefore, most common causes for using platelet transfusions to treat and prevent bleeding are low blood platelet counts, poor platelet function, trauma, major surgery, haematological malignancies, and bone marrow failure disorders. Platelet concentrates are one of the most commonly used blood products in the world today, and are key to patient care [3].

In most clinical environments, platelets can not be administered directly after collection, necessitating the use of effective storage systems to guarantee product availability and timely support of patients. Platelet Storage maintains cellular viability and function during the time between the collection of platelets and their transfusion. In contrast to red blood cells, platelets undergo progressive biochemical, structural, and functional alterations while being stored; these changes are collectively referred to as the platelet storage lesion. These alterations can affect platelet quality, post-transfusion recovery and clinical efficacy. Thus, the use of platelet transfusion is greatly dependent on the storage conditions such as temperature, storage medium, movement and storage period [4].

The earliest methods of platelet storage were to keep the blood products at cold temperatures of 1 to 6°C, mainly due to the fact that these cold temperatures were known to reduce bacterial growth and maintain the blood product. There is considerable debate in relation to the best temperature for platelet storage. Platelets stored in the refrigerator have a slightly longer lifespan, and they seem to maintain better hemostatic activities, with a reduced risk of bacterial growth, when compared to room temperature storage [5]. The use of cold-stored platelets for major transfusion operations, heart surgery, trauma treatment, and military medicine has gained popularity. The bleeding in these locations must be stopped quickly. Therefore, the careful balancing act between platelet survival and functional haemostatic performance is the main focus of current transfusion research. The main focus of this research is the relationship between storage temperature and platelet biology, function, and clinical performance. The paper explores the differences and similarities between cold-stored and room-temperature platelets, how they affect transfusion outcomes, and the mechanisms behind these variations.

2. Platelet Biology and Hemostatic Function

Platelets are tiny, nucleus-free blood cells that are crucial for preserving vascular integrity and haemostasis. In addition to their role in blood coagulation, platelets release granules containing bioactive molecules that play a role in inflammation, immune defense, angiogenesis, tissue repair, wound healing, and cellular communication [6]. Activated platelets release growth factors, cytokines, chemokines, coagulation factors, and anti-microbial peptides which govern the repair of the vessels and host defense. Platelets play a role in the pathological processes, including thrombosis, atherosclerosis and tumor progression but their main

action is to prevent bleeding through adhesion, platelet activation, aggregation and interaction with coagulation cascade [7]. The classical and contemporary ideas concerning hemostasis are shown in Figure 1(a,b). The classical model is one in which vasoconstriction is followed by platelet plug formation and then by stabilization of the fibrin clot. The modern model, however, shows that there are interactions between vascular, platelet, and coagulation processes, all of which operate at the same time and continuously to provide effective hemostasis.

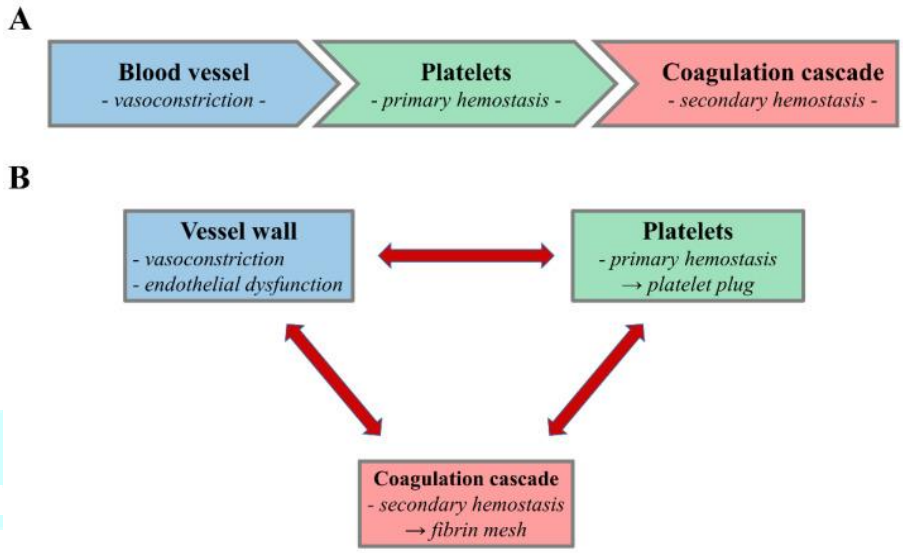

Figure 1: A schematic representation of the haemostatic process. (A) The traditional view of haemostasis as a three-step process that includes vasoconstriction and primary and secondary haemostasis as separate and sequential occurrences. (B) Current understanding of haemostasis as a complicated process in which the vascular wall, platelets, and coagulation system interact and continually impact one another.

2.1 Structure and Physiology of Platelets

Platelets are tiny, anucleated cytoplasmic fragments generated by megakaryocytes of bone marrow and are important mediators for the maintenance of vascular homeostasis. Platelets have a diameter size of about 2-4 μm and a circulating life of 8-10 days. Platelet counts in healthy adults normally vary between 150–400 × 10^9/L. In their physiologic state, platelets remain circulating in a discoid form and constantly survey the vascular system through various receptors and adhesion molecules [8]. During vascular damage, they quickly become activated and change their form into an amoeboid one having several pseudopodia that help with adhesion, aggregation, and clot formation (Figure 2).

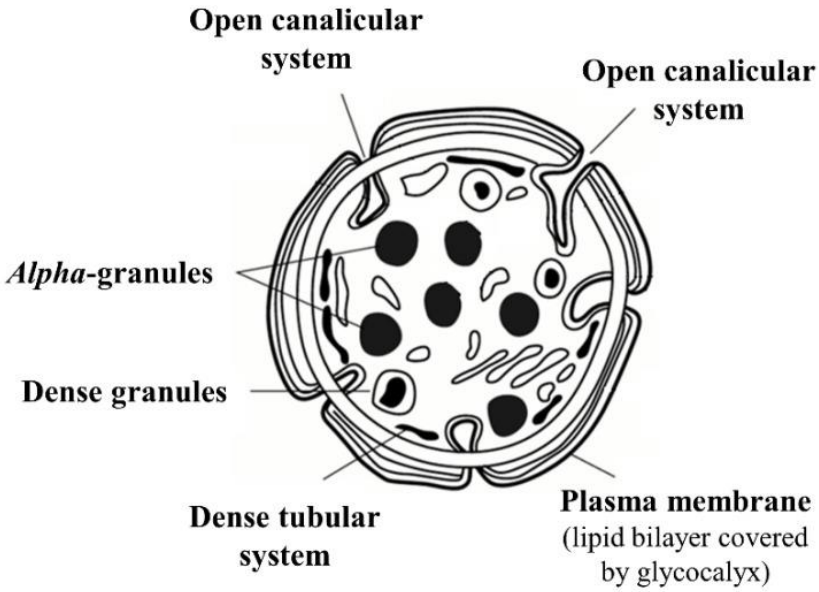

Figure 2: Schematic image of platelets.

Structurally, platelets have a unique plasma membrane enveloped by the negatively charged glycocalyx layer made up of glycoproteins and glycolipids [9]. The glycocalyx suppresses platelet aggregation and regulates their interactions with other cells. Platelets' membranes include a broad range of receptors involved in adhesion, activation, and aggregation, making them very sensitive to vascular damage. Platelets have an open canalicular system (OCS), which is made up of invaginated membranes that come into touch with the external environment. The OCS dramatically increases membrane area and allows for the fast release of granule contents [10]. Platelets have a distinctive structure called the dense tubular system (DTS).

Platelet surface receptors are the primary means by which platelets conduct their numerous tasks (Table 1.). Adhesion receptors such as GPIb-IX-V, GPVI, and collagen-binding integrins help platelets adhere to the damaged endothelium. Activation receptors such as protease-activated receptors (PAR-1 and PAR-4), P2Y1/P2Y12, and thromboxane receptors react to a variety of agonists including thrombin, ADP, and thromboxane A2. The GPIIb/IIIa (αIIbβ3) integrin is essential for aggregation since it promotes fibrin [11].

Table 1. Major Platelet Receptors and Their Functions in Hemostasis

Function	Receptors	Major Ligands
Platelet adhesion	GPIb-IX-V	von Willebrand factor (vWF)
	GPVI	Collagen
	α2β1	Collagen
	α5β1	Fibronectin
	α6β1	Laminin
Platelet activation	PAR-1, PAR-4	Thrombin
	P2Y1, P2Y12	ADP
	TPα, TPβ	Thromboxane A_2
Platelet aggregation	αIIbβ3 (GPIIb/IIIa)	Fibrinogen, vWF

When activated, platelets release biologically active compounds that are stored in their unique membrane-bound compartments inside the cell known as granules. Lysosomal granules, δ-granules, and α-granules are the three types of compartments. The majority of α-granules, which include proteins for blood coagulation, wound healing, inflammation, vascular formation, and immunological response, are found in platelets of the former type [12]. Platelet factor 4, fibrinogen, von Willibrand factor, P-selectin, growth factors, cytokines, and chemokines are examples of these granules. ADP, ATP, serotonin, calcium, magnesium, and polyphosphates are among the small organic and inorganic molecules that make up the second group, δ-granules, which have less than 10 per platelet [13]. Hydrolytic enzymes such cathepsins, phosphatases, and arylsulfatases are found in lysosomal granules and help restructure the extracellular matrix and resolve thrombus in the last phases of wound healing. Platelets react quickly to vascular damage because of the coordinated action of membrane receptors, intracellular signal transmission, and lysosomal granule release. In addition to their well-known activity in clotting, platelets have been connected to immunological processes, angiogenesis, tissue regeneration, inflammatory reactions, and infection defence [14]. Understanding platelets' structure and function is necessary to understand how storage impacts them.

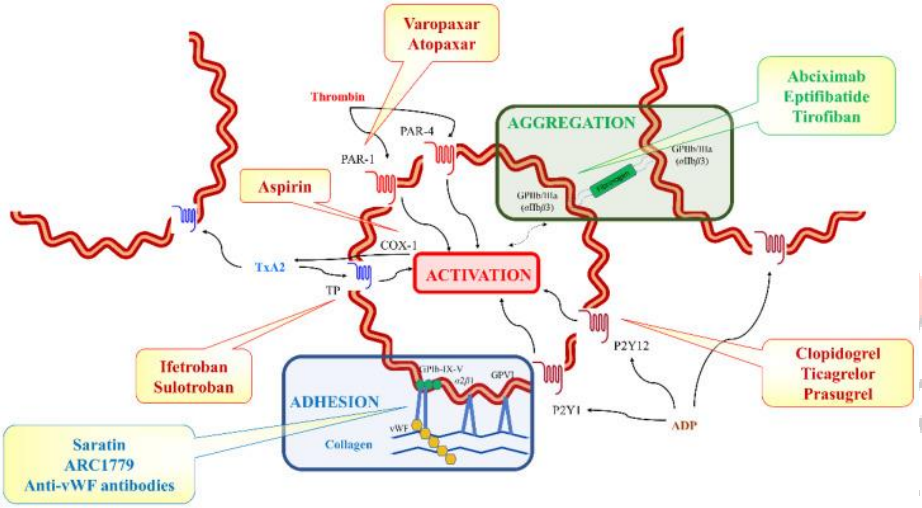

Figure 3: Ligands and receptors linked to platelet adhesion, activation, and aggregation. Some examples of existing and emerging antithrombotic therapies are shown in boxes. Adenosine diphosphate (ADP), cyclooxygenase-1 (COX-1), glycoprotein (GP), protease-activated receptors (PAR), and TP.

2.2 Role of Platelets in Hemostasis

Platelets play a crucial role in primary haemostasis, preventing blood loss from vascular injury. Haemostasis comprises three concurrent processes: platelet adhesion, activation, and aggregation [15]. Injury to the endothelium lining results in the exposing of subendothelial collagen and von Willebrand factor (vWF). Thus, platelets will attach to the injured surface, and in situations of elevated shear stress, such as in arteries, platelet adhesion transpires via the interaction between von Willebrand factor and GPIb-V-IX receptor complexes.

The activation of adhering platelets triggers signalling pathways that induce calcium influx and promote the release of potent agonists such as adenosine diphosphate (ADP), thromboxane A2 (TxA2), and thrombin. These agonists augment the recruitment and activation of platelets via an autocrine/paracrine mechanism. Moreover, platelet activation leads to the exposure of phosphatidylserine on the membrane

surface, creating a procoagulant environment conducive to thrombin production and the activation of the coagulation cascade [16].

The concluding phase entails platelet aggregation, triggered by the activation of glycoprotein IIb/IIIa (αIIbβ3) receptors and the binding of fibrinogen and von Willebrand factor, therefore forming a connection between neighbouring platelets. This results in the creation of a platelet block, subsequently reinforced by fibrin [17]. Endothelium-derived inhibitors such as nitric oxide and prostacyclin restrict platelet activity to damage sites, ensuring that the process stays localised. Figure 3. Schematic representation depicting the mechanism of platelet-mediated haemostasis, which encompasses platelet adhesion to exposed collagen and von Willebrand factor, intracellular activation via ADP, thromboxane A2, and thrombin, phosphatidylserine exposure, and platelet aggregation through glycoprotein IIb/IIIa.

3. Clinical Implications of Platelet (Patho)Physiology

The hemostatic balance is achieved with the help of platelets, and any imbalance in terms of the quantity or activity of the latter leads to a pathological state. Bernard-Soulier syndrome and Glanzmann thrombasthenia are two kinds of genetic conditions affecting platelets' ability to adhere or aggregate, leading to bleeding tendency [19]. Not only platelets have a primary function in the process of hemostasis, but they also contribute to coagulation by serving as a site for the activation of coagulation factors and release of procoagulant factors such as tissue factor, factor V, and von Willebrand factor. Any issues concerning both mechanisms result in increased risk of bleeding due to insufficient thrombin and clot generation [20]. Figure 4. Macroscopic representation of thrombi formed in different vascular beds. (A) Arterial thrombus consisting of rich platelet content with little amount of fibrin and erythrocytes. (B) Venous thrombus containing rich amount of fibrin with entrapment of erythrocytes.

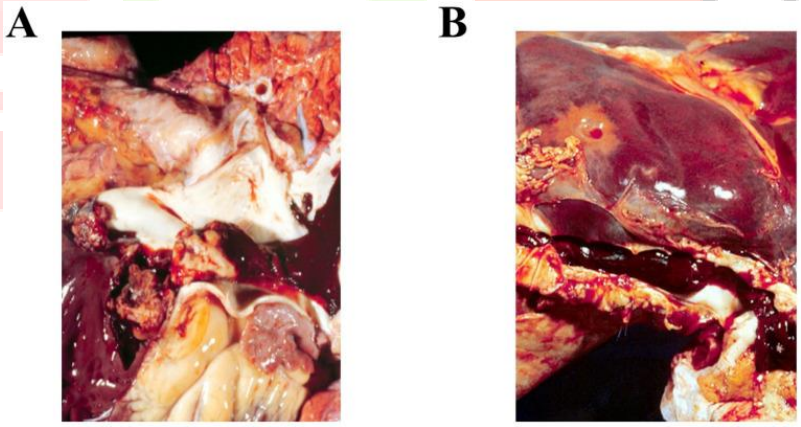

Figure 4: Macroscopic appearance of a (**A**) white thrombus in a patient with carotid artery occlusion and of a (**B**) red thrombus in a patient with deep vein thrombosis.

Platelet activation has been linked to arterial thrombosis, myocardial infarction, stroke, diabetes, and atherosclerosis, all of which are classified as thrombotic disorders. Venous thrombi are more fibrinous (and include more red blood cells), while arterial thrombi are more platelet-rich ("white thrombi") [21]. Platelets have traditionally been assumed to have more important roles in arterial thrombosis, although they may also play roles in venous thrombosis via interactions with coagulation factors, endothelial cells, and inflammatory pathways. The understanding of platelet physiology has aided in the creation of antiplatelet medications that impede platelet adhesion, activation, and aggregate. These medications are classified into four categories: COX-1 inhibitors, P2Y12 receptor inhibitors, protease-activated receptor (PAR) inhibitors,

and glycoprotein IIb/IIIa antagonists. These are still important treatments for the prevention and treatment of thrombotic cardiovascular diseases [22].

3. Current Methods of Platelet Collection and Storage

3.1 Platelet Collection Techniques

Whole Blood-Derived Platelets: Donated whole blood is centrifuged and components are separated to give rise to whole blood-derived platelets. The PRP/buffy coat fractions are gathered and pooled from several ABO-compatible donors to achieve the therapeutic dose of platelets. This approach is favored because it is an economical option and provides an opportunity to produce all three blood products from a single donation, red blood cells, plasma and platelets [23].

Apheresis Platelets: These are platelets that have been collected directly from one donor by using automated cell-separation devices. In the process, platelets are removed but the other blood components are returned to the donor. One donation will normally give a full therapeutic dose [24].

3.2 Storage Requirements

Platelet storage is designed to preserve cell viability and haemostatic performance while minimising bacterial contamination. All worldwide regulatory organisations recommend rigorous storage conditions to ensure product safety and effectiveness. The best storage bag materials are often constructed of high gas permeability polyethylene bags, which permit the interchange of oxygen and carbon dioxide, supporting biological metabolism and regulating pH. During traditional storage, it is also critical to keep the goods under continual moderate agitation. Agitation improves gas exchange, reduces platelet aggregation, and promotes uniform nutrition distribution [25]. Pathogen reduction technologies are becoming increasingly popular to boost microbiological safety, and other processing techniques, such as irradiation, may be utilised to reduce the risk of transmission of graft-versus-host disease.

3.3 Standard Room Temperature Storage

Currently, platelet preservation at room temperature is the standard practice. Platelet concentrate is kept at 20-24°C with agitation and has a shelf life of 5-7 days. Room temperature increases platelet lifetime and functioning after transfusion by preserving platelet cellular metabolism and cell membrane integrity [26]. Despite its popularity, there are a few disadvantages to using this kind of storage. Platelet storage lesions are unavoidable as a consequence of the ongoing metabolic process, which involves glucose depletion, increased lactic acid generation, pH reduction, and platelet dysfunction. Another significant disadvantage of keeping platelets at this temperature is the increased vulnerability to bacterial growth [27].

3.4 Alternative Storage Strategies

Cold Storage: Refrigeration of platelets at 1-6°C is called cold storage, and was thought to be abandoned long ago because of the post-transfusion platelet survival problem, but now there is renewed interest because of its improved hemostatic properties and its minimal potential for bacterial growth. Cold-stored platelets are known to have better adhesion, aggregation and clot-formation characteristics especially in actively bleeding trauma and surgical patients. However, recent research has demonstrated that it is possible to store platelets at cold temperatures for as long as 14 days, and further research is in progress to see if longer storage times are possible [28].

Cryopreservation: Cryopreservation is another approach which allows long-term platelet storage at ultra-low temperatures, usually with the use of a cryoprotectant like dimethyl sulfoxide (DMSO). Platelet products can be frozen for a number of years and are particularly useful in military applications, in remote

areas, and when supplies of platelets are low. But the freezing and thawing process can mess up platelet shape and function, making the use of platelets a common practice difficult [29].

Novel Preservation Technologies: The new developments in the technology of platelet preservation have been aimed at enhancing the quality of storage and shelf life. Partial substitutes for plasma used to maintain pH, reduce metabolic deterioration and reduce transfusion related adverse reactions: platelet additive solutions (PAS). The varying effect on platelet quality during prolonged storage that different PAS have shown has been reported [30].

5. Room-Temperature Stored Platelets: Functional Characteristics

4.1 Platelet Storage Lesion

The combination of biochemical, metabolic, structural and functional alterations of platelets during ex vivo storage is termed as platelet storage lesion (PSL). These changes are gradually leading to platelet death and hemostatic dysfunction that affects the rate of recovery after transfusion and clinical outcomes. Platelets are metabolically active after being collected and can undergo many changes during storage, which depends on the conditions used in collection [31] .

The importance of PSL is related to its direct effects on the quality of platelets. Platelets undergo membrane remodeling, activation of intracellular signaling pathways, loss of receptor functions and decreased responsiveness to physiological agonists during storage. Structural changes can involve changes in platelet shape, granule content, and membrane integrity. These changes may lead to reduced platelet survival after transfusion and to their decreased efficiency in hemostasis.

4.2 Metabolic Alterations During Storage

Platelets need a continuous supply of energy to keep their membranes and ion gradients intact and their functions operational. Thus, platelet storage lesion is characterized by metabolic changes which are one of the earliest changes to occur [32].

Glucose Consumption: Glucose serves as the primary energy substrate for platelets. Metabolism of glucose via glycolysis and oxidative phosphorylation still occurs in platelets during storage. Even at room temperature, metabolic activity is high and glucose is gradually depleted. Glucose utilization can be accelerated resulting in energy deficits that can negatively affect the function and viability of platelets. Cold storage on the other hand will slow down the metabolic reactions; this will help to decrease the amount of glucose used and will enable the preservation of more energy for a longer period.

Lactate Production: During glycolysis, the metabolic by-product of glycolysis is lactate. The increased production of lactate is a feature of the storage lesion in platelets and is a reflection of the continued anaerobic metabolism. High levels of lactate can cause the storage medium to become more acidic, and are correlated with poor platelet quality. Several studies have shown that room temperature platelets accumulate more lactate than refrigerated platelets due to their higher metabolic rates.

pH Changes: Maintenance of physiological pH is critical for platelet survival and function. Excessive glucose consumption and lactate production result in a gradual decrease in pH during storage. Acidic conditions have a negative effect on membrane integrity, enzyme activity and platelet responsiveness. If the pH is below 6.2 it is usually harmful and can cause permanent platelet damage. COLD STORAGE PRESERVES pH STABILITY: reduction of metabolic activity, and reduction of lactate production.

4.3 Morphological Changes

Platelet morphology is greatly affected by temperature of storage. Normal platelets are discoid in shape, which is necessary for normal circulation and function. Increased changes in the cytoskeletons and membranes of platelets cause them to gradually assume a spherical shape during storage [33].

Along with shape change, there is also membrane remodeling, such as phospholipid redistribution, receptor clustering and changes in membrane fluidity. These changes impact platelet adhesion to vascular surfaces and coagulation factors. Altered platelet architecture is also due to changes in the cytoskeleton (actin filaments and microtubules). Many of these changes are associated with an increased hemostatic responsiveness, but also with a decrease in circulatory survival in cold storage [34].

4.4 Platelet Activation During Storage

A characteristic feature of platelet storage lesion is spontaneous platelet activation. Storage related activation occurs even when the vascular injury is not present, and is increased progressively over the storage time [35]. A few markers of activation are: increased surface expression of P-selectin (CD62P), activated glycoprotein IIb/IIIa, and phosphatidylserine. These are markers of degranulation and alterations in platelet functional status. Platelet factor 4, β-thromboglobulin, ADP, serotonin and several cytokines are released from the α-granules and dense granules of activated platelets. These mediators are also involved in the hemostatic function, but release of these occurs too early in storage, resulting in decreased availability of granule contents after transfusion. One of the other effects of activation is the generation of platelet-derived microparticles. The membrane vesicles are procoagulant-rich and contain coagulation proteins, both of which are abundant in these small vesicles. Microparticles are generated to a greater extent during storage and especially in activated platelets. Microparticles can stimulate the generation of thrombin, but an overproduction of them can be a sign of poor quality platelets [36].

4.5 Impact of Temperature on Cellular Metabolism

Room-Temperature Storage

The currently recommended method for platelet preservation is still the room-temperature storage (20-24°C) which is known to yield better post-transfusion platelet recovery and circulation time. Platelets stored under these conditions, however, have a high metabolic rate. The development of storage lesion is due to continuous glucose utilization, lactate accumulation, pH decline and progressive activation. In addition, the room temperature storage allows favorable conditions for bacterial proliferation which reduces the shelf life to the range of 5-7 days [37].

Cold Storage

Enzymatic activity and cellular metabolism are decreased during cold storage (1-6C) and so are glucose consumption and lactate production. Therefore, pH is more stable and several functional characteristics related to hemostasis are maintained. Platelets stored at refrigeration temperature exhibit greater adhesion, aggregation and thrombin-generating ability. But platelet survival is also shortened after transfusion due to cold-induced changes, which makes platelets less long-lived although they are more effective in the immediate post-transfusion period [38].

4.6 Molecular Mechanisms Influenced by Temperature

Platelet molecular biology is highly sensitive to temperature. Cold storage causes alterations to membrane glycoproteins that affect platelet adhesion and clearance, including alterations to GPIbα and integrin αIIbβ3. Increased clustering and conformational change help increase activation but also help increase the recognition of the receptors following transfusion to the hepatic macrophages.

Intracellular signal transduction pathways that regulate calcium mobilization, protein kinases, and cytoskeletal pathways are also influenced by storage temperature. Platelets stored at cold temperatures have altered signaling responses that promote the speed of hemostatic activity. In addition, temperature affects apoptosis-related processes, such as mitochondrial dysfunction, phosphatidylserine exposure, and activation of caspase pathways. The molecular events involved in this decrease in platelet survival during extended storage. Knowing these temperature sensitive mechanisms is crucial for developing an optimized storage strategy and enhancing the clinical efficacy of platelet transfusion therapy [39].

6. Cold-Stored Platelets: Functional Characteristics

6.1 Historical Perspective

Platelets have been stored at refrigerated temperatures since early transfusion medicine. Previously, platelets were routinely kept at 1-6°C as it was deemed to slow down the growth of bacteria and preserve blood products. Research in the 1960s and 1970s however showed that cold stored platelets had a shorter post transfusion survival and very rapid clearance. This led to the introduction of room temperature storage (20-24°C with constant agitation) as standard method as it offered better platelet recovery and survival after transfusion [40].

In recent years, interest in cold-stored platelets has re-emerged. New knowledge about platelet biology has emerged that refrigerated platelets may have greater hemostatic activity, while circulating for a shorter period of time. Especially, the needs of trauma care, cardiac surgery, military medicine and massive transfusion protocols have fueled this resurgence of interest, as rapid hemostasis may be more crucial to survival than extended platelet survival.

6.2 Mechanisms of Cold-Induced Changes

- **Membrane Remodeling**

Low temperatures cause structural changes in platelet membranes that cause platelets to become triggered. Chilling changes the fluidity of the membranes and leads to a redistribution of the membrane phospholipids, which therefore leads to changes in the plasma membrane architecture of these platelets. All of these changes promote enhanced platelet responsiveness and procoagulant activity [41].

- **Glycoprotein Alterations**

Cold Storage has an impact on the expression and organisation of important platelet glycoproteins, such as glycoprotein Ibα (GPIbα), and glycoprotein IIb/IIIa (αIIbβ3). Clustering and conformational changes of these receptors promote adhesion to damaged vascular surfaces and recognition and clearance by liver macrophages following transfusion.

- **Enhanced Activation State**

Platelets have a partially activated phenotype in the refrigerator, with higher expression of activation markers like P-selectin and phosphatidylserine. This activation causes them to be better able to form clots but may shorten their lifespan after transfusion.

6.3 Advantages of Cold Storage

- Preservation of platelet hemostatic function is one of the major benefits of cold storage. Refrigerated platelets have greater adhesion to collagen and von Willebrand factor, and have more robust aggregation activity than room-temperature-stored platelets. They have properties that allow them to be especially useful in actively bleeding patients.
- Platelets that have been stored in the cold have more thrombin-generating capacity and are more likely to cause rapid clot formation. Functional tests such as thromboelastography have shown enhanced clot formation and clot stability that could lead to better bleeding control.
- This is because the lower storage temperature greatly slows the growth of bacteria, which is a common problem in room temperature platelet storage. Therefore using refrigerated platelets provides better microbial safety and can reduce the risk of bacterial infection transmitted by platelet transfusion.
- Cold storage will cause a metabolic retardation thus minimizing the rate of glucose consumption, lactate production, and pH decline. This may lead to a lower rate of metabolic deterioration, which may enable platelets to be stored for longer than the normal 5-7 days that they are stored at room temperature, some studies suggesting storage times of up to 14 days or more [42].

6.4 Limitations

- Cold-stored platelets have increased hemostatic activity, but decreased survival following transfusion. The alterations in the membrane caused by refrigeration shorten the circulating life of platelets by increasing their clearance rate by the reticuloendothelial system.
- Many activation markers, such as P-selectin and phosphatidylserine, have been found to be more highly expressed in cold storage. Such alterations enhance the clotting ability, but can cause a decrease in platelet recovery and survival after transfusion.
- Regulatory and standardization concerns are limiting the use of cold stored platelets. It has been difficult to ensure a uniform adoption of this product due to differences in the storage procedures, shelf-life recommendations, and quality assessment criteria. Standardised guidelines can only be developed with further clinical evidence [43].

6.5 Emerging Evidence Supporting Cold Storage

There is increasing evidence that platelets that are stored in the cold are clinically useful. Adhesion, aggregation, generation of thrombin and strength of the clot are consistently better than room-temperature-stored platelets in the laboratory. Improved hemorrhage control and survival has been observed in animal models of traumatic bleeding. Initial clinical studies with cold stored platelets in trauma, cardiac surgery, and bleeding patients indicate that these platelets are effective at achieving hemostasis while being safe. In addition, some studies are currently under way to investigate their use in transfusion clinics and recent clinical trials have shown that refrigerated platelets may be useful for patients who need immediate hemostatic support [44]. The evidence is mounting and cold storage is becoming a more and more attractive approach to optimizing platelet transfusion therapy in bleeding patients.

7. Impact of Storage Temperature on Clinical Transfusion Outcomes

Storage conditions play a significant role in platelet viability, hemostatic function and clinical transfusion efficacy. Although room temperature (20–24°C) platelets are the standard product for routine transfusion of platelets for prophylaxis, there is a growing body of evidence that cold-stored platelets (1–6°C) may have important benefits in the care of bleeding patients [45].

7.1 Hemorrhage Control

Cold stored platelets have been shown to exhibit greater hemostatic activity and are therefore useful in emergency situations where prompt control of bleeding is needed. Platelets stored in a refrigerator have superior adhesion, aggregation and thrombin generation in trauma patients leading to quicker clot formation and stabilization. This has also been found in surgical procedures, particularly cardiac, vascular and major orthopedic surgeries where there is substantial blood loss. As a result, the use of cold-stored platelets is being evaluated for incorporation into massive transfusion protocols, in which rapid hemostasis is a critical component [46].

7.2 Platelet Count Increment

One of the most important indicators of transfusion effectiveness is the Corrected Count Increment (CCI), which is a measure of platelet recovery after transfusion. The longer the circulatory survival of room-temperature platelets, the higher the CCIs. Cold stored platelets, on the other hand, are removed faster from circulation due to the changes in membrane and glycoproteins caused by cold storage. Posttransfusion platelet increments, as determined by platelet recovery studies, have always been found to be lower with cold stored platelets than with the more active, fresh-frozen platelets [47].

7.3 Bleeding Prevention

Platelets at room temperature are the most desirable for transfusion to prevent bleeding in the stable thrombocytopenic patient. They last for a long time, which means that they can help to support platelets for longer and so demand fewer platelet transfusions. The activity of cold-stored platelets in clot formation is excellent, but the platelets may lack the optimal ability to be used as a prophylactic due to their shorter stay in circulation [48].

7.4 Outcomes in Trauma and Emergency Medicine

Cold-stored platelets have recently attracted considerable interest in resuscitation, military medicine and trauma treatment. These properties, such as improved hemostatic, decreased risk of bacterial contamination and longer storage time, make them desirable for prehospital and battlefield use. Platelets can be stored in the fridge and can be used in damage control resuscitation, where they can help to control the bleeding earlier and improve the management of trauma-induced coagulopathy [49].

7.5 Outcomes in Oncology and Hematology

Chronic thrombocytopenia, hematologic malignancies, and chemotherapy-induced thrombocytopenia are situations that frequently require multiple platelet transfusions as prophylaxis. In the above environments room temperature platelet is still better since it offers better platelet count recovery and longer circulation time. There is currently no supporting evidence to support the routine use of cold-stored platelets for longer term platelet support in oncology and hematology patients [50].

8. Challenges in Clinical Adoption

Although there is a growing interest in the use of cold stored platelets, there are several reasons for not yet having a broad clinical practice of these. A major challenge is the lack of clear knowledge about the clinical benefits of cold-stored and room-temperature platelets, based on large, randomized controlled trials in different patient groups [51] . Standardization is also a problem point because there are differences in the procedures for which platelets are stored, when they are refrigerated, how long they are stored, platelet additive solution, and the criteria used for quality assessment. The adoption process is more complex because the regulations differ from country to country. Secondly, blood banks have to solve the problem of

balancing the availability of room temperature platelets for prophylactic use and cold-stored platelets for active bleeding [52] . Defining indications, standardizing manufacturing methods and developing cost-effective inventory management approaches will be key to the successful incorporation of cold-stored platelets into routine transfusion..

Conclusion

Platelets are essential components of the haemostatic process, and the temperature at which they are stored has a direct association with their physiological characteristics. Currently, room-temperature storage is considered the gold standard because it ensures viability, recovery post-transfusion, and suitability for prevention of bleeding among patients with thrombocytopenia. Despite these benefits, room-temperature platelets demonstrate some negative outcomes, such as storage lesion formation, rapid depletion of metabolic capacity, and increased possibility of contamination.

Conversely, lower storage temperatures have positive influence on platelet adherence, aggregation, thrombin generation, and clot formation; therefore, they are recommended for management of hemorrhagic events resulting from trauma or other emergency situations. Cold-platelets show poor circulation lifetime, however, new scientific data from laboratory experiments and preclinical and clinical trials indicate that cold-platelets might be used as a novel drug. Future research related to storage technology, use of additive solutions, pathogens reduction, and personalized transfusions can contribute to improvement in effectiveness of cold-platelets. The findings of randomised clinical trials will enable specialists to define potential applications of cold-platelets and give scientific suggestions about them. Overall, it is necessary to use two platelet types in order to satisfy patient requirements.

REFERENCES

1. Stolla M, Refaai MA, Heal JM, Spinelli SL, Garraud O, Phipps RP, Blumberg N. Platelet transfusion–the new immunology of an old therapy. Frontiers in immunology. 2015 Feb 2;6:28.
2. Scridon A. Platelets and their role in hemostasis and thrombosis—from physiology to pathophysiology and therapeutic implications. International journal of molecular sciences. 2022 Oct 23;23(21):12772.
3. Garraud O, Cognasse F, Tissot JD, Chavarin P, Laperche S, Morel P, Lefrère JJ, Pozzetto B, Lozano M, Blumberg N, Osselaer JC. Improving platelet transfusion safety: biomedical and technical considerations. Blood transfusion. 2015 Nov 16;14(2):109.
4. Aubron C, Flint AW, Ozier Y, McQuilten Z. Transfusion of stored platelets: balancing risks and product availability. International Journal of Clinical Transfusion Medicine. 2016 Nov 11:133-8.
5. Ketter PM, Kamucheka R, Arulanandam B, Akers K, Cap AP. Platelet enhancement of bacterial growth during room temperature storage: mitigation through refrigeration. Transfusion. 2019 Apr;59(S2):1479-89.
6. Clemetson KJ. Platelets and primary haemostasis. Thrombosis research. 2012 Mar 1;129(3):220-4.
7. Vilahur G, Fuster V. Interplay between platelets and coagulation: from protective haemostasis to pathological arterial thrombosis. European Heart Journal. 2025 Feb 1;46(5):413-23.
8. McNicol A, Israels SJ. Platelet dense granules: structure, function and implications for haemostasis. Thrombosis research. 1999 Jul 1;95(1):1-8.
9. Fritsma GA. Platelet structure and function. Clinical laboratory science. 2015 Apr 1;28(2):125.
10. Saboor M, Ayub Q, Ilyas S. Platelet receptors; an instrumental of platelet physiology. Pakistan journal of medical sciences. 2013 May;29(3):891.
11. Joo SJ. Mechanisms of platelet activation and integrin αIIβ3. Korean circulation journal. 2012 May;42(5):295-301.

12. Tokarz-Deptuła B, Baraniecki Ł, Palma J, Stosik M, Syrenicz A, Kołacz R, Deptuła W. Platelets and their role in immunity: formation, activation and activity, and biologically active substances in their granules and extracellular vesicles. International Journal of Inflammation. 2025;2025(1):8878764.
13. Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. Platelets. 2001 Jan 1;12(5):261-73.
14. Liu J, Sukhova GK, Sun JS, Xu WH, Libby P, Shi GP. Lysosomal cysteine proteases in atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2004 Aug 1;24(8):1359-66.
15. Smyth SS, McEver RP, Weyrich AS, Morrell CN, Hoffman MR, Arepally GM, French PA, Dauerman HL, Becker RC, THE F. Platelet functions beyond hemostasis. Journal of Thrombosis and Haemostasis. 2009 Nov 1;7(11):1759-66.
16. Reddy EC, Rand ML. Procoagulant phosphatidylserine-exposing platelets in vitro and in vivo. Frontiers in cardiovascular medicine. 2020 Mar 3;7:15.
17. Fullard JF. The role of the platelet glycoprotein IIb/IIIa in thrombosis and haemostasis. Current pharmaceutical design. 2004 May 1;10(14):1567-76.
18. Gkaliagkousi E, Ritter J, Ferro A. Platelet-derived nitric oxide signaling and regulation. Circulation research. 2007 Sep 28;101(7):654-62.
19. Badulescu OV, Ciocoiu M, Vladeanu MC, Huzum B, Plesoianu CE, Iliescu-Halitchi D, Bojan A, Iliescu-Halitchi C, Bojan IB. The role of platelet dysfunctions in the pathogenesis of the hemostatic-coagulant system imbalances. International Journal of Molecular Sciences. 2025 Mar 19;26(6):2756.
20. Mann KG. Thrombin generation in hemorrhage control and vascular occlusion. Circulation. 2011 Jul 12;124(2):225-35.
21. Lippi G, Favaloro EJ. Venous and arterial thromboses: two sides of the same coin?. InSeminars in Thrombosis and Hemostasis 2018 Apr (Vol. 44, No. 03, pp. 239-248). Thieme Medical Publishers.
22. Xu XR, Carrim N, Neves MA, McKeown T, Stratton TW, Coelho RM, Lei X, Chen P, Xu J, Dai X, Li BX. Platelets and platelet adhesion molecules: novel mechanisms of thrombosis and anti-thrombotic therapies. Thrombosis journal. 2016 Oct 4;14(Suppl 1):29.
23. Yazer MH, Razatos A, Sayers M. Whole blood derived and apheresis platelets: opinions and preferences—the results of a national survey of blood collectors. Transfusion. 2023 Jun;63(6):1224-9.
24. Moog R. Apheresis techniques for collection of peripheral blood progenitor cells. Transfusion and Apheresis Science. 2004 Dec 1;31(3):207-20.
25. Vit G, Klüter H, Wuchter P. Platelet storage and functional integrity. Journal of Laboratory Medicine. 2020 Oct 25;44(5):285-93.
26. Vassallo Jr RR. Preparation, preservation, and storage of platelet concentrates. Rossi's Principles of Transfusion Medicine. 2016 Apr 26:227-34.
27. International Society for Biological and Environmental Repositories (ISBER). Collection, storage, retrieval and distribution of biological materials for research. Cell Preservation Technology. 2008 Mar 1;6(1):3-58.
28. Mack JP, Miles J, Stolla M. Cold-stored platelets: review of studies in humans. Transfusion Medicine Reviews. 2020 Oct 1;34(4):221-6.
29. Murray KA, Gibson MI. Chemical approaches to cryopreservation. Nature Reviews Chemistry. 2022 Aug;6(8):579-93.
30. Johnson L, Vekariya S, Wood B, Tan S, Roan C, Marks DC. Refrigeration of apheresis platelets in platelet additive solution (PAS-E) supports in vitro platelet quality to maximize the shelf-life. Transfusion. 2021 Jul;61:S58-67.

31. Shrivastava M. The platelet storage lesion. Transfusion and Apheresis Science. 2009 Oct 1;41(2):105-13.
32. Van Der Meijden PE, Heemskerk JW. Platelet biology and functions: new concepts and clinical perspectives. Nature Reviews Cardiology. 2019 Mar;16(3):166-79.
33. Watts SE, Tunbridge LJ, Smith K, Lloyd JV. Storage of platelets for tests of platelet function: effects of temperature on platelet aggregation, platelet morphology and liberation of β-thromboglobulin. Thrombosis research. 1986 Nov 1;44(3):365-76.
34. Lipowsky R. Remodeling of membrane compartments: some consequences of membrane fluidity. Biological chemistry. 2014 Mar 1;395(3):253-74.
35. Liu C, Su Y, Guo W, Ma X, Qiao R. The platelet storage lesion, what are we working for?. Journal of Clinical Laboratory Analysis. 2024 Jan;38(1-2):e24994.
36. Smith CW. Release of α-granule contents during platelet activation. Platelets. 2022 May 19;33(4):491-502.
37. Trochanowska-Pauk N, Walski T, Bohara R, Mikolas J, Kubica K. Platelet storage—Problems, improvements, and new perspectives. International Journal of Molecular Sciences. 2024 Jul 16;25(14):7779.
38. Liu H, Song L, You Y, Li Y, Duan X, Jiang Y, Joyce DC, Ashraf M, Lu W. Cold storage duration affects litchi fruit quality, membrane permeability, enzyme activities and energy charge during shelf time at ambient temperature. Postharvest Biology and Technology. 2011 Apr 1;60(1):24-30.
39. Gitz E, Koekman CA, van den Heuvel DJ, Deckmyn H, Akkerman JW, Gerritsen HC, Urbanus RT. Improved platelet survival after cold storage by prevention of glycoprotein Ibα clustering in lipid rafts. haematologica. 2012 Dec;97(12):1873.
40. Ketter PM, Kamucheka R, Arulanandam B, Akers K, Cap AP. Platelet enhancement of bacterial growth during room temperature storage: mitigation through refrigeration. Transfusion. 2019 Apr;59(S2):1479-89.
41. Tablin F, Wolkers WF, Walker NJ, Oliver AE, Tsvetkova NM, Gousset K, Crowe LM, Crowe JH. Membrane reorganization during chilling: implications for long-term stabilization of platelets. Cryobiology. 2001 Sep 1;43(2):114-23.
42. Johnson L, Tan S, Wood B, Davis A, Marks DC. Refrigeration and cryopreservation of platelets differentially affect platelet metabolism and function: a comparison with conventional platelet storage conditions. Transfusion. 2016 Jul;56(7):1807-18.
43. Shea SM, Thomas KA, Spinella PC. The effect of platelet storage temperature on haemostatic, immune, and endothelial function: potential for personalised medicine. Blood Transfusion. 2018 Jul 30;17(4):321.
44. Drossos PV, Fortis SP, Anastasiadi AT, Pavlou EG, Tsantes AG, Spyratos GA, Papageorgiou EG, Nomikou EG, Stamoulis KE, Dryllis G, Tzounakas VL. Cold vs. room temperature: a comparative analysis of platelet functionality in cold storage. Biomedicines. 2025 Jan 27;13(2):310.
45. Jimenez-Marco T, Castrillo A, Hierro-Riu F, Vicente V, Rivera J. Frozen and cold-stored platelets: reconsidered platelet products. Platelets. 2022 Jan 2;33(1):27-34.
46. Milford EM, Reade MC. Comprehensive review of platelet storage methods for use in the treatment of active hemorrhage. Transfusion. 2016 Apr;56:S140-8.
47. Reddoch-Cardenas KM, Bynum JA, Meledeo MA, Nair PM, Wu X, Darlington DN, Ramasubramanian AK, Cap AP. Cold-stored platelets: A product with function optimized for hemorrhage control. Transfusion and Apheresis Science. 2019 Feb 1;58(1):16-22.
48. Reddoch-Cardenas KM, Bynum JA, Meledeo MA, Nair PM, Wu X, Darlington DN, Ramasubramanian AK, Cap AP. Cold-stored platelets: A product with function optimized for hemorrhage control. Transfusion and Apheresis Science. 2019 Feb 1;58(1):16-22.

49. Riley BC, Phuong J, Hasan RA, Stansbury LG, Hess JR, Roubik DJ. Cold-stored versus room-temperature platelets for hemostasis in combat trauma patients. Transfusion. 2025 Jul;65(7):1344-51.
50. Wang Y, Zhang L, Ma N, Wang Y. Platelet Transfusion for patients with cancer: an update. Transfusion Medicine and Hemotherapy. 2025 Dec 12;52(6):379-89.
51. Drossos PV, Fortis SP, Anastasiadi AT, Pavlou EG, Tsantes AG, Spyratos GA, Papageorgiou EG, Nomikou EG, Stamoulis KE, Dryllis G, Tzounakas VL. Cold vs. room temperature: a comparative analysis of platelet functionality in cold storage. Biomedicines. 2025 Jan 27;13(2):310.
52. Johnson L, Waters L, Roan C, Lei P, Mahajan J, Portier M, Winskel-Wood B, Marks DC. Preparation of cold-stored platelets on-demand: A novel approach to inventory management. Transfusion. 2025 Oct;65(10):1903-13.