Oxidants and Antioxidants in Medical Science
www.oamsjournal.com
DOI: 10.5455/oams.130915.rv.019

Invited Review

ScopeMed

Storage lesions in blood components

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Received: August 26, 2015
Accepted: September 13, 2015
Published: December 30, 2015

ABSTRACT

Blood transfusion is a life-saving intervention and refers to the use of blood and its components for therapy. Transfusion supports various forms of medical care and hence, there is an ever-increasing need and demand for blood. The main principles of transfusion lie in safe and effective blood supply. In order to ensure sufficient quality of blood transfused and to prevent wastage, component therapy was introduced. It involves the transfusion of specific component(s) rather than whole blood.

This review explores the history of storage; changes occurring during storage and the current developments in storage techniques of blood and its components. Blood and its components can be stored under various conditions with the addition of additive solutions. Whole blood can be stored up to 35 days, while erythrocytes can be stored up to 42 days at 4°C. Platelets are stored at 22-24°C for 5-7 days. Plasma can be stored at -18°C for 1 year, or at -65°C for 7 years. The storage solutions vary for each component and efficient storage solutions are under development.

The storage of blood and its components in *ex vivo* conditions causes the formation of storage lesions. These storage lesions, in turn cause decreases in the functioning and efficacy of the transfusion. Oxidative stress plays a key role in the formation of the storage lesion. The effects of oxidative stress can be combated to a certain degree by the inherent antioxidant defense system. However, further stress leads to severe irreversible damage to blood and its components, deeming them unfit for transfusion. The prospects of antioxidants as additives in storage needs to be explored.

There is still a dire necessity to develop better management techniques of blood storage and hence, improve the efficacy and shelf life of stored blood.

KEY WORDS: Component therapy, erythrocytes, plasma, platelets, transfusion

INTRODUCTION

Blood transfusion is a life-saving intervention and refers to the use of blood and its components for therapy [1]. There is an ever-increasing need and demand for blood as transfusion supports various forms of medical care such as fetal and obstetric care, surgery and trauma and in the treatment of heart ailments, cancer and degenerative conditions [2]. The main principles of transfusion lie in safe and effective blood supply [3]. Although, the circulation of blood was first demonstrated in 1628, causing the possibility of transfusion to emerge [4], modern transfusion mechanisms are yet to reach their potential and are constantly evolving. The paradigm shift in blood transfusion towards the "safety" of the transfused blood is in accordance with the ever-changing techniques of storage of whole blood and its components [5]. Precipitated by the identification of transfusion-transmitted infections, this shift has led to a re-examination of the quality of stored blood for transfusion and the emergence of component therapy.

COMPONENT THERAPY

Component therapy involves the transfusion of specific component(s) rather than whole blood. Component therapy can be carried out by **(i)** separating blood components by centrifugation after whole blood donation (Figure 1) or **(ii)** apheresis [8]. The technique of apheresis is unique to component therapy, which is defined as the withdrawal of blood from the donor, removal of the component(s) required for transfusion and the remaining components transfused back into the donor [9], with the utilization of an automated apheresis instrument. Component therapy ensures that one unit of whole blood is used for multiple patients and reduces the risk of blood exposure and adverse transfusion related complications [10]. Whole blood is transfused in cases of severe blood loss. Erythrocytes are transfused in cases of anemia while platelets are transfused during thrombocytopenia and clotting disorders. Plasma and its associated factors are transfused in liver diseases and coagulation factor deficiencies [11].

Whole Blood and Erythrocytes

Blood is the important body fluid that delivers necessary substances such as nutrients and oxygen to the cell and transport metabolic waste away from the cells. Blood supplies oxygen to the tissues bound to hemoglobin and also supplies nutrients such as glucose, amino acids and helps in the removal of waste such as carbon dioxide, urea and lactic

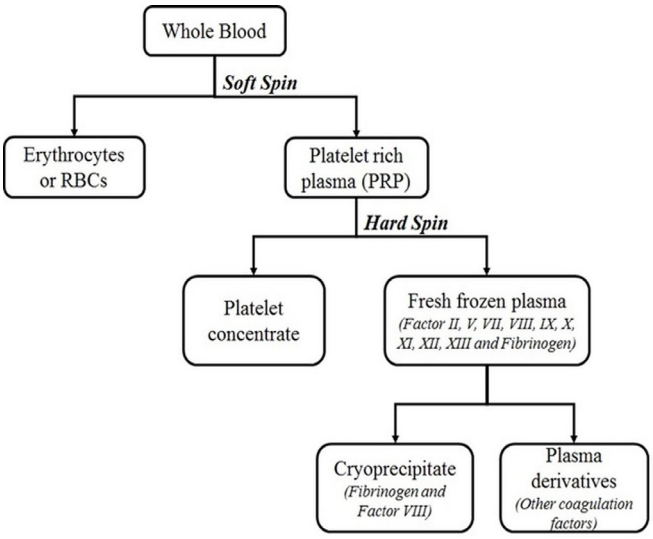

Figure 1. Component therapy by centrifugation of donated whole blood [6, 7]

acid. It helps in regulation of body pH and temperature. Blood pH is regulated to stay within the range of 7.35-7.45 making it slightly basic. [12, 13]. Blood is composed of cellular components, *i.e.* erythrocytes, leucocytes and thrombocytes, which are held in suspension in plasma [14].

Red blood cells (RBCs or erythrocytes) are one of the major cellular components of the blood. These are 7.2 μm in diameter, circular, biconcave, enucleate discs (on maturity), containing hemoglobin (Hb) which transport oxygen and carbon dioxide. Hemoglobin is made up of "heme", an iron containing compound, belonging to the protoporphyrin group, and "globin", a protein containing four polypeptide chains. The affinity of the heme group to oxygen and other heme groups, accounts for the oxygen carrying capacity of erythrocytes. The life span of a RBC is approximately 120 days, after which the iron is extracted and reutilized to form hemoglobin, while the cell itself dies [14].

History

Successful storage of blood was reported by Rous and Turner in 1916 [15]. The storage solution contained citrate and dextrose and was used to store and transfuse blood into rabbits. The same solution was used during the World War I by Oswald Robertson [16]. The development of acid-citrate-dextrose (ACD) solution occurred during World War II and the Spanish Civil War by Loutit and Mollison [17-19]. The CPD solution (citrate, phosphate and dextrose) was used extensively for whole blood storage. However, the addition of adenine by Simon [20] caused the emergence of CPDA or CPDA-1 (citrate, phosphate, dextrose and adenine) solutions [21]. As the different types of "additive solutions" were developed, each with their own modifications of the earlier available solutions, there was a concurrent development of new and improved storage containers as well. The old technique of using bottles to store blood, gave way to using bags, which facilitated the separated storage of blood components, and hence, a need and surge in the number of specific-component-storage solutions. The blood was first collected into CPD solution, separated into its various components, and each component was then stored in its own storage solution [22]. The first solution developed for storage of erythrocytes was developed by Beutler called BAGPAM which consisted of sodium bicarbonate, sodium carbonate, sodium phosphate, adenine, glucose and mannitol [23, 24]. Due to decrease in ATP during storage in this solution, SAG solution was developed (composition of saline, adenine and glucose). Mannitol was later added to the same solution to form SAGM, which is the preferred commercially used RBC storage solution today [25]. The presence of mannitol has been shown to effectively reduce hemolysis [23] by scavenging free radicals and stabilizing the erythrocyte membrane [14]. Blood stored in CPD has a storage period of 21 days [26] while CPDA-1 allows 35 days [27] of whole blood storage. SAGM, on the other hand allows for 42 days of erythrocyte storage [28]. The constituents of the modern storage solutions of erythrocytes and whole blood are listed in Table 1.

Table 1. Composition of storage solutions for whole blood and erythrocytes [29-35]

Constituents (g/l)	Whole blood storage solutions				Erythrocyte storage solutions			
	ACD	CPD	CP2D	CPDA-1	SAGM	AS-1	AS-3	AS-5
NaCl	---	---	---	---	8.77	9	4.1	8.77
$NaHCO_3$	---	---	---	---	---	---	---	---
Na_2HPO_4	---	---	---	---	---	---	---	---
NaH_2PO_4	---	2.22	2.22	2.22	---	---	-----	-----
Citric acid	4.7	3.27	3.27	3.27	---	---	0.42	---
Sodium citrate	13.3	26.3	26.3	26.35	---	---	5.88	---
Adenine	---	---	---	0.27	0.17	0.27	0.3	0.3
Guanosine	---	---	---	---	---	---	---	---
Dextrose (glucose)	30.0	25.5	46.4	31.9	9	22	10	9
Mannitol	---	---	---	---	5.2	7.5	---	5.25
pH	5.0	5.6	5.6	5.6	5.7	5.5	5.8	5.5
Anticoagulant	---	---	---	---	CPD	CPD	CP2D	CPD

ACD: acid-citrate-dextrose; **CPD:** citrate-phosphate-dextrose; **CP2D:** citrate-phosphate-dextrose-dextrose; **CPDA:** citrate-phosphate-dextrose-adenine; **SAGM:** saline-adenine-glucose-mannitol; **AS:** additive solution

Erythrocyte storage lesion

Erythrocytes are simple cells which are prone to changes and modifications due to the following reasons: **(i)** constant presence in an environment of oxygen (prone to oxidative stress and hemoglobin auto-oxidation) and **(ii)** absence of nucleus and other organelles (no repair or macromolecule generation machinery).

During storage, RBCs undergo structural and functional changes that may reduce function and viability after transfusion [36]. These changes accompanying the storage of RBCs are known as the "storage lesion", which can be defined as a series of biochemical and biomechanical changes in the RBC and storage media during *ex vivo* preservation that reduce RBC survival and function. Storage of the erythrocytes involves the accumulation of products of glycolysis, primarily protons, leading to a decrease in pH and hence, acidosis. This slowly causes a decrease in the rate of glycolysis and ATP formation, which in turn leads to loss of deformability with the formation of reversible echinocytes and eventually, formation of irreversible spheroechinocytes. Further changes involve loss of membrane by vesiculation [23, 37-39]. Decrease in 2,3-DPG (diphosphoglycerate) is observed, which translates to increased affinity of hemoglobin to oxygen, consequently leading to decreased capacity of the erythrocytes to release oxygen into tissues [40, 41]. Reduction in the antioxidant defense systems, protein oxidation and lipid peroxidation also occur, in turn causing vesiculation and loss of deformability [5, 36]. Stored erythrocytes have decreased oxygen affinity and delivery, increased adhesion to the endothelium and reduced life span. An overview of the erythrocyte storage lesion has been illustrated in Figure 2.

Platelets

Thrombocytes or platelets are the smallest formed cells in blood. They are anucleate, disc-shaped, membrane bound cell fragments that are formed by megakaryopoiesis in bone marrow and released into the blood stream. Their concentration in blood ranges between 150,000-450,000 cells/μl. Platelets are vital in preserving vascular integrity and maintaining hemostasis. Platelet transfusions are life-saving procedures during surgery, chemotherapy and for patients with bleeding disorders. Hence, they are stored at 22°C under conditions of agitation, but to a limited period of 5 -7 days [44].

History

During the 1870s, the existence of platelets and their contribution to hemostasis was described. But, it was only during 1910 that the transfused platelets were shown to decrease the risk of bleeding in thrombocytopenic patients. The routine availability of platelet transfusions became a reality only around the 1970s. This became possible when Scott Murphy and Frank Gardner in 1969 [45] reported that platelets could be stored at 22±2°C for up to 3 days and still maintain their hemostatic function. Subsequent improvements such as use of new platelet additive solutions (PAS) and improved storage containers enabled the availability of platelets for transfusion even after 5-7 days of storage. At present, studies are being conducted to increase the possibility of extended platelet storage [46].

Currently PAS are being used to replace large portion of plasma in platelet suspensions during storage [47]. This reduces the risk of contamination by viruses and bacteria in the residual plasma. It also reduces the plasma-associated transfusion side effects and improves storage conditions. PAS contain varying quantities of glucose, citrate, phosphate, potassium, magnesium and acetate. Acetate serves as a substrate for aerobic respiration and maintains the pH level [48]. Various PAS that are currently used are listed in Table 2. Studies are being conducted to improve the efficacy and shelf life of stored platelets. Gulliksson has suggested that platelets could be stored for 18-20 days at 20-24°C with an optimized additive medium that can be capable of inhibiting platelet aging [50].

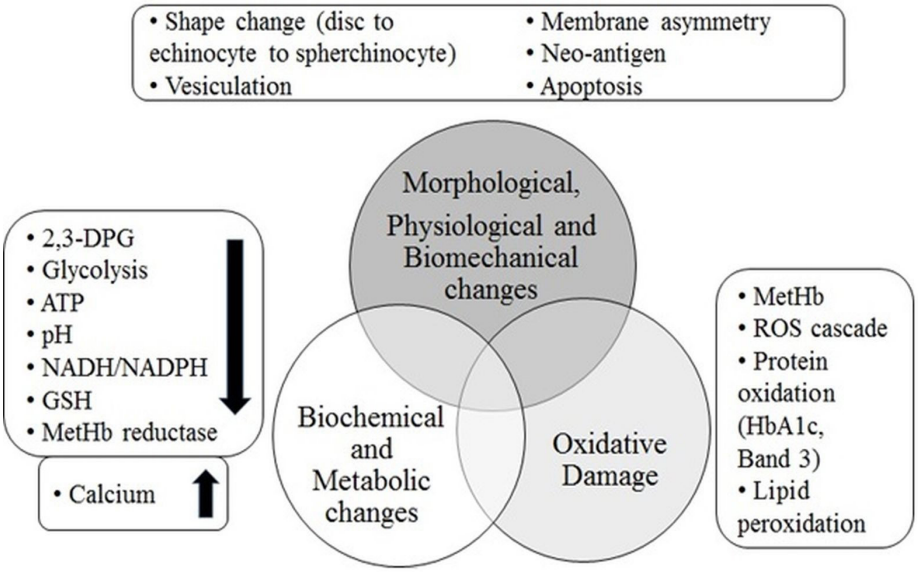

Figure 2. Erythrocyte storage lesion [5, 19, 22, 40, 42, 43]

Table 2. Composition of various platelet additive solutions (PAS; in mmol/l) [49]

Composition	TSol (PASII)	Composol (GAC)	InterSol (PASIII)	SSP + (PASIIIM)	GASP-BIC
NaCl	115.5	90.0	77.3	69	110
Acetate	30	27	28.2	41	15
KCl	-	5	-	5	5
$MgCl_2$	-	3	-	1.5	3
Na_2HPO_4	-	-	28.2	26	4
Na_3-citrate	10	10	10.8	10	-
Citric acid	-	-	-	-	7.5
Gluconate	-	30	-	-	-
Glucose	-	-	-	-	30
pH	7.2	7	7.2	7.2	5.2

Platelet storage lesion

Platelets have a natural life span of 8-12 days. But, the life span of stored platelets collected for therapeutic or prophylactic transfusion is currently limited to 5-7 days at 22-24°C, with agitation. This limitation is to attenuate the risk of bacterial growth and diminish the effects of platelet storage lesion (PSL). PSL correlates with reduced *in vivo* recovery and hemostatic activity after transfusion [51]. PSL comprises of all the deleterious changes that occur from the time of blood collection from the donor until the time the platelet concentrate (PC) is administered to the patient [52].

The discoid shape of the platelets is gradually lost within few days of storage at 22°C. The number of micro-vesicles increase due to separation of tendrils and fragmentation of cell membrane [53]. The pH of the PC decreases to < 6.4 after 5-7 days of storage at 22°C. The platelet size and aggregation response to agonists decrease rapidly during storage. Stored platelets are activated in response to various stimuli as well as a result of exposure to foreign surfaces and mechanical trauma [54]. This in turn leads to the formation of micro-aggregates which requires conformational changes in platelet glycoprotein complex GPIIb/IIIa and expression of surface receptors [52]. Proteolysis also adds to the loss of membrane glycoproteins. Platelets undergo time-dependent structural and functional changes such as mitochondrial damage, increased phosphatidylserine, metabolic failure, membrane lysis and release of lactate dehydrogenase (LDH); that are indicative of apoptosis [55, 56]. The changes occurring during platelet storage and the factors that lead to PSL have been summarized in Figure 3 and Table 3, respectively.

Plasma

Plasma is the non-cellular component of whole blood, which comprises of water, sugars, fats, proteins and salts. The main function of plasma is to transport components such as blood cells, nutrients, waste products, antibodies, clotting factors and hormones throughout the body. It is a pale yellow liquid that makes up around 55% of the total volume of whole blood. It contains 90% water, 8% proteins, 1.1% organic substances and 0.9% inorganic ions. The proteins comprise of albumin (60%), globulins (36%) and fibrinogen (4%)" [58].

Plasma is generally used to prevent or control bleeding and treat burns. Apart from using plasma for transfusions, they are also used for manufacturing albumin, coagulation factor concentrates and intravenous immunoglobulins in large quantities [22, 59].

Table 3. Factors influencing the development of platelet storage lesions [52]

Factors	
Collection techniques	Composition of anticoagulant/ preservative solution
	Blood flow rate
	Ratio of anticoagulant
	Centrifugation force
	Resting period before resuspension
Storage conditions	Temperature and storage period of whole blood before processing and storage
	High cellular content
	Volume and composition of suspension media
	Final plasma concentration in storage media
	Type of agitation
Storage containers	Plastic bag composition
	Pack size and thickness of plastic
	Gas transfer properties of plastic
	Thickness of container wall
Treatment after collection	Extent of leukodepletion
	Extent of plasma removal
	UV-B irradiation
	γ-irradiation
	Cryopreservation
	Lyophilisation

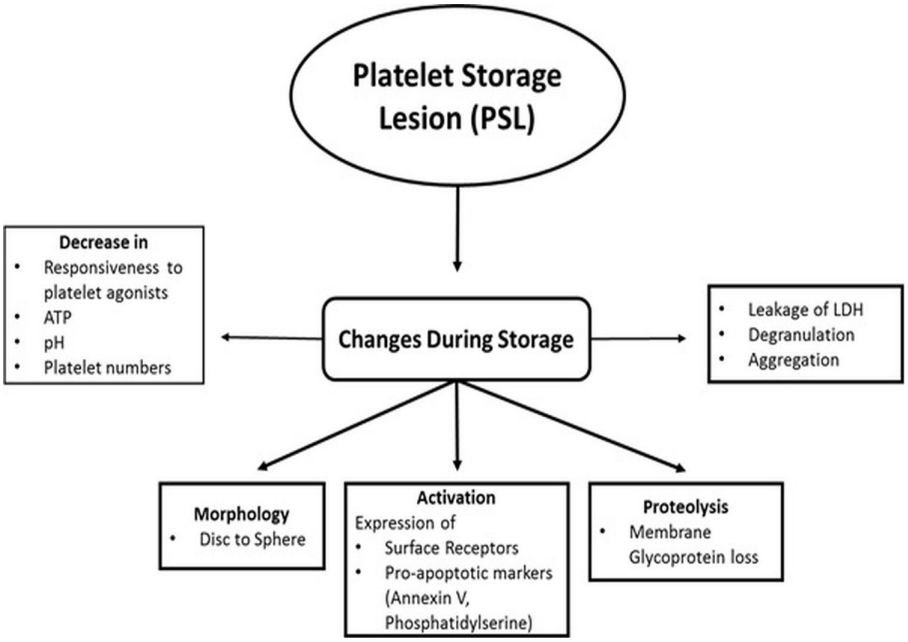

Figure 3. Changes during the platelet storage lesion [57]

Plasma separated from whole blood is generally diluted with 1 part of CPD anticoagulant to 4 parts of plasma, making up a concentration of around 80%. The term fresh frozen plasma (FFP) is used when the above units are frozen within 8 hours of collection. However when they are frozen between 8 to 24 hours after collection, they are termed as frozen plasma (FP). Plasma can be stored at -18°C for 1 year, or at -65°C for 7 years. However, at 1-6°C, it can be stored for a maximum of 5 days [22, 60].

Plasma storage lesion

Changes in plasma is a good indicator of oxidative stress, as it reflects the changes occurring in blood. Human plasma is endowed with a robust antioxidant defense mechanism to combat the changes occurring during storage. Protein sulfhydryl groups have also shown to contribute to the antioxidant capacity and their oxidation indicates protein oxidation [59, 61]. The proteases (serine, cysteine, aspartic and matrix metalloproteases) present in plasma are released from activated, lysed or dying neutrophils and mononuclear phagocytes. Plasma must be frozen immediately after separation, to prevent the proteases from damaging proteins. Plasma also possesses an innate ability to counteract these proteolytic enzymes through protease inhibitors (α1-protease inhibitor, tissue inhibitor of metalloprotease, α2-macroglobulin and plasminogen activator inhibitor-1). Another alternative method is the use of protease inhibitors in the storage solution. Ethylenediaminetetraacetic acid (EDTA) or citrate (Ca^{2+} chelators) help in preventing not only coagulation, but also in the inhibition of Ca^{2+}-dependent proteases [62].

During storage, proteins get modified through; (1) oxidation of Pro, Arg, Lys, Thr, Glu or Asp side chains or cleavage of protein backbone, (2) incorporation of lipid peroxidation products (4-hyrdroxy-2-nonenal and malondialdehyde) into Cys, His or Lys residues, or (3) formation of advanced glycation end products [63]. Lipid peroxidation also occurs during storage. Presence of cholesteryl ester hydroperoxides in plasma is considered as a direct evidence for ROS mediated injury [64].

PROSPECTS OF ANTIOXIDANTS AS ADDITIVES IN STORAGE

There is a dire need to prolong the storage period and improve the efficacy of stored blood and its components. Although there has been constant development of storage solutions and containers, the shelf life of blood and its components have not improved drastically. Oxidative stress plays an important role in the formation of the storage lesion in blood and its components [65-67]. There exists an inherent antioxidant system in the blood in order to combat oxidative stress. However, during storage, there is a reduction in blood antioxidant capacity, leading to increased susceptibility to oxidative stress. There is a possibility that the antioxidant defense system can be enhanced by the addition of antioxidants during storage. The effectiveness of antioxidants as additives during storage have been investigated in animal and human models, as shown in Table 4.

CONCLUDING REMARKS

There has been extensive progress in the field of blood transfusion science. The paradigm shift from quantity to quality of transfused blood and its components has given rise to component therapy, hence reducing blood wastage. However, the increasing demand for blood and its components can only be met by improving their efficacy and shelf life.

Table 4. Antioxidants as additives in blood storage [67-75]

Parameters	Results	References
Whole blood and erythrocytes		
Vitamin C was added to samples in CPD, stored at 25°C for 6 days	Increases activities of ATP and SOD, decreases concentrations of MDA, plasma K^+ and superoxide radicals	Zan *et al*., 2005
Hemolysis or kinetics of hemoglobin breakdown in erythrocytes exposed to the used vitamins with different concentrations [**C** (0.5, 0.8, 2 and 4 mM)]	Vitamin C was the strongest hemolytic agent in comparison with the other vitamins	Ibrahim *et al*, 2006
Whole blood pretreated with **Vitamin C** (60 mM) and **Vitamin E** (2 mM) for 30 min before inducing oxidative stress	Antioxidative property of Vitamin C and Vitamin E in aqueous and lipid phases of erythrocytes was observed	Reddy *et al*, 2007
Inhibition of suicidal erythrocyte death by **Vitamin C**	Significantly attenuated the suicidal erythrocyte death following cell shrinkage, energy depletion, and oxidative stress.	Mahmud *et al*, 2010
L-carnitine was added to samples in CP2D and AS-3, stored at 4°C for 42 days	The uptake of L-carnitine during storage was associated with less hemolysis and higher RBC ATP levels	Arduini *et al*, 1997
L-carnitine was added to blood in CPDA-1 and stored at 4°C for 20 days	Hemoglobin and sulfhydryls were maintained; catalase and glutathione peroxidase decreased in groups with additive; hemolysis increased	Soumya *et al*, 2015
Platelets		
L-carnitine was added to human platelet concentrates and stored at 22°C for 5 days	Decreased lactate concentration, glucose consumption, mitochondrial metabolic activity and increased oxygen consumption in samples with L-carnitine	Deyhim *et al*, 2015
Plasma		
Curcumin was added to blood in CPDA-1, stored for 20 days. Plasma was separated and analyzed	Antioxidant enzymes and sulfhydryls ameliorated, TBARS and protein carbonyls reduced in curcumin samples. AOPP increased	Carl *et al*, 2014
Vitamin C was added to blood in CPDA-1, stored for 25 days. Plasma was separated and analyzed	Superoxide dismutase, protein sulfhydryls and carbonyls were maintained. AOPP and catalase increased	Vani *et al*, 2015

There is a plethora of research towards understanding the formation of storage lesions. Several factors are involved in the formation of storage lesion and increased OS is one such factor. Different techniques have been developed to minimize the adverse effects of storage. Antioxidants as additives in storage solutions are being explored towards prolonging the storage period and improving the efficacy. Nevertheless, there is still a dire necessity to develop better management techniques of blood storage and hence bring about efficient blood storage practices.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Leela Iyengar and Jain University for their support.

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Conflict of Interest: None declared