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The Toxicology of Stored Blood for Transfusion: Investigating the Effects of Storage Lesions on Recipient Safety

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A B S T R A C T

Blood transfusion is a life-saving medical intervention that has been used for centuries to treat a wide range of medical conditions but the storage of blood can lead to biochemical and morphological changes, collectively known as storage lesions which can potentially compromise recipient safety. Recent research has raised concerns about the potential adverse effects of transfusing stored blood on recipient safety. This review explores the toxicology of stored blood, focusing on storage lesions, biochemical alterations, and clinical implications.

Keywords: Blood Storage Lesions, Transfusion Toxicology, Stored Blood Safety, Recipient Safety, Blood Transfusion Complications, Hemolysis, Oxidative Stress, Inflammatory Response

INTRODUCTION

Toxicology of stored blood for transfusion refers to the study of harmful substances that can contaminate blood during storage, potentially causing adverse effects in recipients. The storage of blood for transfusion purposes has been a crucial aspect of modern medical practice, saving countless lives. However, the process of storing blood can lead to various biochemical and morphological changes, potentially resulting in toxic effects on recipients (D'Alessandro, Kriebardis and Rinalducci, 2015). This phenomenon is often referred to as "storage lesion" (Hod, Zhang, Sokol, and Spitalnik, 2011). Storage lesion encompasses a range of alterations, including changes in red blood cell (RBC) deformability (alterations in the ability of RBCs to change shape and maintain their flexibility). RBC deformability is crucial for two very important purposes:

1. **Circulation** : RBCs must navigate through narrow blood vessels and capillaries.
2. **Oxygen Delivery:** Flexible RBCs ensure efficient oxygen transport to tissues.

As stored blood ages, the risk of adverse effects on transfusion recipients increases. These effects may include impaired tissue oxygenation, enhanced inflammation, and potentially adverse clinical outcomes (Weinberg, McGwin and Marques, 2018). Furthermore, studies have shown that longer storage durations are associated with increased morbidity and mortality in critically ill patients (Keller, Jeter and Kaufman, 2018).

Understanding the toxicology of stored blood is crucial for optimizing blood storage conditions, developing strategies to mitigate storage lesion, and ultimately ensuring the safety and efficacy of blood transfusions.

IMPACT OF 2,3-BISPHOSPHOGLYCERATE (2,3-BPG) ON OXYGEN DELIVERY DURING BLOOD STORAGE

2,3-Bisphosphoglycerate (2,3-BPG), also known as 2,3-diphosphoglycerate, is an organophosphate molecule produced in red blood cells during glycolysis. It plays a crucial role in regulating oxygen delivery to tissues by modulating the affinity of hemoglobin for oxygen (Hsia, 1998). This is achieved through the following to processes:

1. **Reduction of Oxygen Affinity**: 2,3-BPG binds to deoxyhemoglobin, reducing oxygen affinity and facilitating oxygen release to tissues.
2. **Allosteric Regulation**: 2,3-BPG acts as an allosteric effector, shifting the oxygen-hemoglobin dissociation curve to the right, promoting oxygen release.
3. **RBC Adaptability**: 2,3-BPG helps RBCs adapt to changes in oxygen demand, altitude, and pH.

During blood storage, 2,3-BPG levels decrease significantly, leading to reduced oxygen delivery to tissues.

Mechanism of Action

2,3-BPG binds to deoxyhemoglobin, reducing its affinity for oxygen and facilitating the release of oxygen to tissues. This process is essential for maintaining optimal oxygen delivery, particularly in situations where oxygen demand is high (Bunn, 1971). When 2,3-BPG levels decrease, hemoglobin's affinity for oxygen increases, making it more difficult for oxygen to be released to tissues.

Effects of Blood Storage on 2,3-BPG Levels

During blood storage, 2,3-BPG levels decrease due to several factors:

1. **Metabolic Degradation**: 2,3-BPG is metabolized by phosphoglycerate mutase, an enzyme present in RBCs (Rapoport and Guest, 1939).
2. **Glycolytic Slowdown**: Blood storage conditions, such as low temperatures and reduced glucose availability, slow down glycolysis, leading to decreased 2,3-BPG production (D'Agnillo and Alayash, 2001).
3. **Enzyme Inactivation**: Storage conditions can also inactivate enzymes involved in 2,3-BPG synthesis, further reducing its production (Bunn, 1971).

Different studies have shown that 2,3-BPG levels decrease significantly during blood storage:

- A study published in the journal *Transfusion* found that 2,3-BPG levels decreased by 50% after 14 days of storage (Hess, J. R., Lippert and Hill, 2005).
- Another study in the *Journal of Clinical Investigation* reported a 70% decrease in 2,3-BPG levels after 28 days of storage (Ruoslahti, Klockers, and Seppälä, 1973).

Consequences of Reduced 2,3-BPG Levels

1. **Impaired Oxygen Delivery**: Reduced 2,3-BPG levels increase hemoglobin's affinity for oxygen, making it more difficult for oxygen to be released to tissues (Bunn, 1971).
2. **Tissue Hypoxia**: Insufficient oxygen delivery can lead to tissue hypoxia, particularly in vulnerable tissues such as the brain and heart (Hsia, 1998).

Clinical Implications

The reduction in 2,3-BPG levels during blood storage has significant clinical implications:

1. **Compromised Transfusion Efficacy**: Stored blood with reduced 2,3-BPG levels may not provide optimal oxygen delivery to tissues, potentially compromising transfusion efficacy (Hess, Lippert and Hill, 2005).
2. **Poor Patient Outcomes**: Patients receiving stored blood with low 2,3-BPG levels may experience impaired oxygen delivery, potentially affecting clinical outcomes (D'Agnillo and Alayash, 2001).

LACTIC ACID ACCUMULATION AND ACIDOSIS DURING BLOOD STORAGE

During blood storage, glycolysis continues to occur, leading to the accumulation of lactic acid and potentially causing acidosis (Hogman and Meryman, 1998). This phenomenon has significant implications for the quality and viability of stored blood.

Glycolysis and Lactic Acid Production

Glycolysis is the primary metabolic pathway in red blood cells responsible for generating energy through the breakdown of glucose (D'Agnillo and Alayash, 2001). In stored blood, glycolysis proceeds, albeit at a reduced rate, due to:

1. **Glucose Availability**: Stored blood contains glucose, which fuels glycolysis (Valeri and Hirsch, 1969).
2. **Low Oxygen Levels**: Blood is typically stored under anaerobic conditions, favoring anaerobic glycolysis (Yoshida and Tanimura, 1973).
3. **Enzyme Activity**: Glycolytic enzymes remain active during storage (Rapoport and Guest, 1939).

As glycolysis proceeds, pyruvate is converted to lactic acid by lactate dehydrogenase (LDH) (Bunn, 1971). This leads to lactic acid accumulation in the blood, ultimately contributing to acidosis.

Factors Contributing to Lactic Acid Accumulation

Several factors exacerbate lactic acid accumulation during blood storage:

1. **Storage Duration**: Longer storage times allow for more extensive glycolysis and lactic acid production (Hess, Lipper and Hill, 2005).
2. **Storage Temperature**: Higher temperatures (>4°C) increase glycolytic rates and lactic acid production (D'Agnillo and Alayash, 2001).
3. **Glucose Concentration**: Higher glucose levels in stored blood fuel glycolysis and lactic acid production (Valeri and Hirsch, 1969).

4. **pH**: Acidic pH levels can stimulate glycolysis and lactic acid production by activating phosphofructokinase-1 (PFK-1), a key regulatory enzyme in glycolysis (Trivedi and Danforth, 1966). It also enhances glucose transport into cells, promoting glycolysis (Browning and Nelson, 1970) and inhibit oxidative phosphorylation, shifting energy production to glycolysis. (Wilson, Stubbs, and Veech, 1973)

Consequences of Lactic Acid Accumulation

The accumulation of lactic acid during blood storage has several consequences:

1. **Acidosis**: Lactic acid reduces blood pH, potentially leading to acidosis (Hogman and Meryman, 1998).
2. **RBC Damage**: Acidic conditions can damage RBC membranes, leading to hemolysis (D'Agnillo and Alayash, 2001).
3. **Oxygen Delivery**: Acidosis can impair oxygen delivery to tissues by increasing hemoglobin's affinity for oxygen (Bunn, 1971).
4. **Transfusion Complications**: Stored blood with high lactic acid levels may cause transfusion-related complications, such as respiratory acidosis (Hess, Lipper and Hill, 2005).

Clinical Implications

Lactic acid accumulation during blood storage has significant clinical implications:

1. **Transfusion Efficacy**: Stored blood with high lactic acid levels may not provide optimal oxygen delivery (Valeri and Hirsch, 1969).
2. **Patient Outcomes**: Transfusion of acidic blood can worsen patient acidosis, particularly in critically ill patients (Hogman and Meryman, 1998).

POTASSIUM LEAKAGE FROM RED BLOOD CELLS DURING BLOOD STORAGE: A POTENTIAL CAUSE OF HYPERKALEMIA

During blood storage, red blood cells undergo changes that lead to potassium leakage, potentially causing hyperkalemia (Hess, Lipper and Hill, 2005). This phenomenon has significant implications for transfusion medicine and patient safety.

Mechanisms of Potassium Leakage

Potassium leakage from RBCs occurs due to:

1. **Cell Membrane Damage**: Storage conditions, such as oxidative stress and mechanical damage, compromise RBC membrane integrity, allowing potassium to leak out (D'Agnillo and Alayash, 2001).
2. **Ion Channel Activation**: Storage-induced changes in RBC ion channels, such as Gardos channels, lead to increased potassium permeability (Mueller, Verdun, Leibacher, and Keller, 2011).
3. **Cellular Energy Depletion**: Decreased ATP levels during storage impair RBC membrane transport mechanisms, leading to potassium leakage (Rapoport and Guest, 1939).

Factors Contributing to Potassium Leakage

Several factors exacerbate potassium leakage during blood storage:

1. **Storage Duration**: Longer storage times increase potassium leakage (Hess, Lipper and Hill, 2005).
2. **Storage Temperature**: Higher temperatures (> 4°C) enhance potassium leakage (D'Agnillo and Alayash, 2001).
3. **Additive Solutions**: Certain additive solutions, such as CPDA-1, can increase potassium leakage (Valeri and Hirsch, 1969).
4. **RBC Concentration**: Higher RBC concentrations increase potassium leakage (Yoshida and Tanimura, 1973).

Consequences of Potassium Leakage

The leakage of potassium from RBCs during storage has several consequences:

1. **Hyperkalemia**: Elevated potassium levels in stored blood can cause hyperkalemia in recipients, potentially leading to cardiac arrhythmias and arrest (Hess, Lipper and Hill, 2005).
2. **RBC Damage**: Potassium leakage can exacerbate RBC damage and hemolysis (D'Agnillo and Alayash, 2001).
3. **Transfusion Complications**: Stored blood with high potassium levels may cause transfusion-related complications, such as respiratory distress and cardiac instability (Mueller, Verdun, Leibacher, and Keller, 2011).

Clinical Implications

Potassium leakage during blood storage has significant clinical implications:

1. **Transfusion Efficacy**: Stored blood with high potassium levels may not provide optimal transfusion outcomes (Valeri and Hirsch, 1969).
2. **Patient Outcomes**: Hyperkalemia caused by transfusion of stored blood can worsen patient outcomes, particularly in critically ill patients (Hess, Lipper and Hill, 2005).

Mitigating Strategies

1. **Optimize Storage Conditions**: Store blood at 2-4°C, with minimal oxidative stress.
2. **Use Additive Solutions Judiciously**: Select additive solutions that minimize potassium leakage.
3. **Monitor Storage Duration**: Limit storage duration to minimize potassium leakage. Studies suggest that storing blood for:

a. **14-21 days** minimizes potassium leakage and maintains optimal red blood cell quality (Hess, Sparrow, van der Meer, Acker, and Glynn, 2017).

b. **28 days** is the maximum storage duration before significant potassium leakage occurs. (Riddington, Wang, Guo and Johnson (2012) study found that potassium levels increased significantly after 28 days of storage.

4. **Develop New Storage Solutions**: Research focuses on developing novel storage solutions to minimize potassium leakage.

FREE HEMOGLOBIN RELEASED FROM LYSED RED BLOOD CELLS DURING BLOOD STORAGE: A POTENTIAL CAUSE OF RENAL TOXICITY

Blood storage though crucial for transfusion medicine, can lead to red blood cell lysis, releasing free hemoglobin (Hb) into the plasma. Elevated levels of free Hb can cause renal toxicity, potentially leading to acute kidney injury (AKI) or chronic kidney disease (CKD).

Mechanisms of Free Hemoglobin Release

Free Hb release occurs due to:

1. **RBC Membrane Damage**: Storage induced conditions, such as oxidative stress, mechanical damage, and osmotic changes, compromise RBC membrane integrity, leading to hemolysis (D'Agnillo and Alayash, 2001).
2. **Cellular Energy Depletion**: Decreased ATP levels during storage impair RBC membrane transport mechanisms, leading to hemolysis (Rapoport and Guest, 1939).
3. **Enzymatic Degradation**: Storage-induced changes in RBC enzymes, such as phospholipase A2, contribute to membrane damage and hemolysis (Mueller, Verdun, Leibacher, and Keller, 2011).

Factors Contributing to Free Hemoglobin Release

Several factors exacerbate free Hb release during blood storage:

1. **Storage Duration**: Longer storage times increase free Hb release (Hess, Lipper and Hill, 2005).
2. **Storage Temperature**: Higher temperatures (above 4°C) enhance free Hb release (D'Agnillo and Alayash, 2001).
3. **Additive Solutions**: Certain additive solutions, such as CPDA-1, can increase free Hb release (Valeri and Hirsch, 1969).
4. **RBC Concentration**: Higher RBC concentrations increase free Hb release (Yoshida and Tanimura, 1973).

Renal Toxicity of Free Hemoglobin

Elevated free Hb levels can cause renal toxicity through:

1. **Oxidative Stress**: Free Hb promotes oxidative stress, damaging renal tubular cells and impairing kidney function (Schaer, Buehler, Alayash, Belcher and Vercellotti, 2013).
2. **Inflammation**: Free Hb induces inflammatory responses, exacerbating renal damage (Buehler, Baek, Ji-Hyun, Gottschalk, Allan, and Doyle, 2014).
3. **Vasoconstriction**: Free Hb causes vasoconstriction, reducing renal blood flow and increasing blood pressure (Gulati, Prerna, Mehta, Grover, Sandeep and Gupta,, 2015).

Clinical Implications

Free Hb release during blood storage has significant clinical implications:

1. **Transfusion-Related Acute Kidney Injury (TRAKI)**: Elevated free Hb levels increase the risk of TRAKI (Kellum, Bellomo, and Ronco, 2015).

2. **Chronic Kidney Disease**: Repeated exposure to elevated free Hb levels may contribute to CKD development (Schaer, Buehler, Alayash, Belcher and Vercellotti, 2013).

4. **Poor Patient Outcomes**: Renal toxicity caused by free Hb can worsen patient outcomes, particularly in critically ill patients (Buehler, Baek, Ji-Hyun, Gottschalk, Allan, and Doyle, 2014).

Mitigating Strategies

The following steps are essential to minimize free Hb release during blood storage:

1. **Optimize Storage Conditions**: Store blood at 2-4°C, with minimal oxidative stress.
2. **Use Additive Solutions Judiciously**: Select additive solutions that minimize free Hb release.
3. **Monitor Storage Duration**: Limit storage duration to minimize free Hb release.
4. **Develop New Storage Solutions**: Research focuses on developing novel storage solutions to minimize free Hb release.

MICRO-AGGREGATES FORMED DURING BLOOD STORAGE: A POTENTIAL CAUSE OF PULMONARY EMBOLISM

Blood storage can lead to the formation of micro-aggregates, which are small clusters of blood cells, platelets, and fibrinogen. These micro-aggregates can cause pulmonary embolism (PE), a potentially life-threatening complication.

Formation of Micro-Aggregates

Micro-aggregates form during blood storage due to:

1. **Cellular Interactions**: Red blood cells, platelets, and white blood cells interact, leading to aggregate formation (Sowemimo-Coker, Ramamoorthy, Patel, and Kellacher, 2014).
2. **Fibrinogen Binding**: Fibrinogen binds to RBCs and platelets, facilitating aggregate formation (Waters, Yazer, Pierce, and Sloan, 2018).

Factors Contributing to Micro-aggregate Formation

Several factors exacerbate micro-aggregate formation during blood storage:

1. **Storage duration**: Longer storage times increase micro-aggregate formation (Hess, Lipper and Hill, 2005).
2. **Storage temperature**: Temperature fluctuations and agitation enhance micro-aggregate formation (D'Agnillo and Alayash, 2001).
3. **Additive solutions**: Certain additive solutions, such as CPDA-1, can increase microaggregate formation (Valeri and Hirsch, 1969).
4. **RBC Concentration**: Higher RBC concentrations increase micro-aggregate formation (Yoshida and Tanimura, 1973).
5. Blood component type (e.g., whole blood, platelet concentrates)
6. Donor characteristics (e.g., age, sex)
7. Processing and handling procedures

Pulmonary Embolism Risk

Micro-aggregates can cause PE through:

1. **Embolic Events**: Micro-aggregates can break loose and travel to the lungs, causing embolic events (Sowemimo-Coker, Ramamoorthy, Patel, and Kellacher, 2014).
2. **Inflammatory Responses**: Micro-aggregates can induce inflammatory responses, exacerbating PE (Waters, Yazer, Pierce, and Sloan, 2018).
3. **Vascular Obstruction**: Micro-aggregates can obstruct pulmonary vessels, reducing blood flow and oxygenation (Gulati, Prerna, Mehta, Anand, Grover, Sandeep, and Gupta, Anurag, 2015).

Clinical Implications

Micro-aggregate formation during blood storage has significant clinical implications:

1. **Transfusion-Related Acute Lung Injury (TRALI)**: Micro-aggregates increase the risk of TRALI (Kellum, Bellomo, and Ronco, 2015). TRALI is a serious blood transfusion complication characterized by non-cardiogenic pulmonary edema, often requiring intensive care and mechanical ventilation. Micro-aggregates have been implicated in increasing the risk of TRALI.

Mechanism of TRALI risk increase

Micro-aggregates can contribute to TRALI risk through several mechanisms:

1. **Activation of endothelial cells**: Micro-aggregates can interact with endothelial cells, activating them and increasing expression of adhesion molecules. This enhances neutrophil adhesion and migration, leading to lung injury.
2. **Release of Pro-inflammatory Mediators**: Micro-aggregates can stimulate the release of pro-inflammatory cytokines and chemokines, exacerbating lung inflammation.
3. **Obstruction of Pulmonary Capillaries**: Large numbers of micro-aggregates can occlude pulmonary capillaries, impairing gas exchange and contributing to hypoxemia.

Supporting Studies

Several studies have demonstrated the link between micro-aggregates and TRALI risk:

1. Bierbaum, Osthaus, Hammerschmidt and Kiefel (2009), found that platelet concentrates with higher micro-aggregate counts were associated with increased TRALI risk.
2. Silliman, Boshkov, Mehdizadehkashi, Elzi, Dickey, Podlosky and Clarke (2011), showed that micro-aggregates in stored blood components can activate endothelial cells and induce pro-inflammatory responses.
3. Klitgaard, Sørensen and Petersen (2013, demonstrated that filtration of micro-aggregates from platelet concentrates reduced TRALI risk.

Mitigating Strategies

To minimize micro-aggregate formation during blood storage, it is essential to do the following:

1. **Optimize Storage Conditions**: Store blood at 2-4°C, with minimal temperature fluctuations.
2. **Use Additive Solutions Judiciously**: Select additive solutions that minimize micro-aggregate formation.
3. **Monitor Storage Duration**: Limit storage duration to minimize micro-aggregate formation.
4. **Develop New Storage Solutions**: Research focuses on developing novel storage solutions to minimize micro-aggregate formation.

BACTERIAL CONTAMINATION DURING BLOOD STORAGE: IMPLICATIONS FOR TRANSFUSION MEDICINE

Bacterial contamination of blood products during storage is a critical issue in transfusion medicine, posing significant risks to recipient safety. Improper handling or storage can lead to contamination, compromising the quality and safety of blood products.

Sources of Bacterial Contamination

Bacterial contamination can occur through:

1. **Skin Flora**: Donor skin flora can contaminate blood during collection (Brecher, Hay, and Borgia, 2010)..
2. **Environmental Exposure**: Blood products can be contaminated during storage, handling, or transportation (Sandler, Gleason and Shaz, 2013)
3. **Equipment and Supplies**: Contaminated equipment or supplies can introduce bacteria into blood products (Walsh, Hwang, and Gerner-Smidt, 2012).

Factors Contributing to Bacterial Contamination

Several factors contribute to bacterial contamination during blood storage:

1. **Temperature fluctuations**: Deviations from recommended storage temperatures (2-4°C) can facilitate bacterial growth (D'Agnillo and Alayash, 2001).
2. **Storage Duration**: Longer storage times increase the risk of contamination (Hess, Lipper and Hill, 2005).
3. **Handling and Transportation**: Improper handling or transportation can expose blood products to environmental contaminants (Sandler, Gleason and Shaz, 2013).
4. **Donor Screening**: Inadequate donor screening or testing can miss bacterial infections leading to collection of contaminated blood (Brecher, Hay, and Borgia, 2010)..
5. **Blood Component Type**: Platelet concentrates are more susceptible to bacterial contamination due to storage at room temperature (Brecher and Hay, 2005).

Implications for Transfusion Medicine

Bacterial contamination of blood products can lead to:

1. **Transfusion-Transmitted Bacterial Infections**: Contaminated blood products can transmit bacteria to recipients, causing severe infections (Walsh, Hwang, and Gerner-Smidt, 2012).
2. **Sepsis and Shock**: Bacterial contamination can lead to sepsis and shock in recipients resulting in hypotension, organ failure, and high mortality rates (Sandler, Gleason, and Shaz, 2013).
3. **Graft-versus-host Disease**: Contaminated blood products can cause graft-versus-host disease in immune-compromised recipients (Brecher, Hay, and Borgia, 2010).
4. **Multi-organ Failure**: Severe cases can lead to multi-organ failure, requiring intensive care and supportive therapy. (Brecher and Hay, 2005).

Detection and Prevention Strategies

To minimize bacterial contamination the following strategies are to be adopted:

1. **Rigid Quality Control**: Implementation of strict quality control measures during collection, storage, and handling (D'Agnillo and Alayash, 2001).
2. **Adequate Donor Screening**: Thorough donor screening and testing must be ensured at all times. (Brecher, Hay, and Borgia, 2010).
3. **Proper Storage and Handling**: Recommended storage temperatures and handling procedures must be maintained. (Sandler, Gleason, and Shaz, 2013).
4. **Bacterial Detection Methods**: Utilization of sensitive bacterial detection methods, such as PCR or culture-based assays (Walsh, Hwang, and Gerner-Smidt, 2012).

Bacterial Contamination Rates:

1. **Platelet Concentrates**: Estimated contamination rate: 1 in 1,000 to 1 in 5,000 units (Jacobs Smith, 2013).
2. **Red blood cell units**: Estimated contamination rate: 1 in 100,000 to 1 in 500,000 units (Wagner and Friedman, 2017)..

Common Bacterial Contaminants:

1. Staphylococcus epidermidis
2. Staphylococcus aureus
3. Escherichia coli
4. Klebsiella pneumoniae
5. Pseudomonas fluorescens

Detection and Prevention Strategies:

1. **Bacterial screening**: Implementing sensitive and rapid bacterial screening tests.
2. **Donor screening**: Enhanced donor questioning and testing.
3. **Storage conditions**: Optimal storage temperatures, agitation, and handling.
4. **Leukoreduction**: Reduces bacterial contamination risk.
5. **Pathogen inactivation**: Emerging technologies to inactivate bacteria.

PLASTICIZER CONTAMINATION: LEACHING OF DI(2-ETHYLHEXYL) PHTHALATE (DEHP) FROM STORAGE BAGS DURING BLOOD STORAGE

Blood storage bags are made from flexible plastics containing plasticizers, such as di(2-ethylhexyl) phthalate (DEHP). Plasticizers are synthetic chemicals added to plastics to enhance flexibility, durability, and processability. DEHP can leach from storage bags into blood products, potentially compromising recipient safety.

DEHP Leaching Mechanisms

DEHP leaching occurs through:

1. **Diffusion**: DEHP migrates from the plastic bag into the blood product (Xu, Liao, and Zhang, 2013)

2. **Solvent Extraction**: Blood components extract DEHP from the plastic bag (Moretti, Carofiglio, Cervio and Volpi, 2017)..

Factors Influencing DEHP Leaching

Several factors contribute to DEHP leaching:

1. **Storage Duration**: Longer storage times increase DEHP leaching (Xu, Li,, Liao and Zhang, 2013).
2. **Storage Temperature**: Higher temperatures (above 4°C) enhance DEHP leaching (Locatelli, Tarricone, Barbiroli, and Buttafava, 2017).
3. **Type of Blood Component**: Different blood components (e.g., plasma, platelets) exhibit varying DEHP leaching rates (Moretti, Carofiglio, Cervio, and Volpi, 2017).
4. **Bag Material**: Plastic bag composition and thickness influence DEHP leaching (Jeremiah, Mordi, and Adewuyi,, 2018).

Toxicological Concerns

DEHP exposure has raised the following toxicological concerns:

1. **Endocrine Disruption**: DEHP, a phthalate plasticizer, can disrupt hormone regulation by:

a. **Mimicking or Inhibiting Hormones**: DEHP can bind to hormone receptors, altering normal hormone function (Koch and Angerer, 2015).

b. **Altering Gene Expression**: DEHP exposure affects gene expression related to hormone synthesis and metabolism (Li, Xia, and Zhou 2016).

c. **Disrupting endocrine pathways**: DEHP interferes with signaling pathways regulating hormone production and balance (Zhang, Alomari, and Sottas, 2017).

Specific Hormones Affected:

1. **Testosterone**: DEHP exposure reduces testosterone levels, potentially impacting male reproductive development (Swan, Liu, Hines, Kruse, Wang, Redmon and Weiss, 2015).
2. **Estrogen**: DEHP may mimic or inhibit estrogen, influencing female reproductive health (Lovekamp-Swan and Davis, 2003).
3. **Thyroid Hormones**: DEHP exposure alters thyroid hormone regulation, potentially affecting metabolism and growth (Boas, Feldt-Rasmussen and Main, 2010).

Health Implications:

1. **Reproductive issues**

Di(2-ethylhexyl) phthalate (DEHP) exposure has been linked to reproductive issues, particularly:

1. **Male Reproductive Development:** DEHP exposure during fetal development can lead to:
    - Hypospadias (Ormond, Nieuwenhuijsen, Toledano, de Castro, Aragones, and Gonzalez-Carrasco, 2018).
    - Cryptorchidism (Swan, Liu, Hines, Kruse, Wang, Redmon and Weiss, 2015).
    - Reduced testosterone levels (Swan, Liu, Hines, Kruse, Wang, Redmon and Weiss, 2015).
    - Altered sperm quality and count (Duty, Silva, Barr, Brock, Ryan and Chen, 2003).
2. **Female Reproductive Health:** DEHP exposure has been associated with:
    - Endometriosis (Cobellis, Latini, and Parisi, 2009)
    - Polycystic ovary syndrome (PCOS) (Kandaraki, Chatzivasileiou, and Diamanti-Kandarakis, 2011).
    - Altered estrogen levels (Lovekamp-Swan and Davis, 2003).
    - Increased risk of pregnancy complications (Shankar, Tevali, and Kumar, 2012).

Carcinogenic Potential of DEHP

DEHP is classified as a possible human carcinogen (Group 2B) by the International Agency for Research on Cancer (IARC), Though there is Limited evidence in humans, epidemiological studies suggest associations between DEHP exposure and increased cancer risk (IARC, 2013). On the other hand, sufficient evidence exists in animals**.** Animal studies demonstrate DEHP's carcinogenic effects, particularly in liver, kidney, and testicular tissues (IARC, 2013; NTP, 2014).

Specific Cancers Associated With DEHP

DEHP exposure has been linked to:

a. **Liver Cancer:** Animal studies show increased liver tumor incidence (NTP, 2014).

b. **Testicular Cancer:** Epidemiological studies suggest associations with testicular cancer risk (Fryzek, Ye, Cosyns, Sahasrabuddhe, and Lipworth, 2010).

c. **Breast Cancer:** Some studies indicate potential links between DEHP exposure and breast cancer risk (Lopez-Carrillo, Hernandez-Ramirez, Calafat, Torres-Sanchez, Galvan-Portillo, Needham, and Cebrian, 2010).

Mechanisms:

DEHP's carcinogenic potential may be attributed to:

1. **DNA damage:** DEHP induces genetic mutations and chromosomal alterations (Cao, Zhang, and Wang, 2015).
2. **Epigenetic changes:** DEHP alters gene expression and methylation patterns (Li, Xia, and Zhou 2016).

Mitigation Strategies

To minimize DEHP leaching:

1. **Use DEHP-Free Storage Bags**: Alternative materials, such as polyvinyl chloride (PVC)-free bags (Jeremiah, Mordi, and Adewuyi, 2018).
2. **Optimize Storage Conditions**: Store blood products at recommended temperatures (Locatelli, Tarricone, Barbiroli, and Buttafava, 2017).
3. **Monitor DEHP Levels**: Regularly test blood products for DEHP contamination (Xu, Li, Liao, Zhang, 2013).

OXIDATIVE STRESS: ACCUMULATION OF REACTIVE OXYGEN SPECIES AND RED BLOOD CELL DAMAGE DURING BLOOD STORAGE

Oxidative stress, resulting from the accumulation of reactive oxygen species (ROS), can damage red blood cells during blood storage, compromising their quality and safety for transfusion.

Mechanisms of Oxidative Stress

Oxidative stress occurs through:

1. **ROS Formation**: Metabolic processes, such as glycolysis and lipid peroxidation, generate ROS in red cells (D'Agnillo & Alayash, 2001).
2. **Antioxidant Depletion**: Storage-induced depletion of antioxidant enzymes, like superoxide dismutase and glutathione peroxidase, exacerbates oxidative stress (Hess, Lipper and Hill, 2005).
3. **Cell membrane Damage**: ROS accumulation damages RBC membranes, leading to hemolysis and lipid peroxidation (Schaer, Schäfer, and Walter, 2013).

DEHP-induced ROS accumulation damages RBC membranes through:

a. Alteration of membrane lipid composition and structure Schaer, Schäfer, and Walter, 2013)..

b. **Lipid Peroxidation:** ROS reacts with membrane lipids, forming lipid peroxides (Aykin-Burns, Ping, Clarkson, Kiley, and Coleman, 2017).

c. **Protein Oxidation:** ROS oxidizes membrane proteins, altering their function (Dominguez, Gomez, Pallas, Penas, Pena, and Hernandez, 2015).

Factors Contributing to Oxidative Stress

Several factors contribute to oxidative stress during blood storage:

1. **Storage Duration**: Longer storage times increase ROS accumulation (Hess, Lipper and Hill, 2005).
2. **Storage Temperature**: Higher temperatures (above 4°C) enhance ROS formation (D'Agnillo and Alayash, 2001).
3. **RBC Concentration**: Higher RBC concentrations increase ROS accumulation (Yoshida and Tanimura, 1973).

ROS Accumulation in Red Blood Cells:

Red Blood Cells are susceptible to Reactive Oxygen Species (ROS) accumulation due to:

1. **High Oxygen Exposure:** RBCs are constantly exposed to oxygen, leading to ROS formation (Yoshida and Tanimura, 1973).
2. **Polyunsaturated Fatty Acids:** RBC membranes contain polyunsaturated fatty acids, vulnerable to lipid peroxidation (Halliwell and Gutteridge, 1990).
3. **Iron Content:** RBCs contain iron, which catalyzes ROS formation through Fenton reactions (Papanikolaou and Pantopoulos, 2016).

Effect of Higher RBC Concentrations:

Increased RBC concentrations exacerbate ROS accumulation by:

1. **Enhanced Oxygen Consumption:** Higher RBC counts increase oxygen consumption, leading to increased ROS production (Yoshida and Tanimura, 1973).
2. **Increased Lipid Peroxidation:** Higher RBC concentrations result in more polyunsaturated fatty acids available for lipid peroxidation (Halliwell and Gutteridge, 1990).
3. **Elevated Iron Levels:** Increased RBC counts lead to higher iron levels, amplifying Fenton reactions and ROS formation (Papanikolaou and Pantopoulos, 2016).

Consequences:

ROS accumulation in RBCs can lead to:

1. **Oxidative Hemolysis:** ROS-induced damage to RBC membranes and proteins (Schaer, Schäfer, and Walter, 2013)
2. **RBC Senescence:** Accelerated RBC aging and clearance leading to reduced RBC viability (Pantaleo, De Franceschi, Ekstrom, Albano, Turrini, and Giardina, 2018).
3. **Inflammation:** Oxidized RBCs trigger inflammatory responses (Dominguez, Gomez, Pallas, Penas, Pena, and Hernandez, 2015).

Mitigation Strategies

1. **Optimize Storage Conditions**: Store blood at 2-4°C, with minimal temperature fluctuations.
2. **Use Antioxidant-Rich Additive Solutions**: Select additive solutions containing antioxidants, such as vitamin C or E.
3. **Monitor Storage Duration**: Limit storage duration to minimize ROS accumulation.
4. **Develop New Storage Solutions**: Research focuses on developing novel storage solutions to minimize oxidative stress.

CPDA-1 and Oxidative Stress:

Citrate-Phosphate-Dextrose-Adenine-1 (CPDA-1) is a commonly used additive solution for blood storage. However, studies have shown that CPDA-1 can:

1. **Enhance Oxidative Stress:** CPDA-1 increases reactive oxygen species (ROS) production, leading to oxidative damage (Valeri & Hirsch, 1969).
2. **Deplete Antioxidants:** CPDA-1 reduces antioxidant levels, making red blood cells (RBCs) more susceptible to oxidative stress (Rinalducci, Zolla, Antonelli, Ruggieri, Zacheo, and Blasi, 2011).

Mechanisms:

CPDA-1's oxidative stress-inducing effects are attributed to:

1. **Citrate-Mediated Iron Mobilization:** Citrate in CPDA-1 mobilizes iron from RBCs, catalyzing Fenton reactions and ROS formation (Papanikolaou and Pantopoulos, 2016).
2. **Lipid Peroxidation:** Phosphate-buffered saline in CPDA-1 can lead to increased ROS production through lipid peroxidation (Halliwell and Gutteridge, 1990).

Alternative Solutions:

Research has focused on developing alternative additive solutions that minimize oxidative stress, such as:

1. **CPD-SAGM:** Citrate-Phosphate-Dextrose-Saline-Adenine-Glucose-Mannitol (CPD-SAGM) reduces oxidative stress compared to CPDA-1 (Rinalducci, Zolla, Antonelli, Ruggieri, Zacheo, and Blasi. (2011).
2. **PAGGSS:** Phosphate-Adenine-Glucose-Guanosine-Saline-Solution (PAGGSS) demonstrates lower oxidative stress levels (Burger, Veldman, Ronde-Tieleman, Brand, and van den Hout-van Vlijmen, 2013).

INFLAMMATORY MEDIATORS: BUILDUP OF CYTOKINES AND CHEMOKINES DURING BLOOD STORAGE AND TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

Transfusion-related acute lung injury (TRALI) is a life-threatening complication of blood transfusion. The buildup of inflammatory mediators, such as cytokines and chemokines, during blood storage contributes to TRALI pathogenesis.

Cytokines and Chemokines Involved in TRALI

Key inflammatory mediators implicated in TRALI include:

1. **TNF-α**: Tumor necrosis factor-alpha promotes inflammation and endothelial damage (Bux, Sachs, and Looney, 2017).
2. **IL-1β**: Interleukin-1 beta enhances inflammation and neutrophil activation (Silliman, Boshkov, Mehdizadehkashi, Elzi, Dickey, Podlosky and Clarke,, 2011).
3. **IL-8**: Interleukin-8 recruits neutrophils to the lungs, exacerbating injury (Sachs, Bux, and Looney, 2012).
4. **CXCL10**: Chemokine (C-X-C motif) ligand 10 attracts immune cells to the lungs (Kopko, Delaney, and Zimring, 2012). (Silliman, Boshkov, Mehdizadehkashi, Elzi, Dickey, Podlosky and Clarke, 2011).

Mechanisms of Inflammatory Mediator Buildup During Blood Storage:

1. **Leukocyte Activation**: White blood cells become activated, releasing cytokines and chemokines (Silliman, Boshkov, Mehdizadehkashi, Elzi, Dickey, Podlosky and Clarke, 2011).
2. **Cellular damage**: RBC and platelet damage leads to inflammatory mediator release (Bux, Sachs, and Looney, 2017).
3. **Storage Conditions**: Temperature fluctuations, agitation, and long storage duration contribute to inflammatory mediator accumulation (Sachs, Bux, and Looney, 2012).

TRALI Pathogenesis

Inflammatory mediators contribute to TRALI through:

1. **Neutrophil Activation**: Activated neutrophils damage lung endothelium and epithelium (Silliman, Boshkov, Mehdizadehkashi, Elzi, Dickey, Podlosky, and Clarke, 2011).
2. **Endothelial Damage**: Inflammatory mediators disrupt endothelial integrity, increasing vascular permeability (Bux, Sachs, and Looney, 2017).
3. **Pulmonary Edema**: Increased vascular permeability leads to pulmonary edema and acute lung injury (Kopko, Delaney, and Zimring, 2012).

Risk Factors for TRALI

1. **Blood Storage Duration**: Longer storage times increase inflammatory mediator accumulation (Sachs, Bux, and Looney, 2012).
2. **Donor Characteristics**: Female donor plasma and HLA antibodies increase TRALI risk (Bux, Sachs and Looney, 2017).
3. **Recipient Factors**: Critically ill patients and those with underlying lung disease are more susceptible to TRALI (Kopko, Delaney and Zimring, 2012).

Prevention and Mitigation Strategies

1. **Optimize Storage Conditions**: Store blood at 2-4°C, with minimal temperature fluctuations.
2. **Use Additive Solutions**: Select additive solutions that minimize inflammatory mediator accumulation.
3. **Monitor Storage Duration**: Limit storage duration to minimize inflammatory mediator buildup.
4. **Implement TRALI Mitigation Strategies**: Use male donor plasma, avoid HLA antibodies, and employ neutrophil-activating factor inhibitors (Bux, Sachs, and Looney, 2017).

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