Strategies for Reducing Blood Transfusion in Cardiac Surgery

An essay submitted for partial fulfillment of master degree in anesthesia

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Introduction

The practice of modern transfusion medicine began with the discovery of blood groups by Landsteiner. Even though his work won the Nobel Prize in 1930, the full impact of his discovery lagged; and other developments such as arterial anastomosis, blood component therapy, refrigeration of blood components, organization of blood banks, use of anticoagulation, and the urgency of treating war-injured patients were necessary to bring transfusion into the modern era.

As early as 1943, it was recognized that blood transfusion could spread diseases, especially hepatitis. Since that time, other problems such as risks associated with paid donors and concerns about disease transmission, including the current epidemic of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and transmission of hepatitis C, raised awareness of the problems associated with blood transfusion almost to the point that the benefits of blood transfusion are overlooked. It is important to realize that the viral and parasitic infectious risks of blood transfusion are dramatically increased in third world countries or in areas

where modern blood banking practices are not available. ***(Stover et al., 1998)***

Transfusion of red cells causes immunomodulation, although the extent and type of immune deficit is controversial. In some blood banks, leukocyte reduction of red cells is used routinely. With non–leukocyte reduced transfusions in randomized trials, multiorgan failure and death occur in as many as 10% of transfused intensive care unit (ICU) patients, versus 5% in recipients of leukocyte reduced transfusions. Transfusion related acute lung injury may be the most common complication of transfusion, although this remains controversial. As many as 1 in 20 patients experienced a transfusion-related death in some studies. ***(Bilgin et al., 2004)***

Blumberg and co-workers suggest that as many as 1 in 40 or 50 patients receiving non–leukocyte reduced transfusions died in excess of that seen in recipients of leukocyte reduced transfusions. The added cost of leukocyte reduction may limit universal acceptance of this technique, but there is some evidence that red cell transfusion-related immunomodulation is a cause of significant morbidity, and this morbidity may be reduced by leukocyte reduction of red cells. ***(Blumberg et al., 2002)***

It is difficult to define the benefits of blood transfusion, as randomized trials to support the use of blood products to treat disease do not exist. Blood transfusion was accepted long before the complications associated with transfusion could be documented. Many traumatic injuries (especially war-related injuries) were almost universally fatal before the advent of blood transfusion. The practice of blood transfusion saved countless lives long before the complications of this therapy were recognized. ***(Lewisohn, 1955)***

Enhanced oxygen-carrying capacity, improved hemostasis associated with blood component therapy, and volume support of cardiac output are three accepted benefits of blood transfusion. Adams and associates, in 1942 on the basis of clinical observations and animal studies, introduced the "10/30" rule of blood transfusion. These authors suggested that the minimal ideal level of oxygen-carrying capacity is maintained by a hematocrit of around 30% and hemoglobin of 10 g/dL. Because of the risks of transfusion with associated costs, and lack of clear evidence regarding the benefit of blood transfusion, the 10/30 arbitrary rule has fallen into disfavor. ***(Adams and Lundy, 1942)***

A task force of the American Society of Anesthesiologists (ASA) developed a consensus statement concluded that "red blood cell transfusions should not be

dictated by a single hemoglobin 'transfusion trigger' but instead should be based on the patient's risk of developing complications of inadequate oxygenation". They developed guidelines for transfusion of packed red cells in adults which are:

- Transfusion for patients on cardiopulmonary bypass with hemoglobin level ≤ 6.0 g/dL is indicated.
- Hemoglobin level ≤ 7.0 g/dL in patients older than 65 years and patients with chronic cardiovascular or respiratory diseases justifies transfusion.
- For stable patients with hemoglobin level between 7 and 10 g/dl, the benefit of transfusion is unclear.
- Transfusion is recommended for patients with acute blood loss more than 1,500 ml or > 30% of blood volume.
- Evidence of rapid blood loss without immediate control warrants blood transfusion. ***(American Society of Anesthesiologists, 1996)***

Physiology of Haemostasis

Haemostasis:

Haemostasis means prevention of blood loss. When a small blood vessel is cut or damaged, the injury initiates a series of interrelated events that will finally lead to the formation of a blood clot. This seals off the damaged vessel and prevents further blood loss. A very fine balance between many complex interrelated systems must be maintained to stop bleeding, while at the same time preventing intravascular coagulation.

The factors involved include the vascular endothelium, subendothelial collagen, platelets, and the clotting and fibrinolytic systems ***(Dyekin, 1987).***

Introduction

The human haemostatic system has evolved as a remarkably orchestrated scheme of linked activities designed to preserve the integrity of blood circulation. Haemostasis is regulated to promote blood fluidity under normal circumstances. It is also prepared to clot blood with speed and precision to arrest blood flow and prevent exsanguinations whenever and wherever the integrity of the circulation is disrupted.

The major components of the haemostatic system are:

1- The vessel wall.

2- Plasma proteins (the coagulation and fibrinolytic factors).

3- Platelets. ***(Konkle and Schafer, 2005)***

The haemostatic mechanisms include three processes:

1- Primary haemostasis.

2- Coagulation.

3- Fibrinolysis. ***(Petrovitch, 2003)***

PRIMARY HAEMOSTASIS (PLATELET PLUG):

Platelets are cytoplasmic fragments released into blood from bone marrow megakaryocytes circulating with an average life span 7 to 10 day. These terminal cell fragments lack nuclei and therefore have limited capacity to synthesize new protein ***(Konkle and Schafer, 2005).***

The formation of platelet plug depends on the interaction between the damaged vascular endothelium and the platelets ***(Dyekin, 1987).***

Primary haemostasis (platelet plug) takes place within seconds of vascular injury and involves the action of platelet and blood vessels ***(Petrovitch, 2003).***

The formation of platelet plug is divided into three processes:

A- Adhesion.

B- Activation and release.

C- Aggregation.

A) Adhesion

Vascular intimal injury diminishes locally the antiplatelet properties of the endothelium, whereas previously cryptic thrombogenic subendothelial substances (e.g. collagen) become exposed to flowing blood. ***(Konkle and Schafer, 2005).***

Platelets spread along the surface of the damaged blood vessel and adhere to the subendothelial collagen layer via:

1. Glycoprotein receptors which are:

a. Glycoprotein Ib (GPIb) which is a specific receptor on the platelet surface that acts as a binding site for vWF ***(Kroll et al., 1987).***

b. Adhesion is also facilitated by means of specific platelets membrane collagen receptors including GPIa/IIa and GPVI (***Andre et al., 2000).***

2. Von Willebrand (vWF) factor:

Is synthesized by both endothelial cells and megakaryocytes where it is stored in alpha granules ***(Dewit et al., 2001).***

Von Willebrand factor bridges platelets to the damaged subendothelium ***(Dion et al., 2004).***

B) Activation and release

Adhesion initiates platelet activation: activation can also be produced by thrombin, adenosine diphosphate (ADP) thromboxane A2 (TXA2) and platelet activation factor (PAF) ***(Shattil and Bennett, 1989).***

The activation process causes the platelets to change shape from a flattened disk to a spheroid and extend multiple pseudopods. The platelets undergo a release reaction extruding the contents of their alpha and dense cytoplasmic granules, and release multiple compounds into the blood, such as serotonin, clotting factors V and VIII, fibrinogen and many other chemical mediators important for primary haemostasis and the subsequent coagulation process.

With sufficient stimulus, the platelets synthesize thromboxane A2, a prostaglandin which stimulates further ADP release and also has potent vasoconstrictor actions ***(Petrovitch, 2003).***

C) Aggregation

The released ADP, TXA2 and PAF, in turn, activate nearby platelets at the site of injury causing them to stick and clump together in a process called aggregation.

Aggregation also requires the presence of a glycoprotein complex on the surface membrane of platelets. This complex is made of GPIIb and GPIIIa. Fibrinogen is an essential factor for normal aggregation in that it binds to GPIIb/GPIIIa complex and links one platelet to another forming platelet plug ***(Ware and Heistand, 1993).***

The platelet plug is sufficient on its own to complete haemostasis after small superficial injury, however, larger injury require the plug to be stabilized by fibrin ***(Laffan, 2005).***

Secondary Haemostasis (The Coagulation)

Basic Principles of the Coagulation Mechanism:

Coagulation involves the interaction of many plasma proteins, called clotting factors (Table 1) which interact in various reaction sequences to produce fibrin. Most of the clotting factors circulate in an inactive form, called a procoagulant molecule or proenzyme. During the process of coagulation, a portion of this protein molecule is cleaved off and the remaining protein becomes an active cleavage enzyme, called a serine protease. The "activated clotting factor" cleaves off a portion of the next procoagulant clotting electing factor, which "activates" that factor in succession. In a chain reaction-like fashion, one factor "activates" another, until fibrinogen

(factor I) is cleaved to form fibrin. The proper interaction of many of the clotting factors requires the presence of a phospholipids surface. This phospholipid surface can be provided by tissue factor (**extrinsic to blood**) or by the surface of platelets when they become activated and expose platelet factor3 (PF3) phospholipid (**intrinsic to blood**). Because the process of coagulation requires a phospholipid surface, the production of fibrin is localized to the site of vascular injury-where tissue factor is exposed to blood and where platelets are activated, exposing PF3 ***(Petrovitch, 2003).***

Some of the reactions of the coagulation cascade involve the formation of a reaction complex in which two clotting factors are bound in a particular spatial arrangement on a phospholipid surface and together activate the next clotting factor. In the reaction complex, one of the clotting factors serves as a cofactor and is not an actual cleavage enzyme. Factors V and VIII serve as cofactors and are also known as the labile factors because their coagulant activity does not last long in stored blood. Transfusion of large quantities of packed (RBCs) leads to a deficiency of these labile factors, Va and VIIIa ***(Petrovitch, 2003).***

Most of the coagulation proteins are synthesized by the liver. Their normal structure and function are dependent upon normal hepatic activity. Four of the clotting factors, (II, VII,