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IMPORTANCE OF DIURETICS PRE-BLOOD TRANSFUSION

Running title: Diuretic Pre-Blood Transfusion

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Abstract:
Blood transfusion is a fundamental life saving measure in several critical medical conditions, and the elderly population above the age of 60 years are the most common age group indicated for blood transfusions. This age group is liable to many complications of blood transfusion due to the high prevalence of associated co-morbidities such as cardiac failure and renal dysfunction. Transfusion associated circulatory overload is one of the serious and common complications of blood transfusion occurring in up to 6% of patients receiving blood transfusion. It is associated with significant morbidity and mortality and, therefore, should be meticulously prevented and treated. Loop diuretics have long been used prophylactically prior to blood transfusion – particularly among high risk patients – to prevent or reduce the development of this deleterious condition. This article aims at discussing the importance of using diuretics in patients receiving blood or blood product and discussing the impact of their use on reducing transfusion associated circulatory overload.

Keywords: *Blood transfusion, diuretics, importance, transfusion.*

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INTRODUCTION:

Blood transfusion is a fundamental life saving measure in several critical medical conditions. It is estimated that 112.5 million blood units are donated every year worldwide [1]. In the United states, about 21 million blood units are donated annually, and one patient in indicated for blood transfusion for two seconds[2]. Red blood cells are the most common blood component being transfused with about 36000 units used daily. Plasma and platelets come next with transfusion of 10000 and 7000 units on daily basis [2]. Developed countries have a higher donation rates than developing countries. It is estimated that the blood transfusion rate is 9 times higher in developed than developing countries [1]. The transfusion rate in developed countries is 32.1 per 1000 individuals annually versus 4.6 per 1000 people annually in developing countries[1].

Elderly population above the age of 60 years are the most common age group indicated for blood transfusions [2], and the main indications at this age include cardiovascular operations, major trauma, blood loss with organ transplantation, and haematological malignancies[3,4]. In the United States, 1.7 million individuals were diagnosed with cancer and required blood transfusion at one point of their life[2]. Among adults, trauma related blood loss and pregnancy related complications constitute the main causes of blood transfusion [3,5,6]. Anaemia is the most common indication of blood transfusion in children. It is estimated that approximately 100000 children in the United states are born with sickle cell anaemia annually and require blood transfusion for life [2].

Whilst blood transfusion is essential for life-threatening conditions, it is may be associated with serious complications. Acute serious complications include acute haemolysis, transfusion allergic reaction up to anaphylaxis, transfusion related lung injury, febrile reaction, transmission of bacterial, fungal, or viral infection, coagulopathy, metabolic derangement, and transfusion associated circulatory overload[7]. Delayed haemolysis, purpura, transfusion associated immunomodulation, iron overload, and micro-chimerism are the most common delayed complications of blood transfusion [7-9]. Despite being serious, most of the blood transfusion associated complications can be prevented via adopting certain precautions [10,11]. One of these precautions is the prophylaxis use of diuretics before blood transfusion [12], and this article will discuss the importance and impact of using diuretics in patients receiving blood transfusion.

USE OF DIURETICS AFTER BLOOD TRANSFUSION

One of the main acute serious complications of blood transfusion in transfusion associated circulatory overload [13]. It is estimated to occur in 5.8% of patients receiving blood transfusion [14]. Transfusion associated circulatory overload occurs due to water retention and volume excess in patients who receive large volume of blood or blood products over short time [10]. This volume excess results in circulatory overload and accumulation of fluid in lungs with subsequent development of pulmonary oedema. This circulatory overload also leads to renal function compromise and myocardial dysfunction. For decades, diuretics – particularly loop diuretics – have been used by many physicians before blood transfusion to reduce water retention and transfusion-related circulatory overload [15]. The rate of prophylactic diuretic use before blood transfusion ranges in literature from 39% to 43% [16,17], and they are particularly administered for patients who are at risk of circulatory overload such as patients with heart failure or renal dysfunction [16].

Transfusion-associated circulatory overload

To date, there is no approved standardized definition to transfusion associated circulatory overload. The International Society of Blood Transfusion (ISBT) proposed a definition for the condition to allow early diagnosis and prompt management. It defined transfusion associated circulatory overload as a condition occurring within six hours of transfusion of blood or blood products characterized by one or more of the following symptoms and signs: hypertension, tachycardia, acute respiratory distress, worsening pulmonary oedema, or positive fluid balance[18]. Patients who develop transfusion associated circulatory overload typically present with dyspnoea, orthopnoea, palpitation, headache, and dizziness. Laboratory profile may reveal elevated levels of brain-type atrial natriuretic peptide [19].

Pathophysiology of transfusion-associated circulatory overload

The exact pathophysiology of transfusion-associated circulatory overload remains elusive. It is thought that the excess volume of fluid transfused to the patient results in acute elevation of the intravascular fluid volume leading to increased venous return, increased pulmonary capillaries pressure and subsequently pulmonary oedema [20]. This is particularly common among patients with cardiac failure, congestive heart disease, or renal compromise. However, excess fluid overload does not seem to be the only pathophysiological mechanism responsible for transfusion associated

circulatory overload because about 20% of patients develop the condition after transfusion of a single unit of blood or blood product containing around 300 milliliter [21]. A second mechanism for transfusion associated circulatory overload was thought to be due to an inflammatory response towards the transfused blood. This theory was supported by the significant reduction (around 50%) of the rate of transfusion associated circulatory overload in patients who had received blood products with reduced leucocytes [22]. It is proposed that the stored blood products accumulate considerable quantities of inflammatory mediators that, when transfused, interact with the host endothelium leading to endothelial damage and extravasation of fluids to the extravascular volume leading to pulmonary oedema [21].

Mechanisms of action of diuretics prior to blood transfusion

Diuretics are thought to reduce transfusion associated circulatory through various mechanisms. On pulmonary level, loop diuretics can relax the smooth muscles of the respiratory airway and subsequently enhance the pulmonary compliance and reduce respiratory distress [23]. They can also reduce venous congestion through increasing venous dilatation, venous return, and venous capacity leading to diffusion of fluid and excess volume from the alveolar space to the intravascular space [24,25]. On renal level, loop diuretics act at the ascending loop of Henle via blocking a co-transporter for sodium, potassium, and chloride ions leading to water excretion and subsequently recusing circulatory overload [26].

Impact of diuretics administration among patients receiving blood or blood products

Administration of diuretics is important to reduce transfusion associated circulatory overload and its associated morbidity and mortality. It is estimated that more than one third (38.5%) of cases of transfusion associated circulatory overload are severe or even life-threatening [12]. The mortality rates reported ranged from 1.2-7.3% in literature studies[12,27]. Saraji and Tejani, in their review of 8 studies assessing the impact of using loop diuretics before blood transfusion, reported that diuretic use had a significant positive impact on reducing transfusion associated complications particularly circulatory overload in most of the studies [12]. Nand *et al*., studying the effect of using frusemide in patients with chronic anaemia necessitating frequent blood transfusion, found that frusemide resulted in significant reduction of pulmonary capillary wedge pressure in comparison to control (P<0.001).

In disagreement with these results, some authors reported that the use of diuretics was not effective in improving the pulmonary function among patients receiving blood transfusion. For instance, Sakar et al. reported that the pulmonary function tests were not different between patients who were administered loop diuretics and those who were not[12]. Pulmonary distress was not shown to be improved after using frusemide among patients undergoing blood transfusion as reported by Balegar *et al [28]*. Whilst controversy still exists about the efficacy of loop diuretics in reducing transfusion associated circulatory overload, it remains a common prophylactic measure adopted by at least one third of physicians to reduce potential serious complications [29].

CONCLUSION:

Prophylactic diuretic use prior to blood transfusion is a common practice among more than one third of patients receiving blood or blood products. Diuretics are essential to prevent or reduce transfusion-associated circulatory overload. Diuretics act by several mechanisms to reduce volume excess and pulmonary oedema. They relax the airway smooth muscles and subsequently enhance lung compliance, dilate the veins resulting in reduced venous congestion and fluid extravasation to the alveoli, and they act directly on renal tubules increasing the water excretion leading to a systemic reduction in hydrostatic capillary pressure and fluid transfer from intravascular to extravascular compartment particularly at the pulmonary capillary bed. Various studies have reported a significant positive effect of loop diuretics on reducing transfusion associated circulatory overload, enhancing the pulmonary function, and decreasing the respiratory stress. However, other researchers denied any significant difference between using and not using loop diuretics on patients' outcome. To date, controversy still exits about using diuretics prior to blood transfusion and clear-cut guidelines for practice are lacking. Future multicentric double blinded studies are recommended to state solid basis for the impact of prophylactic use of diuretics among patients receiving blood or blood products.

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