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Recommended Citation

Moiz, B., Sharif, H., Bawany, F. (2009). Transfusion related acute lung injury--TRALI: an under diagnosed entity. *Journal of the Pakistan Medical Association*, 59(1), 39-41.

Available at: http://ecommons.aku.edu/pakistan_fhs_mc_pathol_microbiol/41

Transfusion related acute lung injury — TRALI: An under diagnosed entity

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Abstract

Transfusion related acute lung injury (TRALI) is a life-threatening complication of transfusion of blood and its components resembling acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). TRALI is a particular form of ARDS that follows blood transfusion and is caused by donor-derived antibodies present in the transfused products, reacting with the recipients' blood cells, inducing release of inflammatory mediators thus compromising lung functions. Anti-HLA antibodies are the most frequently indicted inducers in this category. Literature search has not revealed any documented case of TRALI from Pakistan. This in no way implies that TRALI is non-existent in this part of the world but rather indicates that many clinicians may be unaware of the condition or may not recognize transfusion as the cause and like in other parts of the world, is almost certainly under-diagnosed. The lack of agreement on the definite cellular and molecular mechanisms underlying the development of TRALI renders the task of improving the safety of blood transfusion far more complex and potentially quite expensive. This review discusses the modern concepts of pathogenesis of TRALI along with its clinicopathological manifestations and management with the aim to improve awareness of our clinicians towards this dreadful and potentially fatal condition.

Introduction

Transfusion Related Acute Lung Injury is probably an under-diagnosed and underreported condition.¹ Non cardiogenic pulmonary oedema following blood transfusion was first described by Barnard in 1951.² However, not much was known about the condition until 1985, when Popovsky et al documented acute respiratory distress syndrome following blood transfusions as a distinct clinical entity and coined the term transfusion related acute lung injury (TRALI), which they described in the order of 1 per 5000.³ Since then its recognition has been variable in various studies ranging from as frequently as 1/300 transfusions of red blood cell derivatives⁴ to as low as 1/1323 in a recent study.⁵ Recently, it has been recognized as the most common cause of transfusion related morbidity and fatalities.⁶ This might be the result of global increased awareness for TRALI amongst clinicians. However, only one case has been reported from the South East Asian region

which is from India.⁷

Pathogenesis of TRALI: Current concepts:

All blood components have been implicated in the production of TRALI, but whole blood-derived platelet concentrates have been frequently implicated.⁸ Other components include FFP, Packed RBCs, whole blood, apheresis platelets concentrates, granulocytes, cryoprecipitate and IVIG, and even autologous stem cell transplantation in decreasing order of frequency.⁹ There has also been a case report of TRALI occurring after autologous blood transfusion¹⁰ and also one occurring after infusion of leukocyte depleted blood in a four-year old child.¹¹ Even small volumes of plasma (<60 ml) are sufficient to trigger the reaction¹² and its likelihood increases if blood is donated by multiparous females.¹³ It has also been shown that haematologic malignancies or underlying cardiac disease make the patients at increasing risk of developing TRALI.¹⁴

Although TRALI develops within six hours of transfusion,³ most occurrences take place during transfusion or within the first one to two hours after it. The pathogenesis of TRALI is complex and there is lack of agreement on any one hypothesis. It can result from both immune mechanisms such as donor derived anti HLA and granulocyte antibodies (HNA) against recipient's white cells¹⁵ or may be non-immune resulting from neutrophil priming agents such as lysophosphatidylcholines and proteins like CD40 ligand which are abundant in stored cellular blood components.¹⁶⁻¹⁸ A 2-event model for the pathogenesis of TRALI has been proposed: According to this, 2 distinct events are necessary before the patient is at risk for the development of TRALI. The first event (e.g., recent surgery, severe infection, or traumatic injury) causes priming of polymorphonuclear cells (PMNs) and activation of pulmonary endothelial cells. This results in the pulmonary sequestration of PMNs. The second event is the transfusion of biologically active mediators (Anti-HLA antibodies, Anti-granulocyte antibodies) present in stored blood components. These biologically active mediators are able to activate the primed adherent PMNs, resulting in pulmonary endothelial damage, capillary leak, and further injuries similar to ARDS.⁸ These biologically active agents are probably not present in the initial phases of storage, but develop over time.¹⁶ Thus, blood components with longer storage times may be more likely to be associated with TRALI. It should

be appreciated that the lungs are the main organs affected by the disorder. This is perhaps because of unique pulmonary microvasculature which allows 25% of all blood neutrophils to be sequestered even under physiological conditions.¹⁹

In addition to donor antibodies against recipient antigens on the surfaces of leukocytes, the infusion of donor leukocytes into recipients having antibodies directed against donor leukocytes has also been hypothesized.²⁰ Although neutrophils are the centre of attraction in pathogenesis of TRALI, yet it has also been reported in neutropenic patients,²¹ though very rarely. In these patients, the infusion of vascular endothelial growth Factor (VGEF), an effective permeability increasing factor has been implied. More research is needed to explore if neutropenia is protective against TRALI.

Clinical and laboratory diagnosis of TRALI:

Detection of TRALI in a patient is a diagnostic dilemma and medical personnel should apprehend this new onset of acute lung injury (ALI) developing during or within 6 hours of blood transfusion in the absence of other cause of lung injury like shock, septicaemia and aspiration. Criteria for the clinical diagnosis of TRALI have been defined^{22,23} and include rapid onset of tachypnoea, cyanosis, dyspnoea, and fever with and without hypotension. Hypertension has also been reported by few. Hypoxaemia ($\text{PaO}_2/\text{FiO}_2 < 300$ mmHg or $\text{pO}_2 < 90\%$ at room air in the absence of impaired left ventricular function) and bilateral lung infiltrates in the chest radiograph are the hallmark of the disorder. It is also important to determine that pulmonary oedema is not due to cardiac disease or volume overload. Also, TRALI needs to be distinguished from anaphylactic transfusion reactions,¹ and transfusion related circulatory overload.

Various laboratory tests are available for detection of antibodies (HLA class I and II and HNA) in both patient's and donor sera. For HLA, enzyme immunoassay and immunofluorescence are preferred techniques while HNA antibodies are usually detected by immunofluorescence but HNA-3a which is associated with severe TRALI is detected by agglutination.²⁴ These tests are not standardized and can be performed only in reference labs. The sophisticated techniques coupled with their low sensitivity and specificity²⁵ failed to popularize them for diagnostic purpose.

Thus, the diagnosis of TRALI is much the matter of skilled clinical judgment, expertise and awareness of clinicians. The significance of the correct diagnosis lies in the fact that most of the patients recover within 24-48 hours without permanent sequel.²⁶ However, a variable mortality of 11% to 45% has been reported.^{1,3} Concerns have been raised as being an under diagnosed condition, this fatality rate might represent the tip of an iceberg.²⁷

Treatment and prevention of TRALI:

The treatment of TRALI is generally supportive and similar to that for adult respiratory distress syndrome⁸ and consists of aggressive respiratory support, including supplemental oxygen and mechanical ventilation. Hypovolaemia needs to be corrected and use of diuretics may be detrimental. There is no role of treatment with corticosteroids.²⁸ Extra Corporeal Membrane Oxygenation has been successfully used for a particularly aggressive case of a four year old.¹¹ Plasmapheresis has been beneficial in one patient which is logical considering the immune nature of the disease.²⁹ Additional blood component therapies should not be withheld if clear indications for transfusion exist.¹⁸ Use of endobronchial adrenaline may be useful as suggested by animal models.³⁰

The prevention of TRALI remains problematic, and clear recommendations do not currently exist. Blood donors with increased levels of particular HLA or granulocyte antibodies (e.g., multiparous females) have been implicated as important in the etiology of TRALI, but direct cause and effect has yet to be proven. Study by Palfi et al in 2001 showed that adverse effects were observed in critically ill patients when they were transfused with plasma from multiparous blood donors.³¹ However as granulocyte and anti HLA antibodies may or may not be detected in these donors; the routine use of screening plasma for these antibodies is not justified.³² Moreover, simple exclusion of females from donation process will obviously reduce the donor pool in countries where females generously donate blood.³³ Thus an optimal approach would be to use plasma from such multiparous donors for preparing protein derivatives only³¹ while policy of using male donors for preparation of plasma seems more logical. For the prevention of non immune mediated TRALI, it has been suggested to use either fresh blood or wash the cellular blood products to remove neutrophil priming agents before transfusion in recipients who appear to be at risk. But both these approaches interfere with the prompt issuing of blood products by the blood bank at the same time increases the risk of bacterial contamination.¹⁵

Future directions:

Although the 2-event model and the various mechanisms satisfactorily explain most cases of TRALI, they fail to explain why TRALI occurs with autologous transfusion, or does not occur when antibodies are transfused into patients with corresponding antigens. Such data indicates that TRALI is probably a multifactorial disorder. Further study is needed to define its etiology, detect its incidence and risk factors (with special consideration to our part of the world), pathophysiology, and optimum treatment. There is also a need to study the

effects of low-dose epinephrine or methoxamine on the pulmonary vasculature and control of blood pressure during and before the occurrence of TRALI initially in animal models. For this, there is a need to explore the factors that can predict TRALI, because the mechanisms underlying the pathogenesis of TRALI are still doubtful which make the task of improving the safety of blood transfusions extremely problematic and cost- ineffective.

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