Respiratory transfusion reactions

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Key words:
TRALI; TACO; TAD; pulmonary edema; blood components; heart failure

Cite as:
Zdrav Vestn. 2017; 86(9–10):414–21.

Received: 9. 2. 2017
Accepted: 13. 6. 2017

Abstract

Respiratory transfusion-related reactions are infrequent, partly also because recognition and reporting of these reactions is still underutilized. This article describes the most important respiratory transfusion reactions, their pathophysiology, clinical picture and treatment strategies. Respiratory transfusion-related reactions are either primary or secondary. The most important primary transfusion-related reactions are TRALI- transfusion-related acute lung injury, TACO- transfusion-associated circulatory overload, and TAD- transfusion-associated dyspnoea. TRALI is immune-associated injury of alveolar basal membrane, which becomes highly permeable and causes non-cardiogenic pulmonary oedema. The treatment of TRALI is mainly supportive with oxygen, fluids (in case of hypotension) and rarely also with mechanic ventilation. TACO is caused by volume overload in predisposed individuals, such as patients with heart failure, the elderly, infants, patients with anaemia and patients with positive fluid balance. Clinical picture is that of a typical pulmonary cardiogenic oedema, and the therapy is classical: oxygen and diuretics, and in severe cases also non-invasive or invasive mechanical ventilation. TAD is usually a mild reaction of unknown cause and cannot be classified as TACO or TRALI, nor can it be ascribed to patient's pre-existing diseases. Although the transfusion-related reactions are not very common, knowledge about them can prevent serious complications. On the one hand, preventive measures should be sought, and on the other hand early recognition is beneficial, so that proper treatment can take place.

Cite as: Zdrav Vestn. 2017;86(9–10):414–21.

DOI: 10.6016/ZdravVestn.2493

1. Introduction

Transfusion-related reactions are rare complications of transfusion, but if a severe reaction occurs, the right action and treatment is needed to prevent serious complications. More than 95 % of reactions are mild and not life threatening. Less than 5 % of transfusion related reactions are either life threatening reactions or reactions with long term consequences, such as transmission of infectious diseases. In Slovenia the main cause of life threatening transfusion reactions are the respiratory ones (1-2).

Respiratory transfusion reactions (RTR) are divided into two groups. Both groups have similar respiratory symptoms, the only difference being the site where the pathological process takes place. In primary transfusion reactions, the main pathological focus is in the lung and in secondary reactions it is outside the lung. The term 'respiratory

transfusion reaction' is usually reserved for primary transfusion reactions. Primary transfusion reactions are: Transfusion-Related Acute Lung Injury or TRALI, Transfusion-Associated Circulatory Overload or TACO, and Transfusion-Associated Dyspnoea or TAD. Secondary transfusion reactions are: haemolytic transfusion reaction, anaphylactic transfusion reaction and bacterial infections due to transfusion. Whenever physicians are confronted with RTR they have to exclude haemolytic and anaphylactic reactions and bacterial sepsis as possible differential diagnoses (3).

2. TRALI

The incidence of TRALI is 1 per 10,000 transfusions (4). In 2008, SHOT (British Serious Hazards of Transfusion) and FDA (Food and Drugs Administration) published TRALI as most common death related transfusion reaction (5). The main characteristic of TRALI is non-cardiogenic pulmonary oedema, which happens within 6 hours after transfusion. The leading symptom is dyspnoea with hypoxaemia, chills and fever, transient hypertension followed by hypotension, cyanosis and clinical picture of pulmonary oedema. Most symptoms occur within few minutes up to 6 hours after transfusion (6). Transient neutropaenia or leukopenia can also be observed at the very beginning of the transfusion related reaction (7). IHN (International Heamovigilance Network) adopted the definition of TRALI from Popovsky and Moore, described in 1985 with the following four main characteristics: an onset of symptoms within 6 hours after transfusion, the lack of volume overload signs, x-ray signs of acute bilateral pulmonary oedema and hypoxaemia (PaO_2 less than 300 mmHg or blood oxygen saturation level less than 90 %) (8,9).

Eighty percent of patients, who were treated properly improve in 24 up to 48 hours. The rest of the patients (20 %) suffer from a severe form of the disease, which many times ends with death. Almost all patients suffering from TRALI need oxygen supplementation, and 72 % of those with a severe course of the disease also need mechanical ventilation (8). TRALI mortality is 10–15 % (10,11). Differential diagnoses are anaphylactic reaction, TACO and bacterial sepsis caused by transfusion.

2.1. Pathophysiology of TRALI

Mechanism of lung injury in TRALI is not fully understood. Activation of the immune system damages basal membranes of endothelium in the lung microcirculation, causing influx of protein-rich fluid into alveolar space and formation of bilateral pulmonary oedema (12). TRALI is divided into two groups by the mechanism of onset. Immune mediated TRALI is caused by antibodies, and non-immune mediated TRALI is caused by biological active substances (BSA). Both activate the immune system and have same clinical consequences (8,12). It was proven in the early 1970's that antibodies against leukocytes cause TRALI (13). The immune TRALI is caused by antibodies against human leukocyte antigens (anti-HLA) and/or against human neutrophil antigens (anti-HNA) (14-16). In most cases (more than 90 %) activation of patient's leucocytes is caused by antibodies in donor's blood, rarely vice versa (patient's antibodies activate donor's leukocytes in a transfused blood product) (17,18). In very rare cases, in patients who have received many transfusions from different donors, one donor's antibodies will activate other donor's leukocytes (19). Antibodies are formed by stimulation of the

immune system with different antigens during pregnancy, after organ or bone marrow transplantation (5,19-21).

2.2. Prevention of TRALI in Slovenia

There are several preventive measures that we implemented regarding TRALI in Slovenia. Since the main cause of anti-HLA and anti-HNA antibody formation is pregnancy, we decided in 2006 not to use plasma from female donors for clinical purposes (we use female plasma only for plasma fractionation) (5,22). Since 2010 we have been filtrating all units of whole-blood before component processing. After filtration, leukocyte count declines below 1×10 (6) per unit of concentrated red blood cells/platelets or in 1 liter of plasma. After 2014 we stopped collecting apheresis platelets from female donors. Platelets collected by apheresis contain up to 200 ml of plasma which is the main source of antibodies. Instead of plasma we use a special solution as a medium for platelets and therefore additionally lower the quantity of possible antibodies. In 2009 we started pathogen inactivation, which is primarily used for lowering the risk of transmission of the infectious diseases, but as it inactivates leukocytes it also lowers the risk of TRALI. Besides the mentioned measures, special emphasis has to be placed on rational use of blood products. By lowering unnecessary use of blood products we lower the chance of transfusion related complications (23).

3. TACO

The incidence of TACO is 1 per 700 transfusions (4). TACO is acute pulmonary oedema caused by volume overload. The most vulnerable group of patients are the elderly over 70 years of age, newborns and babies, patients with positive fluid balance, patients with chronic anaemia, patients with heart failure, and surgical patients. There are two main reasons for TACO. The first is transfusion of multiple blood units and the second one is blood being transfused at too fast a rate, especially in patients with chronic anaemia. Namely, patients with severe chronic anaemia (haemoglobin less than 50 g/l) have hyperkinetic circulation, which is very inadaptable to volume changes. More than 20 % of TACO cases received only one unit of blood (24-26). In most cases symptoms and signs of TACO occur within 6 hours after transfusion. Main characteristics of TACO are dyspnoea, orthopnoea, cyanosis, tachycardia and peripheral oedema. Furthermore, we can observe jugular venous distension, which depicts elevated central venous pressure (CVP), and increment of laboratory indicator of heart failure- NT-proBNP (27).

Table 1: The incidence of respiratory transfusion reactions in the years 2005 to 2015 in Slovenia.

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Σ
No. of reactions (R)	146	191	190	204	173	170	141	162	113	115	119	1724
No. R /1.000 issued units	1.27	1.69	1.66	1.70	1.35	1.40	1.08	1.24	0.93	0.99	1.06	1.31
TRALI	0	1	0	1	2	0	1	1	2	1	0	9
TACO	3	12	14	11	15	12	10	13	9	8	5	112
TAD	0	0	0	2	1	2	4	3	0	1	1	14

NT-proBNP elevated 1.5-fold compared to the basal value (before administration of transfusion) speaks in favour of TACO (11,28). We can observe ECG changes, such as changes in ST segment dynamics and changes in T waves (27). Differential diagnoses are TRALI, anaphylactic reaction, and sepsis caused by transfusion (5).

3.1. Pathophysiology of TACO

Transfused blood elevates CVP and the volume of circulating blood in the lungs which lowers pulmonary compliance. This causes secondary heart failure and pulmonary oedema (24-26).

3.2. Prevention of TACO

The key is in recognising vulnerable groups of patients and observing them carefully during transfusion of blood components. Patients with positive fluid balance should receive diuretics before, during, after or between multiple transfusions. The rate of transfusion should not be faster than 1ml/kg of body weight per hour for critically ill patients and not more than 2–4 ml/hour for the rest of the patients (29).

4. TAD

TAD is a respiratory transfusion reaction that occurs within 24 hours after transfusion. It is usually a mild reaction that can not be attributed to patient's current disease or chronic illnesses. It is confirmed after TACO, TRALI and anaphylactic reactions have been excluded. Red blood cell concentrate is the most common blood component that causes TAD. Clinically, it presents itself as dyspnoea, tachycardia, hypertension, and body temperature elevated by more than 1.5 degree Celsius. In most cases we observe spontaneous improvement (29).

5. Data for Slovenia

From 2005 on, there were 1724 transfusion reactions, which is 1.31 reactions per 1000 transfused units. Eight percent (135 patients) of all transfusion reactions were RTR. Furthermore, 9 cases (7 %) were TRALI, 112 (83 %) TACO and 14(10 %) TAD; 57 cases (42 %) of RTR were life threatening (Table 1). No deaths were recorded. When comparing Slovenia to other EU countries we can observe similar incidence of TRALI but far lower frequency of TACO. Our conclusion is that many cases of TACO still remain unrecognised and consequently unreported, while TRALI is much more recognised and thus also prevented. Most of the TACO cases happen in polymorbid patients that receive many intravenous fluids, so that physicians hardly link new-onset pulmonary oedema with administration of transfusion (1,2).

6. Treatment of respiratory transfusion reactions

New symptoms and signs that occur during or 24 hours after transfusion should call to mind that RTR is possible. Since symptoms are rather unspecific, the key fact is recently administrated blood compound (30). If RTR is suspected, we stop the transfusion immediately and check if the compounds were compatible with the patient and also examine the patient. If the patient has fever, chills, is in respiratory distress and hypotensive, TRALI is the most likely diagnosis. On the other hand, if the patient presents only with respiratory symptoms and no fever, TACO is more plausible. Vital signs should be monitored, X-ray of the chest performed and blood drawn

(electrolites, BUN, creatinine, inflammatory markers, complete blood count, NT-proBNP) (31). It is very difficult to tell apart TRALI from TACO, since the clinical picture is very similar. TRALI causes acute non-cardiogenic pulmonary oedema and TACO causes cardiogenic pulmonary oedema (32). Blood pressure measurement can be helpful; blood pressure is low in TRALI and high in TACO. Additionally, fever is a characteristic of TRALI, but not of TACO. Sometimes we can also observe transient leukopenia in TRALI. NT-proBNP is a marker of heart failure, which is classically elevated in TACO, but not in TRALI (37,38). Pleural effusion analysis also shows exudate in TRALI and transudate in TACO (39). TACO should be suspected more frequently in the elderly, the critically ill, patients with heart failure, renal failure and infants (40). All patients with reduced oxygen saturation need oxygen supplementation (through binasal catheter, venturi mask) (31). TACO is treated in the same way as pulmonary oedema. The patient is placed in an upright position, parenteral diuretics are administrated. Most commonly used diuretic is furosemide, which is a loop diuretic. Higher doses are needed in patients who regularly use diuretics or the ones with known heart failure. Hypertension is treated with nitrates, dyspnoea is relieved with morphine preparations. Recording fluid balance and vital parameters is crucial at all times (41). Risk of TACO is reduced by identifying patients at risk, slowing down the rate of transfusion and by administering diuretics before or during transfusion (42,43). The treatment of TRALI is mainly supportive. Hydration with crystalloid fluids and in resistant cases also administration of inotropic agents is required. If intubation and mechanical ventilation are required, the use of low tidal volumes is recommended (44). The data about corticosteroid usage in the treatment of TRALI is inconsistent, so their regular use is questionable (45). Further to transfusion discontinuation, the treatment of RTR is mainly supportive; the use of guidelines and algorithms can be beneficial (31,38).

7. Conclusions

Even though transfusion reactions are relatively rare complications (0.1 % of all transfusions, and most of them are mild) it is still necessary to observe patients during and after the administration of transfusion. The most common RTR is TACO, which represents 90 % of all RTRs. Most TACOs could be prevented or alleviated by appropriate actions before commencement of transfusion. Therefore, vulnerable groups of patients need to be recognised before transfusion administration. To prevent any transfusion reactions, the physician always needs to ask themselves whether the patient truly needs transfusion and how is that going to affect the patient's health, keeping in mind the patient's comorbidities. Nevertheless, if the reaction does occur, early recognition and fast intervention is crucial.

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