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Analysis of the occurrence of causes of early transfusion reactions of unknown etiology reported to the Regional Center of Blood Donation and Treatment in Katowice - the role of extracellular vesicles contained in the blood component based on a literature review

Aleksandra Janusz[1,2]*, Joanna Janusz[1], Wojciech Dąbrowa[1], Dominika Wendlocha[2], Aleksandra Mielczarek-Palacz[2]

[1]Transfusion Immunology Department, Consulting Laboratory, Regional Center of Blood Donation and Treatment in Katowice, Poland

[2]Department of Immunology and Serology, Faculty of Pharmaceutical Science in Sosnowiec, Medical University of Silesia, Poland

***Corresponding Author:** Aleksandra Janusz, MD, PhD, Department of Immunology and Serology, Faculty of Pharmaceutical Science in Sosnowiec, Medical University of Silesia, Poland.

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Abstract

Recording of transfusion adverse reactions is an important element in ensuring the safety of transfusion of blood components. It enables the analysis of existing threats, which consequently allows the introduction of corrective procedures and appropriate prevention. However, due to the inability to determine the causes of all transfusion reactions, there are currently no established methods of preventing such complications. As a result, it may cause transfusion reactions in subsequent recipients of blood components.

It seems to be important to understand the causes of early transfusion reactions of unknown etiology. For this reason, this study analyses the clinical symptoms of early transfusion reactions reported to the Regional Center of Blood Donation and Treatment in Katowice, for which the cause of their occurrence could not be determined, and the role of extracellular vesicles contained in the blood component in these processes was determined based on the available literature.

Keywords: early transfusion reaction, extracellular vesicles, transfusion of blood components

Introduction

Transfusion of blood components is a medical procedure that often saves lives. However, it may be associated with the risk of adverse transfusion reactions, which constitute a diverse group of adverse reactions of the body to transfusion of blood components **[1,2]**. They may occur during the transfusion or at different times after the end of the transfusion. Some of them, such as the transmission of infectious agents, may appear months or even years after the transfusion of a blood component. Hence, clinical observation of the patient before, during, and after the transfusion is extremely important. Various divisions of transfusion reactions are used in the literature.

The most common criterion of division is the time after transfusion, when clinical symptoms appear, and it divides the transfusion reactions into: early (acute) - up to 24 hours from the blood component transfusion and late (delayed) - over 24 hours. The second criterion of division is the mechanism in which these complications arise, which differentiates the responses to: immunological and non-immunological. There is also a division into the presence or absence of hemolysis in the recipient's blood component. Most often, in the case of hemolytic reactions in the recipient of the blood component, destruction of the donated red blood cells is observed. Sometimes hemolysis affects the recipient's blood cells and it takes place after transfusion of serologically incompatible Fresh Frozen Plasma *(FFP)* or Platelet Concentrate (*PC*) **[1]**. The most common early transfusion reactions include: Acute Hemolytic Transfusion Reaction *(AHTR)*, Febrile non-hemolytic Transfusion Reaction *(FNHTR)*, allergic and anaphylactic reactions to plasma components, Transfusion Related Acute Lung Injury *(TRALI)*, infection or sepsis and Transfusion Associated Circulatory Overload *(TACO)*. However, among the delayed reactions after transfusion of blood components, the most common are: alloimmunization with antigens of red blood cells, white cells and platelets, delayed hemolytic reactions, Post-transfusion Purpura *(PTP*) and Transfusion – Associated *Graft versus Host Disease (TA-GvHD)*, as well as iron overload **[3]**.

Recording of transfusion adverse reactions is an important element in ensuring the safety of transfusion of blood components. It enables the identification of existing threats on an ongoing basis and the need to introduce corrective procedures and appropriate prevention **[2]**. Issuing transfusion recommendations to patients after a transfusion

reaction enables the development of appropriate clinical strategies aimed at reducing the likelihood of occurrence of another transfusion reaction, which may pose a threat to the health and life of patients **[3]**. Due to the effectiveness of this action, irradiation of blood components for patients with acquired and congenital immunodeficiencies was introduced, which contributed to the almost complete elimination of the transfusion graft versus TA-GvHD recipient reaction **[4]**.

Recognition of a transfusion reaction and classifying it to a specific group is possible thanks to appropriate clinical management, e.g., in the case of allergic reactions, administration of antihistamines one hour before the planned blood component transfusion. It also makes it easier to decide on the specific preparation of the blood component intended for the patient who has experienced a transfusion reaction, e.g., filtering (*LDRBC - Leukocyte-depleted Red Blood Cell Concentrate*, *LDPC - Leukocyte-depleted Platelet Concentrate)*, irradiation with doses of ionizing radiation 25-50 Gy (*IRBC – Irradiated Red Blood Cells*, *IPC – Irradiated Platelet Concentrate)*, washing and suspension in plasma replacement fluid (SSP +, SAGM).

The clinical symptoms and causes of non-hemolytic transfusion reactions, as well as the management of these complications, are presented in **Tables 1 and 2**.

Table 1: Clinical symptoms and causes of non-hemolytic transfusion reactions [modified according to 19]

Non-hemolytic transfusion reaction		
Fever	**Allergic reaction**	**Anaphylactic shock**
• The temperature increases by 1 ° C or more during the transfer or within 2 hours of its completion, • Clinical symptoms: chills, feeling cold, muscle stiffness, headache, nausea, vomiting, • Reason: presence of antibodies to leukocyte antigens in the recipient's plasma or accumulation of pyrogenic cytokines in the blood component (during storage).	• Mild allergic reactions are common, • Clinical symptoms: itching, hives, erythema, and redness, • Sometimes: laryngeal edema, hoarseness, bronchospasm, wheezing, retrosternal pain, dyspnoea, agitation and cyanosis, gastrointestinal disturbances such as nausea, vomiting, abdominal pain and diarrhea, • Cause: presence of IgE antibodies against donor plasma proteins and release of vasomotor substances.	• In addition to symptoms typical of mild allergic reactions, there is cardiovascular instability with decreased blood pressure, tachycardia, loss of consciousness, cardiac arrhythmias and cardiac arrest, respiratory symptoms with dyspnoea last longer, • Cause: often in patients with IgA deficiency who have developed anti-IgA antibodies (IgG and IgM classes) activating complement components and antibodies against C4 and • haptoglobin.

Table 2: Management of non-hemolytic transfusion reactions [modified according to 19]

Management of non-hemolytic post-transfusion reactions		
Fever	**Allergic reaction**	**Anaphylactic shock**
• It is recommended to filter RBC and PC units, the maximum number of leukocytes in a blood component that prevents this complication is 5 * 106 leukocytes per unit, • Filtering the blood component during transfusion does not remove pyrogenic cytokines, only reducing the number of leukocytes before storage reduces their release, • Transfusion of LDPC from apheresis selected in a lymphocytotoxic test.	• If the complication was caused by an allergic reaction to plasma protein components, antihistamines are recommended to be used before the next transfusions, and should be administered one hour before the planned transfusion, • sometimes additionally: RBC and PC washed and suspended in 0.9 % NaCl or liquid, • -FFP transfusion only under intensive supervision and for vital reasons only.	• RBC intended for transfusion should be washed in order to remove IgA to the extent that prevents the occurrence of this type of Transfusion complication (e.g., LDRBC washed and suspended in 0.9% NaCl or enrichment fluid), transfuse LDPC apheresis suspended in 0.9% NaCl or enrichment solution, - caution in the use of FFP is advisable, transfusions should only be performed under intensive surveillance.

The inability to determine the causes of all transfusion reactions makes it impossible to implement appropriate procedures to prevent complications. This may result in the occurrence of transfusion reactions in subsequent recipients of blood components.

The studies conducted so far have shown that the clinical symptoms of blood component recipients for whom a causal relationship with the transfusion has not been established may be related to the involvement of extracellular vesicles *(EV)* released from erythrocytes, white blood cells and platelets during collection, transport, preparation and storage of blood components.

Extracellular vesicles are a diverse population of mostly spherical membrane structures released by cells that circulate in the body in a very stable subcellular form and contain a variety of cellular materials. The building blocks of EV are peptides, proteins, mRNA, miRNA, DNA, and lipids. Extracellular vesicles are lipid-enclosed structures that are divided into three categories: exosomes, microvesicles (or ectosomes), and apoptotic bodies. **[5,6,7]**.

Results

The analysis covered 225 cases of transfusion reactions reported to the RCBDT in Katowice in the period from January 1. 2017, to December 31. 2018.

In 113 patients, including 47 (41 %) in 2017 and 54 (59 %) in 2018, the following complications were excluded on the basis of the performed tests and the analysis of clinical symptoms:

a) Hemolytic Transfusion Reaction, *(HTR)*,

b) Transfusion Related Acute Lung Injury *(TRALI)*,

c) Transfusion Associated Circulatory Overload (*TACO)*,

d) Transfusion-associated dyspnoea *(TAD)*,

e) Non-hemolytic Transfusion Reaction *(NHTR)*

f) Hypersensitivity reactions to plasma components.

For this reason, the aim of the study was to assess the clinical symptoms of early transfusion reactions reported to the Regional Center of Blood Donation and Treatment in Katowice, for which the cause of their occurrence could not be determined and, based on the current state of knowledge, the issues of the possible role of extracellular vesicles contained in the blood component in these processes.

Patients and Methods

The analysis covered the medical documentation provided to the Consulting Laboratory of the RCBDT in Katowice, the results of immunohematology tests, and the issued transfusion recommendations of patients with early transfusion reactions. The evaluation period was 2 years.

The causal relationship of the transfusion reaction could not be established in 113 patients. The dominant clinical symptoms were analyzed and found that:

a) 45 % of patients experienced an increase in body temperature from 37^{o} C to 40^{o}C within 10-30 minutes from the start of transfusion,

b) 38 % experienced heart rate and pressure disorders,

c) 36 % experienced chills and anxiety,

d) 25 % of patients experienced dyspnoea.

Clinical symptoms occurred in 95% of patients after the transfusion of Red Blood Cells *(RBC)*, and in the rest of the recipients after Fresh Frozen Plasma *(FFP)*.

Figures 1, 2, and 3 shows the obtained results.

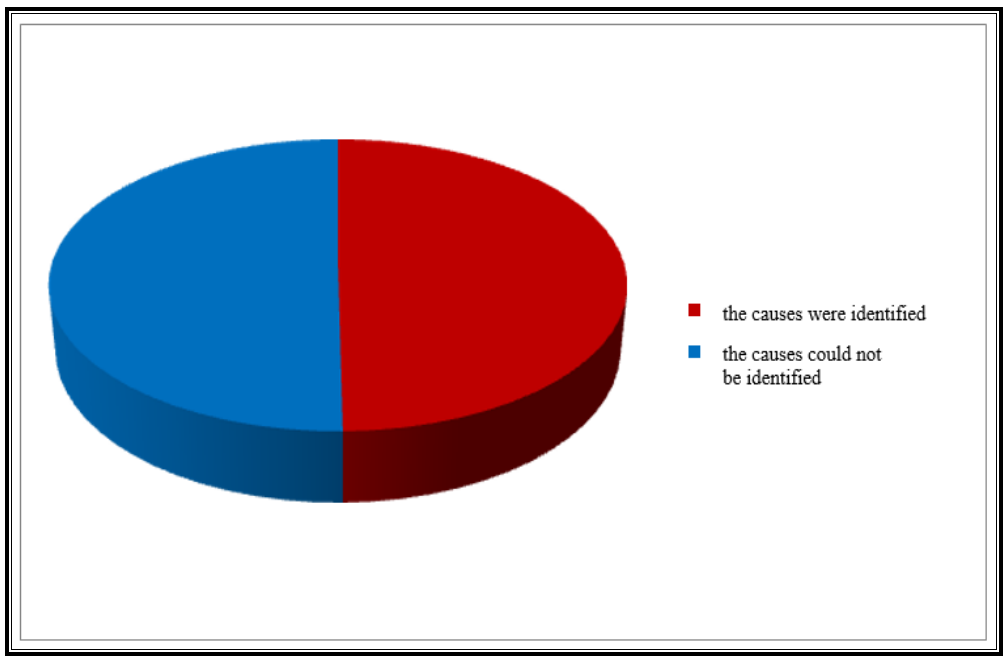

Figure 1: Early transfusion reactions reported to RCBDT in Katowice and causes of the complication [own elaboration]

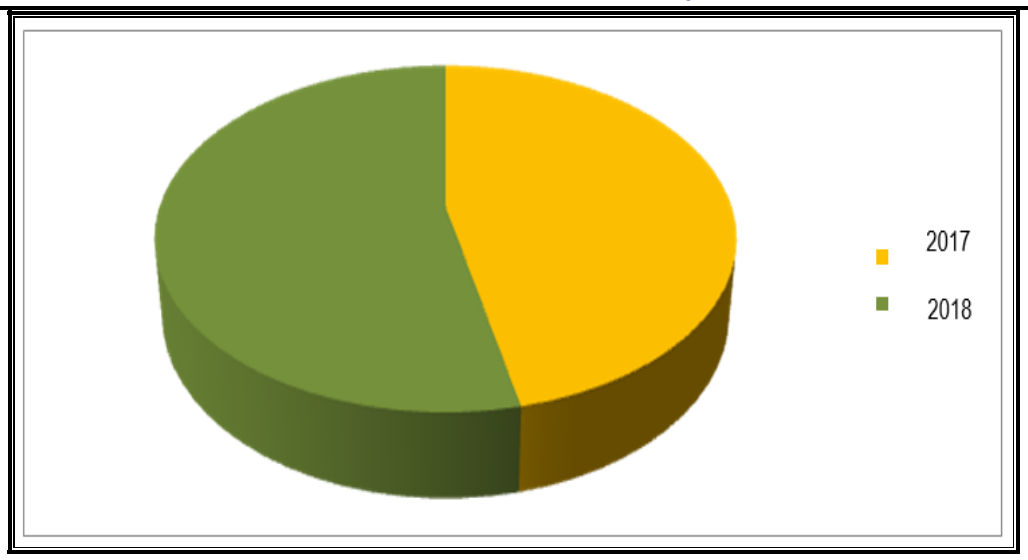

Figure 2: Early transfusion reactions [%] reported to RCBDT in Katowice, for which a causal relationship with blood component transfusions has not been identified taking into account 2017 and 2018 [own elaboration]

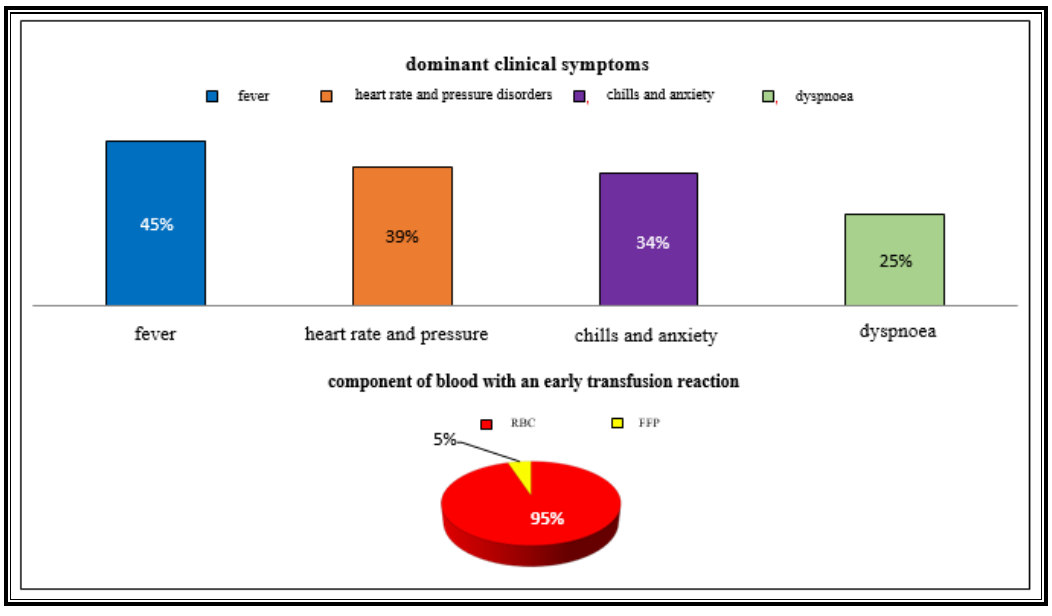

Figure 3: Early transfusion reactions reported to RCBDT in Katowice, in which the causal relationship with blood component transfusion could not be identified [%] including patients with specific clinical symptoms [%] [own elaboration]

Discussion

Recent studies indicate that during the storage of red blood cells, many membrane particles related to adhesion, oxygen transport, regulation of the immune system, and the aging process occur, such as CD44, CD47, CD55, CD59, CD235a, CD147, sCD40L, phosphatidylserine (PS) and also extracellular vesicles *(EV)*. The release of EV from eukaryotic cells is a physiological process that occurs during cell maturation and aging **[8, 9, 10]**.

Extracellular vesicles are a heterogeneous population of cell-derived alveolar bodies either from the endosomal compartment (exosomes) or by plasma membrane exfoliation (microvesicles, oncosomes, and apoptotic bodies). EV contain genetic material in the form of: RNA, miRNA, DNA and miDNA, as well as other molecules such as proteins and lipids, which may be taken up by other cells, both in the immediate vicinity of the source cell and in remote places in the body through fluids biological and influence various processes in the body, both physiological and pathological **[11]**. It has been shown that an increased number of EV is detected in the plasma of patients in the course of many diseases, such as deep vein thrombosis, breast cancer, cardiovascular diseases, diabetes or various types of infections **[12]**. Research has shown that EV influence the immune response. In response to extracellular vesicles derived from cancer cells, there is an increase in the number of CD8 + cytotoxic T cells and mature macrophages, and a decrease in the number of CD4 + T supporting cells, affecting regulatory T lymphocytes and NK (Natural Killer) cells. Microvesicles are released into the bloodstream and then spread systemically where they act in one of three different ways: (1) binding EV to a target cell membrane protein that activates a specific intracellular signaling pathway; (2) the protease in the extracellular matrix cleaves the membrane proteins of the membrane of the extracellular vesicles, which then bind to receptors on the plasma membrane, activating the signaling pathway; (3) the vesicle extracellular membrane attaches to the target cell membrane, causing its contents to be released non-selectively. As EV influence cell-cell interactions, these structures have been the subject of numerous studies aimed at understanding the spreading process of metastasis, but also for identifying biomarkers of disease stage, progression and resistance mechanisms **[13]**. Research is also underway using EV as therapeutic carrier as it has been shown that microvesicles RNA may alter the expression and function of the recipient cell gene. The study

of these structures and their interactions with other cells is necessary for further advances in their clinical applications **[11]**.

Although the presence of extracellular DNA *(ecDNA)* in human plasma in the amount of 250-1500 ng / ml was demonstrated by Mandel and Métais **[14]** in 1948, its influence on the recipient's body after the transfusion of the blood component has not yet been fully identified. It is known that ecDNA, by influencing the activity and viability of neutrophils, has the ability to activate cells of the innate immune system response, increase cytokine release and induce inflammation. It turns out that donor DNA may be transferred to the recipient's organism not only through extracellular vesicles, but also through ecDNA present in plasma, as well as through ecDNA associated with the surfaces of blood components such as: erythrocytes and platelets. It has been shown that ecDNA from human plasma may pass through 0.4-micron filters, indicating that the filtration did not affect the DNA content of the blood component. As 1 ml of plasma contains 1.5 μg of DNA, the total amount of DNA delivered to a patient during a transfusion of one unit of whole blood (500 ml) may be as much as 450 μg. It was also shown that the cellular blood components (RBC: 290 ± 120 ng / ml and RBC: 339.6 ± 114 ng / ml) contained more ecDNA than FFP (2.875 ± 0.996 ng / ml). This may explain the increased incidence of unexplained transfusion reactions after RBC transfusion compared to FFP (95 and 5 %, respectively). It is worth noticing that the production or release of ecDNA present in blood components may be influenced by the methodology of collection and preparation as well as the method of storage of these components. Unfortunately, many studies on the content of ecDNA in blood components have been conducted with the use of different analytical procedures, which makes detailed analysis impossible **[15]**.

In the body, the increased release of extracellular vesicles may occur as a result of cell activation because of stress factors such as: temperature, osmotic pressure changes, tension arising during the flow in the vessels or as a result of factors leading to cell apoptosis **[12]**. On the other hand, *in vitro* concentration of extracellular vesicles in the blood component depends on: the conditions of transport of whole blood collected from donors, the method of separation into individual blood components (RBC, FFP and PC), the composition of the enrichment solutions in which they are suspended, as well as the storage conditions of blood components. Thus, increased EV formation may already occur during the collection and transport of Whole Blood (*WB*). Due to the small size of the extracellular vesicles**,** e.g., 0.2 to 2.0 μm, it is very likely that they may not be removed during preparation and may be present in all blood components obtained from this unit of WB, e.g., in RBC, PC and FFP. It turns out that also during the storage of blood components, a significant release of EV occurs **[16,17]**. Devalet et al. **[18]** showed that during RBC storage there is an increase in the number of EV from red blood cells from 1779 / μl to 218,451 / μl and a decrease in the mean clotting time, from 117.2 ± 3.6 s on the day of collection to 33. 8 ± 1.3 s in the final storage period of this blood component. This may reflect the phospholipid-dependent procoagulant activity that may result in venous thrombosis. These studies are consistent with previous observations indicating an increased risk of venous thrombosis in patients after RBC transfusion **[18]**.

The influence of different types of plastics on the formation of EV released from platelets was also analyzed. Research by Gemmell et al. **[19]** showed that the release of EV (CD41 +) from WB stored in polypropylene containers was higher compared to WB stored in polyvinyl containers **[20]**. Increased release of EV due to activation of platelets due to contact with the container wall was also confirmed in the studies by Bode et al. **[2,3]**. On the other hand, Gelderman et al. [20] showed that in the Platelet Concentrates obtained by apheresis on the 6th day of their storage, a significant increase in EV from platelets (CD41a +), leukocytes (CD45 +), and erythrocytes (CD235a +) is found **[20]**.

The presence of a significant number of EV, mainly of platelet origin, was found in Fresh Frozen Plasma and Cryoprecipitate. The number of released EV correlated with the number of platelets in FFP **[21]**. Probably the release of EV from platelets occurred during the cycle of freezing and thawing blood components. The number of microvesicles in FFP was 250 times higher compared to the number of EV detected in fresh plasma **[18]**. The results of the pooled PC studies showed an increase in EV (CD41 +) in preparations stored for 2–5 days. Other researchers also present observations on the increase in the number of EV (CD42 + CD41 +) in PC during 5 days of their storage **[22]**. In the filtered PC components, the release of EV is higher than in the non-filtered PC **[1]**. Rubin et al. **[23]** studied the release of erythrocyte microvesicles during RBC storage. In other observations of researchers, the effect of temperature on EV release was observed. It has been shown that during RBC storage at 4 ^{o}C, the number of EV released from erythrocytes gradually increases. At the end of the validity of RBC, the increase in erythrocyte EV was 20-fold higher compared to the day on which the blood component was obtained. On the other hand, the studies conducted by Merten et al. **[16]** showed that two hours after RBC transfusion in the recipient's circulation 2.4-fold increase in EV concentration is found in comparison to the concentration before transfusion.

Currently, an important role in regulating the immune response is assigned to low molecular weight ribonucleic acids (RNAs), mainly microRNAs *(miRNAs),* which in the body are transported by extracellular membrane extracellular vesicles and/or in exosomes. EV may thus have an impact, inter alia, on the activity of macrophages, which play an important role in many immune, metabolic and neuroendocrine processes. EV contains miRNAs that, when delivered to target cells, such as macrophages, regulate gene expression by interfering with transcription and translation processes. EV contained in body fluids are actively taken up by macrophages **[24,25]**. MiRNA

molecules absorbed by EV affect the course of the inflammatory reaction, including by activating the secretion of pro-inflammatory cytokines by macrophages M1, additionally enhancing the response to interferon γ *(IFN-γ*) in these cells and the expression of markers characteristic for antigen presenting cells *(APC*). Therefore, the contribution of EV presents in the transfused blood component to the modulation of macrophage activity of the recipient of this component cannot be excluded. Dyspnoea occurred in 25 % of blood component recipients who experienced a transfusion reaction of unknown etiology. Extracellular vesicles contain enzymes necessary for the local synthesis of leukotrienes, which may be responsible for the development and exacerbation of allergy, asthma, and chronic inflammation by promoting the migration of granulocytes **[26]**. This may suggest an involvement of the Es present in the transfused blood component in the generation of these clinical symptoms.

After transfusion of a blood component containing microvesicles of blood cell membranes, they may activate complement components and neutrophils in the recipient's body **[27,28,39]**. Moreover, microvesicles, by binding to granulocytes and lymphocytes, have the ability to induce inflammatory processes by increasing the expression of the CD11b adhesive molecule on the surface of these cells and their phagocytic activity. Extracellular vesicles bind the soluble PECAM-1 (*platelet endothelial cell adhesion molecule 1*) and ICAM-1 *(intercellular cell adhesion molecule 1*), which are markers of inflammation. It has also been shown that EV released from multinucleated cells may induce the release of pro-inflammatory cytokines from endothelial cells. Moreover, in in vitro studies, Gasser et al. **[30]** proved that the Extracellular vesicles resulting from the activation of nucleated cells have the ability to fix complement, which facilitates their destruction. EV may play an important role in intercellular communication and modulation of functions, inter alia, of immune system cells. Recent studies confirm that the increased content of extracellular mitDNA correlates with an increased risk of a transfusion reaction in the recipient.

Extracellular vesicles modulate the activity of immune system cells responsible for maintaining homeostasis of the body, but also those involved in the course of disease processes **[24,25]**. As a result, the recipient of the blood component may experience clinical symptoms such as fever, chills, changes in heart rate and pressure. Similar clinical signs were observed in patients with reported early transfusion reactions in whom a causal relationship to transfusion could not be established. For this reason, it seems necessary to conduct further studies to establish a possible relationship between the occurrence of early transfusion reactions and the presence of EV in the transfused blood components.

Since these molecules, by transporting regulatory factors, enzymes, receptors and signaling molecules, may modulate the functions of the immune system of the recipient of the blood component and are responsible for the release of inflammatory cytokines, due to the activation of monocytes / macrophages and lymphocytes, which may result in adverse transfusion reactions, it seems reasonable to conduct further research in this regard.

Conclusion

The analysis of the causes of early transfusion reactions and the available data from the literature indicate the participation of extracellular vesicles released from erythrocytes, white blood cells, and platelets during the collection, transport, preparation, and storage of blood components in patients whose causal relationship with the transfusion of a blood component cannot be established, which requires further research for potential application in the development of procedures to prevent these reactions.

Conflict of interest: none declared.

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