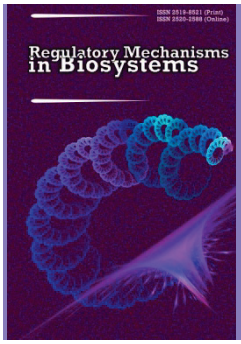

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Effects of allogeneic blood transfusion on the immunity parameters in recipient rabbits

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Blood transfusion is always associated with immunological risks. In animals, immune conflicts can occur, because other than erythrocytes and plasma factors, many other antigens (leukocytes, trombocytes) are not accounted for. This publication is focused on morphological changes in blood of recipient rabbits following allogeneic transfusion. Modeling of blood transfusion was performed on five clinically healthy rabbits by intravenous injection of allogeneic whole blood in estimation of 5.5 mL/kg of body weight. The materials for the study were the blood samples, gathered on the 3rd, 7th, and 23th days after the transfusion. We determined that in the organism of the recipient animals, there occurred post-transfusion leukocytosis. Increase in the number of leukocytes in the experimental animals did not exceed the physiological parameters. After whole-blood transfusion, the amount of lymphocytes and granulocytes in the recipient rabbits did not significantly change over 23 days of the experiment. We recorded significant decrease in the amount of monocytes on the 3–23rd day after allogeneic transfusion in the organism of the recipient rabbits. Following the blood transfusion, percentage of T-lymphocytes in the recipient rabbits increased compared with the initial condition on the 3rd and 7th days of the experimental studies, and decreased on the 23rd day. Percentage of B-lymphocytes in the recipient rabbits after the allogeneic blood transfusion increased compared with the initial level, indicating activation of specific immunity. The whole-blood transfusion led to decrease in the percentage of O-lymphocytes in the recipient on the 3rd day of the experiment, and increase on the 7th and 23rd days of the experiment, as compared with the initial condition. The conducted studies of allogeneic transplantation of whole blood demonstrate that whole-blood transfusion entails a cascade of complex immunological reactions in the recipient animals. The prospects for further research are studies of influence of allogeneic transfusion of blood components on the parameters of specific and non-specific links of immunity of the recipient animals.

Keywords: cellular immunity; hemotransfusion; leukocytes; monocytes; granulocytes; T-lymphocytes; B-lymphocytes; O-lymphocytes; leukocytosis.

Introduction

Transfusion of blood or plasma can cause serious and potentially life-threatening reactions in the recipients. Over the recent decade, transfusion medicine has advanced, and currently many canine patients receive blood or its components. Plasma components such as fresh-frozen plasma (FFP) are mostly used for treatment of coagulopathies (Santo-Domingo & Lewis, 2021). Plasma contains therapeutic levels of functional factors of blood coagulation, transfusion of which is an important element of treatment of many congenital and acquired coagulopathies (Spada et al., 2022).

In allogeneic transplantation, healthy stem cells of the bone marrow, peripheral blood or umbilical blood of donors are used as a source for recovery of hematopoietic function in patients (Wong et al., 2022). Hemotransfusion of erythrocytes can increase the level of hemoglobin in patients and reduce hypoxia. Blood transfusion in animals is always associated with immunological risks. Factors that affect the transfusion effectiveness include immune and non-immune factors (Kang et al., 2023). It has to be noted that transfusion-related complications occur despite correct protocols of blood draw and preparation to transfusion of blood and its components (*in vitro* immune reactions) to recipient animals. Hematological changes and oxidative stress take place as early as the first week of storage, leading to exhaustion of antioxidant system and further accumulation of oxidation products, and also hemolysis of erythrocytes, being pronounced the most at the end of shelf life (Bujok et al., 2022). As is known, blood serum of cats contains natural antibodies that can trigger acute immunological reactions during non-matching-blood transfusion. Unlike cats, blood serum of dogs and rabbits and horses contains no natural antibodies that are capable of causing acute immunological reactions. In recent years, novel natural antibodies have been discovered in cats (Mik antigen) and dogs (DAL antigen) (Lanevschi & Wardrop, 2001; Rozanski & Laforcade, 2004; Weinstein et al., 2007).

Reaction of recipient-animal organisms can be acute and delayed, immunological and non-immunological. When preparing to transfusion, a recipient animal should be subjected to a serological examination (cross-matching with donor's erythrocytes and blood serum of a recipient animal) (Tocci, 2010; Davidow, 2013). We should note that transfusion of allogeneic blood leads to immunological reactions in recipient animals that do not always manifest clinically (Davidow, 2013).

Insignificant immunological reactions occur in recipient animals during activation of immunological markers (cytokines, immunoglobulins). Furthermore, the main diseases in recipients of transfusion cause clinical signs such as inflammations, while additional immunological factors that cause transfusion-related inflammations go unnoticed. Also, we should note the use of various pharmaceutical drugs prior to blood transfusion, which also influence the reaction of the immune system in recipient animals. The literature sources (Muylle et al., 1993; Shanwell et al., 1997; McFaul et al., 2009) suggest that blood transfusion in critically ill people causes acute inflammatory process, accompanied by post-transfusion leukocytosis and increase in the level of pro-inflammatory cytokines. Post-transfusion neutrophil leukocytosis occurred in 45 of 50 patients over 12 h. None of the patients were observed to have eosinophilic leukocytosis and allergic reactions. The study results (Fenwick et al., 1994) were similar to

those of researches on critical patients. In 76% of such patients, there developed post-transfusion neutrophilic leukocytosis. Furthermore, there was seen a positive correlation between leukocytosis and concentration of IL-8 in the erythrocyte mass. Moreover, the patients that had received allogeneic blood transfusion (Izbicki et al., 2004) had no clinical signs characteristic of acute allergic reactions.

Insignificant blood-transfusion-caused immunological reactions were also observed in the clinically healthy dogs after autological-blood transfusion. The researchers (McMichael et al., 2010) noted increase in segmented-nucleus neutrophils, fibrogen, and C-reactive protein in the recipient animals after transfusion of 21-day erythrocytes.

Studies also revealed that similar immune reaction was observed in healthy dogs that had received transfusion of 28-day erythrocytes. Those animals were seen to have neutrophilic leukocytosis and increase in the level of proinflammatory cytokine monocyte chemoattractant protein-1 (MCP-1). Results of the both studies demonstrate that transfusion of erythrocytes can cause immunological reactions in healthy dogs, while causing no clinical signs of the transfusion reaction (changes in frequency of cardiac contractions, respiration rate, and body temperature). Also, there is a need for studies and scientific substantiations of immunological reactions in clinically healthy animals, and also feline and canine patients after blood transfusion (Callan et al., 2013).

According to the results of the study (Egorov et al., 2022), after allogeneic transfusion of whole blood to the recipient rabbits, the content of M-class immunoglobulins in blood serum increased on the 3rd day of the experiment, and decreased on the 23rd day.

After allogeneic transfusion of whole blood to the recipient rabbits, the contents of G and A-class immunoglobulins in blood serum decreased over a 23-day experiment. Allogeneic transfusion of whole blood to the recipient rabbits activated the formation of circulating immune complexes in blood serum of the animals, which settle in the perivascular space and cortex of the kidney, and activate complement and inflammation (Egorov et al., 2022).

The literature data (Drannik, 2010) suggest that humoral specific immunity is realized by B-lymphocytes that synthesize five classes of immunoglobulins. Cell-mediated immunity is represented by population of T-lymphocytes, including helpers, killers, and suppressors. A peculiarity of specific immunity is that T- and B-lymphocytes have antigen-identifying receptors on their surface, with the help of which there occurs the process of identification of antigen and differentiation of self- and non-self antigens. If necessary, with time, there activate mechanisms of synthesis of antibodies, or T-lymphocyte-killers, which have a clear specificity to antigens. Once an immune reaction dies out, there remains a specific immunological memory that allows the immune system of animals to quickly react if an antigen invades the organism again (Rabson et al., 2006; Drannik, 2010).

The objective of the study was determining the influence of allogenic transfusion of whole blood on changes in the immune reaction of the recipient animals at cellular level of the recipients' blood.

Materials and methods

The experiments on the animals were carried adhering to the requirements of the General Ethical Principles of Performing Experiments on Animals, approved by the 1st National Congress of Bioethics and the Positions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, and the Law of Ukraine on Protection of Animals from Abuse. A permit for using animals in the experiments according to the scheme was received from the local commission of Bioethics of the National University of Life and Environmental Sciences of Ukraine (as of 10/27/2020), Protocol No. 31-1.

The studies were carried out at the basis of the Bank of Animal Blood NNL of the Department of Surgery and Pathophysiology named after academician I. O. Povazhenko of the National University of Life and Environmental Sciences of Ukraine and in the conditions of the Vetmedservis Education-Research Center. In the experiments, we used five clinically healthy White Pannon rabbits. The diet of the experimental animals corresponded to their need in nutrients and biologically active compounds. The animals had free access to water and fodder. Blood of the donor animals was drawn from the jugular vein using semi-closed method. In the place from blood was to be drawn, the hair of the animals was shaved, and the skin was treated with 70% alcohol solution. During blood collection, the animals were fixated so the tissues were moderately stretched in the region of the jugular vein. The head of an animal was pulled away from the blood draw. In the area of the upper and middle thirds of the neck, we performed puncture of the jugular vein. At the angle of 45°, we injected the needle, puncturing the skin and the vein wall against the blood flow. For convenience of the procedure, the vein below the puncture region was pressed by the finger of left hand. The samples of donor blood from the rabbits were collected into polymer containers with anticoagulant CPDA (citrate, phosphate, dextrose, and adenine) (Malyuk et al., 2022). The recipient rabbits received transfused allogeneic whole blood in the amount of 5.5 mL/kg of body weight. The materials for the study were the blood samples taken from five rabbits on the 3rd, 7th, and 23rd days after transfusion.

The morphological studies of blood (number of leukocytes, lymphocytes, monocytes, and granulocytes) of the animals were performed using a Mindray BC-2800 Vet hematological analyzer (China).

Amount of T-lymphocytes in blood of the rabbits was examined with the use of ram erythrocytes by the method of spontaneous rosette formation according to Jondal et al. (1972). The method of identification of T-lymphocyte number is based on the interrelation between membrane receptors of lymphocytes and indicatory cells (ram erythrocytes). According to the number of erythrocytes, adsorbed by one lymphocyte, we determined extent of the activity of T-cells, because the phenomenon of rosette formation is conditioned by amount of receptors on their surface (Mazurkevich et al., 2014).

Amount of B-lymphocytes in blood of the rabbits was measured according to Mazurkevich et al. (2014). B-lymphocytes on their surface have receptors to C_3 component of the complement, though have no receptors to ram erythrocytes, and therefore a direct interaction of such erythrocytes with B-lymphocytes is impossible. Combining erythrocytes and B-lymphocytes requires mediation by the complement and anti-erythrocyte antibodies. For this purpose, erythrocytes were processed using hemolytic serum containing anti-erythrocyte antibodies. There formed an antigen-antibody complex, with which the complement bonded. Because receptors to C_3 component of the complement have B-lymphocytes, during a rosette formation (by number of lymphocytes that linked three and more erythrocyte-antibody-complement complexes), one can conclude on the number of B-lymphocytes (Fig. 1) (Mazurkevich et al., 2014). Number of O-cells was counted as follows: from 100% overall lymphocytes, we subtracted the total numbers of T-lymphocytes and B-lymphocytes (Duda & Prus, 2019).

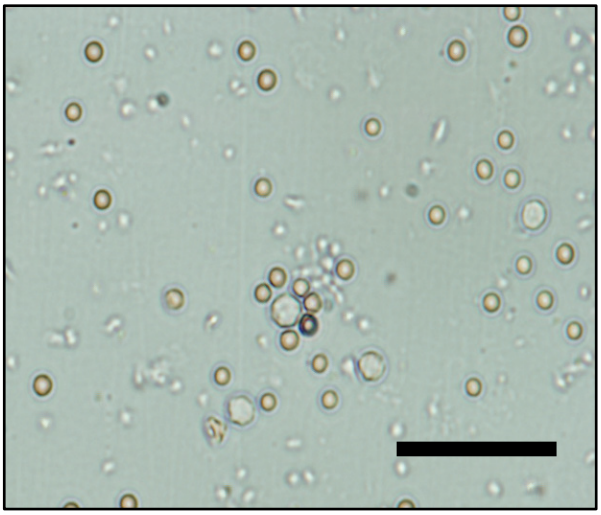

Fig. 1. Rosette-formation reaction between rabbit erythrocytes and ram erythrocytes: bar – 50 μm

The data were statistically analyzed using ANOVA and the Tukey's test. The difference between the parameters was considered significant at $P < 0.05$.

Results

Results of studying quantitative value and percentage parameter of leukocytes and their subpopulations in blood of rabbits on days 3, 7, 23 of the experiment after allogeneic transfusion are presented in Table 1 and Figure 1. As Table 1 demonstrates, after allogeneic transfusion, the number of leukocytes in blood of the recipient rabbits increased by 35.3%, 74.5%, and 43.1% on the 3rd, 7th, and 23rd days of the experiment, respectively. That is, in the recipient animals, post-transfusion leukocytosis took place. We should note that increase in the number of leukocytes in the experimental animals was within the physiological parameters.

Table 1
Dynamics of changes in the number of leukocytes and their subpopulations in blood of the rabbits following allogeneic transfusion of whole blood ($x \pm SD$, $n = 5$)

Cells	Initial condition	3rd day	7th day	23rd day
Leukocytes, 10^9/L	5.06 ± 0.34^{a}	6.82 ± 0.89^{b}	8.78 ± 1.74^{ab}	7.16 ± 1.20^{ab}
Lymphocytes, 10^9/L	2.96 ± 1.37^{a}	3.94 ± 0.78^{b}	5.88 ± 1.12^{ab}	4.70 ± 0.83^{ab}
Monocytes, 10^9/L	0.40 ± 0.16^{a}	0.22 ± 0.08^{a}	0.30 ± 0.16^{a}	0.20 ± 0.07^{a}
Granulocytes, 10^9/L	1.70 ± 0.62^{a}	2.53 ± 0.38^{a}	2.58 ± 0.33^{a}	2.15 ± 0.22^{a}

Note: different letters indicate significant difference between each other within one line of the table according to the Tukey test ($P < 0.05$) with the Bonferroni correction.

Compared with the initial condition, number of lymphocytes in the rabbits after transfusion of whole blood increased by 44.8%, 112.2%, and 69.0% on the 3rd, 7th, and 23rd days of the experiment, respectively. Quantity of monocytes in blood of the experimental animals decreased compared with the initial condition on days 3 and 23 of the experimental studies by two times, and by 25% on the 7th day of the experiment. Number of granulocytes in blood of the experimental animals was also greater than initially on days 3, 7, and 23 of the experiment, by 47.1%, 52.9%, and 52.9%, respectively. Therefore, allogeneic transfusion of blood to the recipient rabbits caused leukocytosis throughout the study period by increasing lymphocytes and granulocytes.

Percentage of lymphocytes (Fig. 2) in the rabbits after transfusion of whole blood had not significantly changed by the 3rd, 7th, and 23rd days of the experiment.

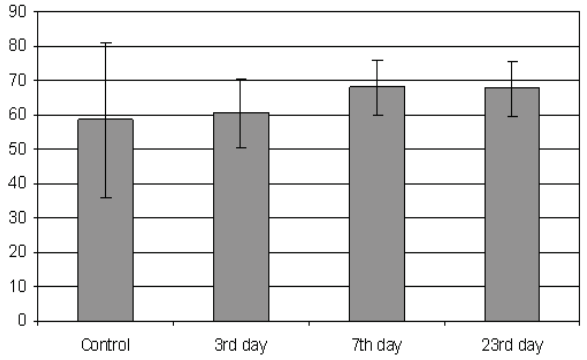

Fig. 2. Dynamics of changes in the ratio of lymphocytes in blood of the rabbits following whole-blood transfusion ($x \pm SD$, $n = 5$): ordinate indicates the share of lymphocytes (%); no significant ($P < 0.05$) differences between the groups were

Percentage of monocytes (Fig. 3) in the rabbits after transfusion of whole blood significantly dropped 2.7, 2.4, and 2.8 times on days 3, 7, and 23 of the experiment, respectively.

Granulocyte percentage (Fig. 4) in the rabbits following whole-blood transfusion did not change significantly.

We should note that we observed no rise in body temperature and no clinical signs of allergic reactions in the recipient rabbits. Percentage of T-lymphocytes in the recipient rabbits (Table 2) after transfusion of whole blood significantly increased compared with the initial condition on the 3rd day of the experiment (by 35.3%). On the 23rd day, percentage of T-lymphocytes significantly decreased (by 21.2%). Such changes in T-lymphocytes in the recipient animals resulted from antigen (humoral and cellular) irritation during allogeneic transfusion. Percentage of B-lymphocytes in the recipient rabbits (Table 2) did not change after allogeneic-blood transfusion.

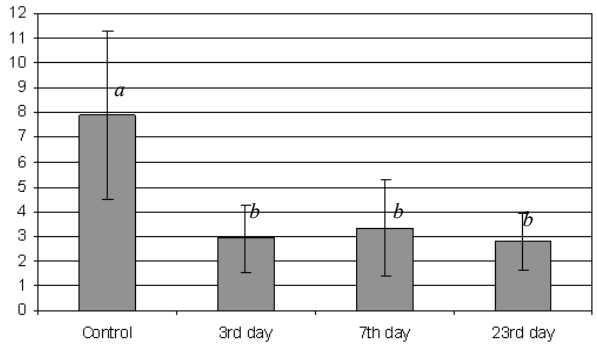

Fig. 3. Dynamics of changes in monocytes in blood of the rabbits following allogeneic whole-blood transfusion ($x \pm SD$, $n = 5$): ordinate indicates the share of monocytes (%); different letters indicate samplings that significantly differ one from another according to the Tukey test with the Bonferroni correction

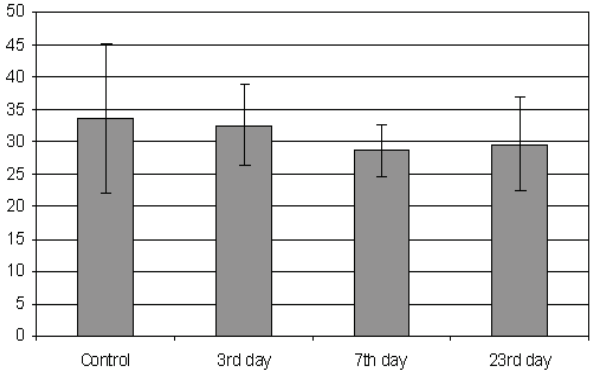

Fig. 4. Dynamics of content of granulocytes in blood of the rabbits following allogeneic-whole-blood transfusion ($x \pm SD$, $n = 5$): ordinate indicates the share of granulocytes (%); no significant differences ($P < 0.05$) between the groups were found according to the Tukey test

Percentage of O-lymphocytes in the recipient rabbits (Table 2) after whole-blood transfusion decreased 3.1-fold and by 25.3%, by the 3rd and 7th days of the experiment, respectively, compared with the initial condition. On the 23rd day of the experiment, this parameter reached the initial level.

Table 2
Dynamics of changes in the ratio (%) of various types of lymphocytes in blood of the rabbits following allogeneic transfusion of whole blood ($x \pm SD$, $n = 5$)

Cells	Initial condition	3rd day	7th day	23rd day
T-lymphocytes	52.9 ± 2.4^{a}	71.6 ± 4.9^{b}	57.6 ± 9.2^{a}	41.7 ± 1.9^{ac}
B- lymphocytes	19.0 ± 2.5^{a}	19.4 ± 1.8^{a}	21.4 ± 2.1^{a}	24.5 ± 1.7^{a}
O- lymphocytes	28.1 ± 1.3^{a}	9.0 ± 1.0^{b}	21.4 ± 1.3^{c}	33.8 ± 1.3^{a}

Note: see Table 1.

Number of T-lymphocytes (Fig. 5) in the experimental animals increased by 92.3%, 2.2 times and 28.2% on days 3, 7, and 23 of the experiment, respectively, compared with the initial number.

Compared with the initial number, B-lymphocytes (Fig. 6) in the experimental animals increased by 2.3 and 2.1 times on the 7th and 23rd days of the experiment, respectively. Therefore, after allogeneic blood transfusion, the number of B-lymphocytes in the recipient animals had been increasing throughout the experiment, indicating activation of specific link of immunity. Number of O-lymphocytes (Fig. 7) in the experimental animals decreased compared with the initial number by 2.2 times on the 3rd day of the experiment and increased by 56.6% and 2.0 times on the 7th and 23rd days, respectively. The increase in O-lymphocytes on the 7th and 23rd days of the experiment clearly indicates the activation of the immune response not only by specific link of immunity but by non-specific as well.

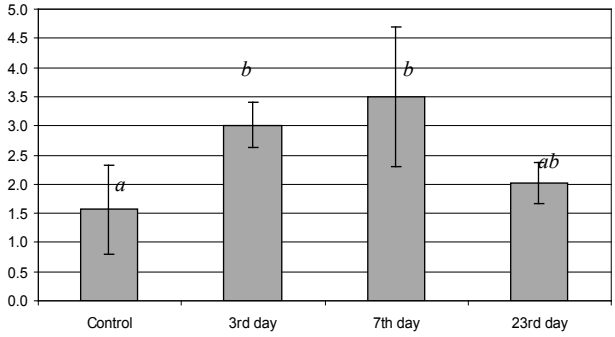

Fig. 5. Changes in the number of T-lymphocytes in the rabbits after allogeneic transfusion of whole blood (x ± SD, n = 5): ordinate indicates the number of T-lymphocytes (10^9/L); different letters indicate samplings that are significantly different between each other according to the Tukey test with the Bonferroni correction

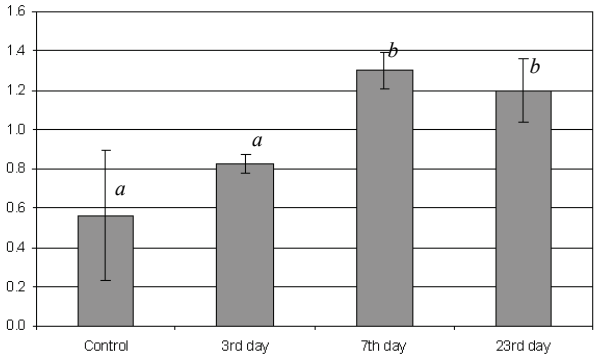

Fig. 6. Dynamics of the number of B-lymphocytes in blood of the rabbits after allogeneic transfusion of whole blood (x ± SD, n = 5): ordinate indicates the number of B-lymphocytes (10^9/L); different numbers indicate samplings that are statistically different one from another according to the Tukey test with the Bonferroni Correction

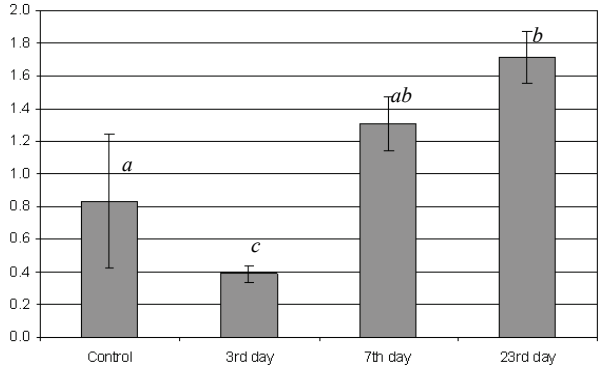

Fig. 7. Dynamics of the number of O-lymphocytes in blood of the rabbits after allogeneic transfusion of whole blood (x ± SD, n = 5): ordinate indicates the number of O-lymphocytes (10^9/L); different letters indicate the samplings that are significantly different from each other according to the Tukey test with the Bonferroni Correction

Discussion

Transfusion of blood and blood components has been extremely relevant in veterinary medicine over the recent years. At the same time, after allogeneic blood transfusion to the recipient animals, there occurs an immune response (Maliuk et al., 2022). Active and mostly efficient transfusion of blood and its components in veterinary medicine is performed in case of various-genesis anemia (post-hemorrhagic, hemolytic, aplastic) in animals (Yagi et al., 2016; Yehorov et al., 2020). As is known, anemia in animals occurs quite often and requires immediate interference of veterinary specialists. Use of whole blood and blood components for treating anemia in animals draws the attention of practicing veterinary doctors. However, reaction of the immune system in recipient animals to transfusion is concerning (Callan et al., 2013; Suddock et al., 2019).

Errors in blood transfusion in veterinary clinics occur during practice of drawing, processing, storing, and transfusing blood. One of the complications associated with blood transfusion is immune reaction that varies by severity from light signs to potentially lethal reactions. Most often, a recipient animal has an immune response not only to transplanted erythrocytes but also products of cell life that formed during storage. While blood components are being stored, pro-inflammatory cytokines form, which can lead to acute immune reactions in animals receiving a transfusion. Concentration of pro-inflammatory cytokines depends on duration of blood storage. Also, immune reactions in recipient animals after whole-blood and blood-component transfusion occur because of neglect by veterinary-clinic personnel regarding identification of blood group and performing a crossmatching (major and minor) (Poh, 2018).

Analysis of the results we obtained suggest that whole-blood transfusion to the recipient rabbits can be positive because allogeneic transplantation of blood to the recipient animals caused no clinical picture of immune response: rectal temperature, pulse rate, and respiratory rate remained within the physiological parameters, and also we observed no TRALI and DIC syndrome. Our results are consistent with the study by Brand (2002).

It has to be noted that after transfusion of whole blood to the recipient animals, we saw leukocytosis in the rabbits on the 3rd, 7th, and 23rd days of the experiment. Our results correlate with the studies by Claus et al. (2022). We also observed that the number of granulocytes in the blood of the experimental animals was higher than the initial amount throughout the study. Our studies are coherent with the studies by a number of authors (Izbicki et al., 2004; McMichael et al., 2010; Callan et al., 2013).

After the transfusion of whole blood, percentages of T, B, and O-lymphocytes in the recipient rabbits also significantly increased compared with the initial number, which is consistent with the experimental data from a number of authors (Izbicki et al., 2004; McMichael et al., 2010; Callan et al., 2013). Therefore, the studies we performed regarding allogeneic transplantation of whole blood suggest that transfusion of whole blood causes a cascade of complex immunological reaction in the recipient animals. We should note that after allogeneic transfusion of whole blood to the recipient rabbits, we observed no pronounced post-transfusion clinical symptoms (tachycardia, tachypnea, edema of the eyelids, auricles, body-temperature rise). Results of those studies are consistent with the data from a number of authors (Izbicki et al., 2004; McMichael et al., 2010).

Conclusion

We determined that the recipient animals underwent post-transfusion leukocytosis. We should note that increase in the number of leukocytes in the experimental animals was within the physiological parameters. According to the results of the study, the amount of lymphocytes in the recipient rabbits increased after whole-blood transfusion by 41.2%, 2.1 times, and 65.5% on the 3rd, 7th, and 23rd days of the experiment, respectively, compared with the initial amount. Number of granulocytes in the blood of the experimental animals increased compared with the initial condition by 48.8%, 51.8%, and 26.5% on the 3rd, 7th, and 23th days of the experiment, respectively. Percentage of T-lymphocytes in the recipient rabbits after transfusion of blood increased by 35.3 % and 8.9% on the 3rd and 7th days of the experimental studies, respectively. We should also note a significant 21.2% decrease in the percentage of T-lymphocytes on the 23rd day. Percentage of B-lymphocytes in the recipient rabbits after transfusion of allogeneic blood increased by 2.1%, 12.6%, and 28.9% on days 3, 7, and 23, respectively, indicating the activation of specific link of immunity. Following the transfusion of whole blood, percentage of O-lymphocytes in the recipient rabbits dropped 3.1 times and by 25.3% on days 3 and 7 of the experiment, respectively. On the 23rd day of the experiment, this parameter increased by 20.3%. The perspectives for further research are study of allogeneic transfusion of blood components and parameters of specific and non-specific links of immunity in the recipient animals.

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The authors declare no conflict of interest.

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