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Acute Hemolytic Reaction After Transfusion of Erythrocyte-containing Blood Components: Causes, Prevention, Clinical Cases

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SUMMARY The article concerns the problem of studying the causes of the development of hemolytic reactions after transfusion of erythrocyte-containing blood components. The ways of preventing hemolysis as a result of blood transfusions are considered. Clinical cases are described.

Keywords: hemolysis, immune development mechanism, non-immune mechanism for the development of an acute hemolytic reaction

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HR - hemolytic reactions
MCHD - Moscow City Health Department
RRT - renal replacement therapy
LDG - lactate dehydrogenase
MO - medical organization
MPS - Membrane Plasma Separation
GUA - general urine analysis
AHR - acute hemolytic reaction
PTC - post-transfusion complication
PTR - post-transfusion reaction
FFP - fresh frozen plasma
FMBA - Federal Medical and Biological Agency
TOQATC - Center for Organization and Quality Assurance of Transfusiological Care
ECBC - erythrocyte-containing blood components

Transfusion of blood components is an invasive manipulation with risks of developing complications after it. Despite the fact that doctors of clinical departments recently keep to a restrictive strategy by reducing the number of unreasonable transfusions, there are groups of patients who cannot go without blood transfusions: with massive blood loss during major surgical interventions, severe concomitant injury and obstetric bleedings, and also a transfusion-dependent contingent in the hematological practice. Post-transfusion complications (PTC) can have consequences from pronounced patient discomfort to large financial losses due to an increase in the duration of inpatient treatment and legal claims. Despite the fact that the risk of transfusion-associated death is quite low: 1 case per 117,000 transfusions [1], at the moment there is a vital need for sufficient awareness of clinicians about the causes, clinical picture and methods of PTS treatment.

The frequency of transfusion-associated risks of post-transfusion reactions (PTR) depends on various reasons and, mainly, on the degree of development of the safety system of the transfusive aid - the hemovigilance system, which is defined as organized procedures for monitoring reactions and complications in donors and recipients [2]. The incidence of post-transfusion complications (PTC) varies widely, despite the international attempts to standardize and unify approaches to registration [3].

E. Vamvakas et al. [4] based on the data of the hemo-safety systems of several countries calculated the probability of a severe acute hemolytic reaction (AHR) and displayed it in the form of a pyramid from the most frequent event to the rare (figure). At the bottom are the most common cases, classified as "almost errors", which were detected in time and did not lead to an incorrectly transfused blood component. In the middle, there are less frequent, but more severe complications, AB0-incompatible transfusions with a frequency of 1 in 40,000 transfusions of erythrocyte-containing blood components (ECBC). At the top of the pyramid is the probability of a fatal outcome from AHR, which is quite rare and amounts to 1 case per 1.8 million doses of ECBC infused [4].

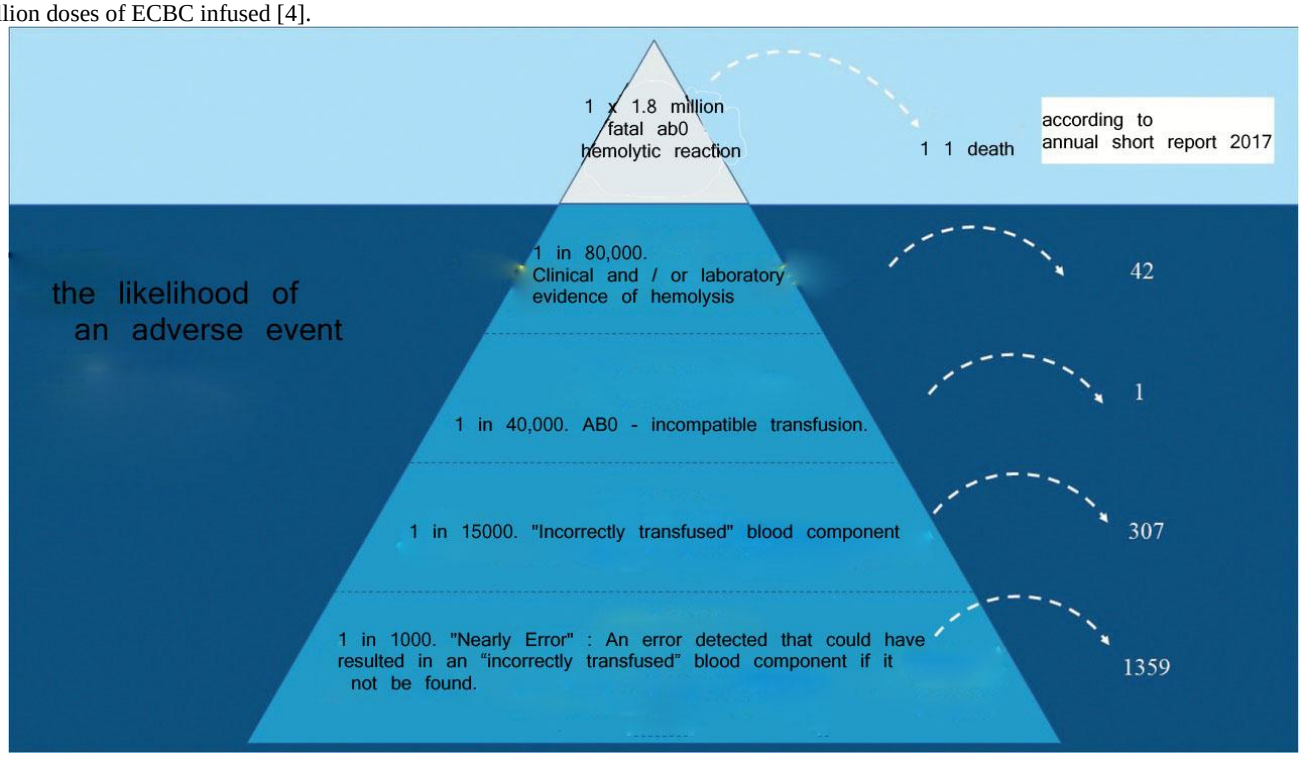

Figure. The calculated likelihood of an acute hemolytic reaction due to AB0 incompatibility: from "almost error" to fatal hemolysis (according to E. Vamvakas et al., [4]) compared with the actual number of cases according to the UK transfusion safety report — "Serious hazards of transfusion" (SHOT) for 2017

In 2017, there were 1,359 reports of "near errors" and 307 of incorrectly transfused blood components, according to the UK's annual reports on the safety of transfusions - "Serious hazards of transfusion" (SHOT). The analysis of these data made it possible to develop and implement preventive measures, which in turn led to a progressive decrease in the number of cases of AB0-incompatibility from 1996 to 2017 from 36 cases to 1, respectively [5].

The exact statistics for the Russian Federation depends on the number of notifications about reactions and / or complications that have occurred in recipients in connection with the transfusion of blood components, submitted to the Federal Medical and Biological Agency (FMBA) by medical organizations (MO) after each detected case. According to the FMBA, in 2017–2018. only 9 and 6 cases of hemolytic PTC were registered, respectively. Of these, 6 - in 2017 and 5 - in 2018 were due to the incompatibility of the donor's and recipient's blood according to the AB0 antigen system due to errors in determining the group affiliation of the recipient's blood in medical organizations, and 3 cases were fatal. Also, in 3 cases in 2017, the cause of hemolysis was the presence of undiagnosed antibodies to erythrocyte antigens of the Duffy (anti-Fya) Kidd (anti-Jka) and Rh (anti-E) systems. One case of hemolytic PTC in 2018 could be associated with the features of the underlying disease - hemolytic anemia - or the presence of anti-erythrocyte antibodies of the unknown specificity [3].

Hemolysis is a rupture of the erythrocyte membrane with the outflow of its contents, which can be acute and delayed. AHR occurs within 24 hours after transfusion, while a delayed one may appear after 14 days or more [6]. By localization, hemolysis is divided into intravascular (within the volume of circulating blood) and extravascular (in the reticuloendothelial system); and according to the mechanism of development - into immune and non-immune. AHR is almost always intravascular hemolysis caused by immune (incompatibility of blood groups according to AB0, or other antigenic systems of Duffy, Kell, Rhesus) or non-immune mechanism (thermal, osmotic and mechanical trauma of erythrocytes in the blood component) [7].

Classical AHR includes a triad of symptoms: fever, back pain, and red or brown urine. Other symptoms of acute hemolysis may also be present: chills, hypotension, renal failure, back pain, or signs of disseminated blood clotting. In practice, when analyzing a large number of clinical cases, the

most common is 80%, and often the only symptom that appears when erythrocytes are destroyed is fever or chills. Renal failure develops only in 36% of cases of acute hemolysis [8]. The time of onset of symptoms can vary from a few minutes from the start of the transfusion to 24 hours after it.

Laboratory signs of hemolysis: the appearance of altered forms of erythrocytes (spherocytes), the presence of free hemoglobin in the blood plasma and its red color, hemoglobinuria; decreased blood levels of fibrinogen and haptoglobin and, conversely, increased blood levels of lactate dehydrogenase and bilirubin [9].

A delayed hemolytic response (HR) is due to an anamnestic response of the immune system to allogeneic antigens from previous transfusions or after pregnancy. The breakdown of erythrocytes is mainly extravascular and clinically less dramatic. Symptoms of jaundice and subfebrile fever are usually present. Laboratory changes can be identical to acute HR and in the study of blood are as follows: anemia, high levels of lactate dehydrogenase (LDG) and bilirubin and low levels of haptoglobin, leukocytosis, the presence of anti-erythrocyte antibodies in the blood and a positive Coombs test [10].

Non-immune reactions are caused by the temperature exposure, osmolarity and mechanical trauma of the erythrocyte membrane in vitro, if the dose of a blood component was adversely affected during transport, storage, or was improperly handled during administration. Thermal effects are subdivided into the heat excess and freezing. Violation of the "cold chain" of a blood component, that is, significant fluctuations in the storage temperature, is possible when a blood component is in household refrigeration equipment and is not transported in isothermal containers, with repeated movements within a medical organization from department to department. ECBC are stored at + 4 ° C, platelet concentrate - at + 22 ° C under constant stirring, fresh frozen plasma (FFP) - at -35 ° C. Overheating of erythrocytes in a blood component is possible when using faulty equipment or heating devices that are not intended for these purposes (RP2-01- "BFA" defroster, microwave oven) and hot water baths left unattended (container under running hot water). Heating a blood component above + 38 ° C can lead to denaturation of proteins, partial changes in their structure and destruction of erythrocytes [11, 12]. Freezing is possible with careless transportation of ECBC with FFP in one isothermal container or inadequate deglycerolization during thawing of cryopreserved erythrocytes [8, 12]. Destruction of erythrocytes is possible with bacterial contamination of a blood component [12]. Osmotic damage can develop when drugs or hypotonic solutions are added directly to the ECBC, for example, 5% glucose solution [13]. Mechanical hemolysis occurs when using: roller pumps in a heart-lung machine, pressure infusion pumps, pressure cuffs or when transfusing through a needle with a small channel diameter [10, 12].

What to do if there is a suspicion of the development of hemolysis? First, you need to stop the transfusion, close the transfusion system and disconnect it from the patient. Then the transfusion system, in conjunction with the residual blood component and the vial used for the compatibility tests, must be stored in medical refrigeration equipment for 48 hours. You also need to inform the responsible transfusion doctor about the suspicion of a post-transfusion reaction. Review all labels: blood component, patient's blood group blank, labeling of the blood sample tube. Determine again: the recipient's blood group and anti-erythrocyte antibodies. Hemolysis can be visually determined as follows: centrifuge the tube with the recipient's blood and assess the degree of the supernatant fluid coloration. The more intense the red color, the stronger the degree of hemolysis.

Can hemolysis be prevented? Not always, although in most cases HR can be completely eliminated. Hemolysis of an immune nature in most cases is associated with incorrect identification [14], and therefore the best way of prevention is to prevent or detect errors at each stage of blood transfusion:

- recipient identification error: instruct the nurse to take a blood sample from the man "right at the window" in the ward, and not give the full name, first name and patronymic of the patient, or the use of the widely used method of numbering beds in intensive care units to depersonalize patients and simplify of the staff work ;
- an error in the identification of a blood sample: an unsigned test tube, incomplete surname, name and patronymic of the patient, absence of a medical history number and department name, presence of patients with the same surname and different initials;
- an error in the compatibility of a blood component: a test for compatibility or a control test of the recipient's blood group using the AB0 system was not performed or they were performed technically incorrectly, while using expired or reagents stored in uncontrolled temperature conditions.

According to M. Delaney et al., the frequency of errors due to incorrect labeling of blood samples was reduced by applying the “zero tolerance” method, that is, refusing to accept a test tube without complete identification of the patient (last name, first name and patronymic, date of birth, unique identification number) [15].

Serological identification of anti-erythrocyte antibodies is a crucial link in the prevention of all immune hemolytic reactions [6, 10]. When detecting alloimmune antibodies, it is necessary to carry out an individual selection of ECBC in the laboratory.

Hemolysis of non-immune etiology in most cases can be prevented by observing the "cold chain" of the blood component: at the stage of storage and transportation, pre-transfusion preparation and manipulation with traceability in all registration forms.

As examples, we cite the results of investigations of the AHR that took place in the institutions of the Moscow Department of Health (MDH) (the names of the MO were not disclosed for ethical reasons).

Investigation 1

A case of non-immune hemolysis after transfusion of erythrocyte suspension. In the MO, a patient with a diagnosis of "portal hypertension (condition after autovenous mesoportal shunting with an autovenous insert)" underwent surgery for shunt thrombosis - relaparotomy, spleno-renal anastomosis, viscerolysis, suturing of perforation of the small and large intestines. The postoperative period was complicated: intestinal fistulas formed, which led to the multiple repeated surgical interventions (relaparotomy) against the background of progressive multiple organ failure and sepsis. The patient's condition remained extremely serious: he was on prolonged artificial ventilation, and vasopressor support of hemodynamics was carried out. It was decided to compensate for severe anemia by transfusion of a single-group erythrocyte suspension (tests for individual compatibility were carried out). After 1 hour 15 minutes from the beginning of the transfusion, the appearance of red-brown urine was noted. At the same time, in the general analysis of urine (GUA), altered erythrocytes were found - 12-15 in the field of view, the reaction to blood - 3+, which indicates intravascular hemolysis and the passage of already destroyed erythrocytes through the kidneys. Forced diuresis was performed to remove free hemoglobin from the bloodstream. After 1 hour 45 minutes from the start of transfusion, the procedure of continuous membrane plasma separation (MPS) was started, while the color of the plasma was red-yellow, which was due to hemolysis. At the 30th minute, cardiac depression was noted, the MPS procedure was discontinued, and resuscitation measures were taken. The patient died 8 hours after the start of the transfusion.

Results of Investigation 1 carried out by the Center for Organization and Quality Assurance of Transfusiological Care (COQATC): all transfusions of blood components in the patient were clinically justified. They were carried out with the selection according to the phenotype of the Rh factor and performing tests for individual compatibility using the indirect Coombs test in the laboratory of the MO, in other words, they

were immunologically compatible with the patient. However, the movement of a blood component was carried out in the MO with violation of the conditions of the "cold chain" of storage. An erythrocyte suspension was ordered and received to provide a planned surgical intervention for another patient one day before the transfusion, and 4 hours elapsed from the moment it was removed from the medical refrigeration equipment in the blood transfusion room to being placed in a household refrigerator in the surgical department (in uncontrolled temperature conditions). The next morning, the ECBC were removed from the household refrigerator of the surgical department and transferred to the intensive care unit, where they were kept for about 6 hours in uncontrolled temperature conditions (at room temperature) until they were placed in the RP2-01-BFA defroster, where the ECBC were warmed up in plasma defrosting mode. It should be noted that "The automatic defrosting device of fresh frozen plasma with light and sound signaling RP2-01-" BFA "is not intended for heating the ESCC, but only for defrosting the FFP and heating the solutions. Laboratory data of erythrocyte suspension residues (State Budgetary Health Care Institution (GBUZ) "Blood transfusion station MCHD"): there is an excess of the reference value of the hemolysis level - up to 9.96% (at a rate of less than 0.8%); in this case, the recipient's blood and donor erythrocytes are immunologically compatible.

Based on the routing of the blood component and laboratory data, it can be concluded that the hemolysis of erythrocyte suspension is non-immune, that is, the breakdown of red blood cells under the influence of the temperature factor during its storage under unacceptable conditions, as well as the likely aggravation of the degree of hemolysis when the blood component is heated in equipment not intended for this. Conclusion: gross violations in the observance of traceability and the cold chain of a blood component in the territory of the MO were found .The erythrocyte suspension container was in improper and uncontrolled conditions of household refrigeration equipment. The stay duration of the container in uncontrolled conditions was more than 24 hours, while the storage of ECBC in uncontrolled temperature conditions for more than 2 hours is unacceptable and can lead to hemolysis of erythrocytes.

Investigation 2

Immune hemolysis after transfusion of ECBC incompatible for antigens of the ABo system. A young patient with moderate iron deficiency anemia underwent transfusions of three doses of ECBC due to signs of a deficiency in the oxygen transport function of the blood. Upon admission to the MO, the blood group was identified as B (III), Rh-positive. On the 3rd day from the beginning of hospitalization, two transfusions of erythrocyte suspension of group B (III), Rh-positive, were carried out in succession. According to the transfusion protocols, a control study of the recipient's blood group and samples for individual compatibility were performed and marked as "compatible". According to the observation diaries, the patient underwent the procedure without complications. On the temperature sheet after transfusion, fever up to 37.8 ° C was noted. The hemoglobin level on the next day after transfusion is 83 g / l. In the GUA on the next day after transfusion, an increase in the level of urobilinoids up to 16 mmol / L is noted. A biochemical blood test was performed once upon admission: glucose content - 5.3 mmol / l; total protein - 70 g / l; creatinine - 131.8 μmol / l; iron - 3.9 μmol / l; total bilirubin - 13.7 μmol / l; sodium - 139 mmol / l; potassium - 4.4 mmol / l; chlorine - 104 mmol / l; creatinine phosphokinase - 158 U / l; aspartate aminotransferase - no reagent; alanine aminotransferase - 42 U / l; LDG - no reagent. On the 7th day after the first transfusion, the patient remained weak at a hemoglobin level of 86 g / l, and therefore the third transfusion of group B (III) ESCC, Rh-positive, was carried out. After transfusion, a fever of up to 38.4 ° C was registered. GUA after the third transfusion (before discharge from the hospital): urine color is orange, transparency is very turbid, relative density is 1.023, pH is 5.5, protein is 0.630 g / l, glucose is 5.5 mmol / l, ketone bodies are 0.5 mmol / L, bilirubin - 50 μmol / L, blood reaction - 300 er / μL, flat epithelium - a lot, leukocytes - 25–38 in the field of view, erythrocytes - 50–60 in the field of view, bacteria - a lot . A biochemical blood test before discharge was not performed for technical reasons. The patient was discharged from the hospital with improvements in outpatient follow-up care. 2 days after discharge from the hospital, he was again hospitalized, but in another MO MCHD with a diagnosis: post-injection abscess of the upper third of the right forearm. The blood group is already A (II), Rh is positive. The patient underwent a clinical diagnostic search due to a complaint of difficulty in urinating. In the biochemical analysis of blood: urea - 50.0 mmol / l; creatinine - 1801 μmol / l. On the 5th day of hospitalization, the patient was diagnosed with acute renal failure, while the severity of the condition required renal replacement therapy (RRT). Considering the absence of a hemodialysis department in the second MO, the patient was transferred to a medical institution, where he had previously received transfusions (upon repeated admission, the blood group A (II) was determined, Rh - positive). After successful restoration of renal function (as a result of a series of RRT procedures), the patient was discharged from the hospital with improvement.

Results of investigation 2: the patient underwent three blood transfusions of inogroup erythrocyte suspension during the initial hospitalization, which caused the development of acute renal failure, which required RRT. At what stage of the pre-transfusion stage the error occurred, it was not possible to establish precisely. Probably, there was a combination of two reasons: at the stage of identification of the patient's blood sample in combination with the failure to perform the control determination of the recipient's blood group according to the ABo system before transfusion. If all compatibility tests were carried out in accordance with the requirements of regulatory documents, an error in determining the patient's blood group would be detected.

DISCUSSION

The described cases demonstrate a direct connection between the human factor and the development of severe post-transfusion complications. Detection of errors in patient identification or identification of a blood sample helps to prevent the development of AB0-incompatible transfusion and to transfer this event to the category of "almost error". It is necessary to raise the awareness of medical personnel about the importance of the human factor in the development of fatal complications during the transfusion of blood components. Discussion of the described errors should be conducted not to punish the guilty employees, but to prevent their occurrence in the future.

In the issue of teaching doctors the skills of transfusiology, an informal and practical approach with the development of an algorithm for combining blood components manually is especially important, and not just a formal receipt of a certificate of completion of a thematic improvement on this topic. It is also unacceptable to replace medical manipulations with nurses or perform compatibility tests by nurses under the supervision of a doctor. According to the current regulations, a doctor must perform all manipulations with blood components.

The strategy of the PTC suppressing is a chain that closes the "vicious circle" and, in the long term, leads to more tragedies. It is necessary to abandon the policy of non-disclosure of real cases of reactions after transfusion of blood components in favor of compiling reliable reporting, on the basis of which the development of effective preventive measures and analysis of their effectiveness will be carried out. It would like to note that if the FMBA is not notified about the PTC, which resulted in an unfavorable outcome, and the patient's relatives turn to the court, then this action will be interpreted as a violation of the order of the Ministry of Health of the Russian Federation No. 348n dated June 3, 2013, and the consequences for the

MO and their leaders will be much harsher. The identification and submission of a report about PTR indicates a high level of organization of the transfusion service in the MO, and not about the low quality of the provided medical care .

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