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Clinical Significance of Blood Transfusions in Animals: A Review

Ramakant[1], T.K. Sarkar[2], Amit Kumar Verma[2], Vipul Thakur[2], Pankaj Kumar Maurya[1], Sachin Gautam[1], V.K. Varun[2], Desh Deepak[2]

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ABSTRACT

Blood transfusion is a simple form of transplantation. Blood transfusion therapy is carryout since long back to improve the oxygen carrying capacity and treat the clinical sign of anaemia. The clinical use of blood transfusion in veterinary practice has recently increased as an emergency life-saving modality because of easy access to blood products along the blood donors or stored blood substitutes. Animal should be screened properly for blood typing and cross matching before the blood transfusion. The quantity of blood has to be transfused based on the clinical status of the recipient animals. Administration of blood products carries an inherent risk of transmission of disease carried by the donor. A transfusion can be rejected and cause profound, potentially life- threatening complications in the recipient. The developments in the techniques for separating different components of the blood have made considerable advancements in demand based treatment in veterinary medicine.

Key words: Animal, Blood, Donors, Life saving, Recipient, Transfusion.

Transfusion is the intravenous transfusion of blood or its components that have important role in life-saving and advanced treatment of critically ill patients. It has become more common in veterinary medicine (Khan and Sharma, 2021). Blood transfusion has been used as a life-saving therapeutic procedure in veterinary medicine for a long time (Kumar, 2017). Blood transfusion is more common in small animal treatment (Davidow, 2013). Blood transfusion therapy can be implemented in critically ill animals with life-threatening anaemia, haemolysis, neonatal isoerythrolysis, immune-mediated diseases, severe non-regenerative conditions, trauma, injury and burn (Tocci, 2010). The blood transfusion depends on several hematological parameters like hemoglobin, hematocrit and total erythrocyte count of the recipient, the type of anemia, blood group, animal size and blood products to be administered (Lanevschi and Wardrop, 2001). First blood transfusion has no untoward effect in cattle. But second or third transfusions may cause anaphylactic shock in animals (Chakrabarti, 2016). Blood transfusion starts with a blood type and it is important to perform blood typing before the start of blood transfusion to avoid incompatibility problems (Kristin, 2009; Esteves *et al*., 2011). Blood transfusion efficacy is assessed by measurement of oxygen tension and saturation in venous blood and blood lactate level (Radostits *et al*., 2007).

Blood transfusion history

The discovery of the theory of blood circulation by British Physician William Harvey in 1628, made possible for the advancement of veterinary medicine (Choudhary *et al*., 2017). The first recorded successful blood transfusion in a dog from another dog saved its life by Physician Richard Lower in 1665. Jean-Baptiste Denis from France and Richard Lower and Edmund King from England reported a successful blood transfusion from sheep to humans; after that, it was prohibited due to reactions. After that, blood transfusion among other species of lamb, dog and human was done by Lower and Denis and given the concept of "like transfuses like" (Choudhary *et al*., 2017). In the early 20th century, there was the discovery of blood anticoagulants, the description of human blood groups and the developments of compatibility assay (Bird, 1971). Karl Landsteiner, an Austrian Physician, discovered the blood groups (A, B and C) in 1900 and emphasized the importance of cross matching before transfusion. George Crile (1907) first time performed a blood transfusion from artery to vein in dogs. Citrate was used as an anticoagulant first time and transfused safely in dogs (Hustin, 1914). Modern veterinary transfusions medicine started dating back to the 1950s, after the availability of appropriate equipments to make blood transfusions practical (Sharma *et al*., 2009). As the advancement in techniques and equipment, transfusion has become more popular in veterinary medicine (Cotter, 1991; Davidow, 2013). Worldwide Donor Day is celebrated every

[1]College of Veterinary Science and Animal Husbandry, Acharya Narendra Deva University of Agriculture and Technology, Kumarganj, Ayodhya-224 229, Uttar Pradesh, India.
[2]College of Veterinary and Animal Sciences, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut-250 110, Uttar Pradesh, India.

Corresponding Author: Ramakant, College of Veterinary Science and Animal Husbandry, Acharya Narendra Deva University of Agriculture and Technology, Kumarganj, Ayodhya-224 229, Uttar Pradesh, India. Email: ramakant.dr2@gmail.com

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year on the 14th June by the World Health Organization (WHO, 2021).

Indications of blood transfusion

Acute hemolysis, haemorrhage, acute or chronic anaemia and hemostatic disorders often require transfusion of whole blood, red blood cells, platelets or plasma (Susan, 2020). Blood transfusion is also indicated in several clinical conditions as acute blood loss, hemophilia -A, coagulopathies, burn anaemic conditions, haemo protozoan diseases, thrombocytopenia and hypoproteinemia (Bhikane and Kawitkar, 2002).

Cattle

Blood transfusion is indicated in pulmonary haemorrhage, abomasal ulcers, enzootic hematuria, rupture of the middle uterine artery in prolapse, heavy infestation of hookworm, theileriosis, anaplasmosis and babesiosis in cattle (Shatanu *et al*., 2019).

Horse

Whole blood transfusion is required in horses if packed cell volume (PCV) is less than 12%, haemoglobin concentration less than 8 g/dl, traumatic injury, haemophilia or a heavy infestation of Strongylus (Shatanu *et al*., 2019).

Dogs and cats

Blood transfusion is needed in dogs when packed cell volume (PCV) is less than 15% or haemoglobin is less than 5 g/dl. There is an urgent need for blood transfusion in cats if PCV is below 12% and haemoglobin below 4 g/dl (Perman and Schall, 1983). Transfusion is indicated in anaemia of various reasons, due to infections or acute/chronic haemorrhage, bleeding disorders such as thrombocytopenia or coagulopathies, poisoning like warfarin and hypoproteinemia due to parasitic infestation (Bhikane and Kawitkar, 2002).

Blood groups

The name of a blood group is based on the specific antigens present on the surface of erythrocytes. These antigens play an important role in inducing immune-mediated reactions and can cause complications while transfusing blood from different blood groups (Kumar, 2017). Among the domestic species, cattle have the most complex and cats have simplest blood groups. There are 12 blood groups in cattle, 7 in sheep, donkey, horse and dog, 5 in goat and 3 in cat.

Blood groups in cattle

The most recognized blood groups in cattle are A, B, C, F, J, L, M, R, S, T and Z. Out of these groups, B and J are the most clinically relevant. Group B has more than 60 antigens, making closely matched blood transfusion difficult. The J antigen is not a true erythrocytes antigen. It is a lipid found in cattle plasma and has anti-J antibodies with a small amount of adsorbed J antigen on erythrocytes. Negative J blood group may show transfusion reactions with transfusion of J- positive blood group (Blackmer and Parish, 2002).

Blood groups in sheep

Seven blood groups are identified in sheep *viz*. A, B, C, D, M, R, X. Group B has more than 52 factors present on the erythrocytes (Blackmer and Parish, 2002). The R system in sheep has similarity with the J system in cattle and group B in sheep is also similar to group B in cattle. The M-L blood group in sheep is associated with the active potassium transport in reticulocytes (Tucker and Ellory, 1971).

Blood groups in goat

There are five blood groups *viz*. A, B, C, M and J are identified in goats which is similar in sheep (Blackmer and Parish, 2002). Many of the similar reagents are used for blood typing of sheep and goats.

Blood groups in horses

The most recognized blood groups in horses are A, C, D, K, P, Q and U, with more than 30 antigens (Farcada *et al*., 2007). Due to the various possible antigenic combinations, universal donor horse is not possible. Before blood transfusion, cross matching must be performed to minimize transfusion reactions (Hurcombe *et al*., 2007). In horses, blood groups vary with breeds. Thoroughbreds and Arabian breeds have a high prevalence of antigens Aa or Qa whereas standard breds lack antigen Qa. Aa and Qa alloantigens are extremely immunogenic hemolysins (Wilkins, 2004). Donkey factor is the unique donkey and mule erythrocyte antigen and is responsible for neonatal isoerythrolysis in mule but it is not found in the horse (Mc Clure *et al*., 1994).

Blood groups in dogs

The blood group system in dogs includes DEA (Dog Erythrocytes Antigens) 1.1, DEA 1.2, DEA 3, DEA 4, DEA 5 and DEA 7. Blood group DEA 1.1 and 1.2 are the most important blood groups and are found in 60% dogs (Hohenhaus, 2004). Donors negative for DEA 1.1, 1.2 and 7 are universal blood donors (Sharma *et al*., 2009). Blood group DEA 1.3 is found in German shepherd dogs in Australia (Symons and Bell, 1991). Blood group DEA 4 is high frequency and can cause hemolytic transfusion reactions in DEA 4-negative dogs previously sensitized by DEA 4-positive blood transfusions (Melzer *et al*., 2003). Blood groups DEA 3, 5 and 7 can cause delayed transfusion reactions in dogs lacking these antigens but are previously sensitized to these antigens (Wardrop, 2008).

Blood groups in cats

Blood group system in cats includes A, B and AB. Giger (2009) reported that 95% of the American cats having Blood group A. Most of the Indians and 30 % of cats in UK belong to blood group B (Farcada *et al*., 2007). AB blood group is extremely rare and found in DSH/DLH cats. Blood group AB is also found in breeds in which group B is present *e.g*. Abyssinian, British shorthair, Birman, Norwegian forest, Persian Somali and Scottish fold (Wenk *et al*., 1996). A novel Mik antigen is also found in DSH cats (Weinstein *et al*., 2007). The anti-A, anti-B and anti-Mik are naturally occurring

alloantibodies present in cats (Weinstein *et al*., 2007). Less transfusion reactions in cats due to blood group A have weak hemagglutinins and hemolysins against type B erythrocytes. Due to the transfer of anti-A alloantibodies from colostrums, neonatal isoerythrolysis occurs in A or AB blood group kittens of B blood group queen (Giger, 1992). Blood transfusions among Mik positive and Mik negative cats can cause acute post-transfusion hemolysis (Weinstein *et al*., 2007). Cats have naturally occurring antibodies in plasma called allo-antibodies or iso-antibodies against the other blood group (Sharma *et al*., 2009).

Principles of cross matching blood

Major and minor cross matching tests are done for agglutinating or hemolytic reactions between donor and recipient. Agglutinating tests are sufficient for dogs and cats whereas in horses agglutinating and hemolytic tests are required because of the presence of agglutinating and hemolytic antibodies in equines (Jain, 1986). Cattle, sheep and goats require hemolytic antibodies and complement tests (Divers, 2005).

The major cross match evaluates for the presence or absence of antibodies, whether naturally occurring or induced, in the recipient against donor erythrocyte antigens (Kumar, 2017). A major crossmatch should always be performed in animals with strong naturally occurring antibodies, as in cats or animals with induced antibodies from prior transfusion. Crossmatch should also be performed even if the same donor blood is given for repeated transfusion after several days (Kumar, 2017).

The minor crossmatch has same steps as in major crossmatch but evaluates for the presence or absence of detectable antibodies in donor plasma against recipient erythrocytes. Minor cross matching is of little significance because the volume of plasma donated is very small compared to the recipient and is diluted in the recipient, particularly when merely erythrocytes are transfused (Giger, 2000).

Hurcombe *et al.* (2007) reported that transfusion of packed erythrocytes might consist of adequate antibodies against recipient erythrocytes to induce unfavourable reactions in horses and dogs. For the crossmatch testing, ethylene diamine tetraacetic acid (EDTA) tube as well as clot tube from the recipient animals is preferred. Plasma should not be used in place of serum because this causes increased rouleaux formation and difficulty in the interpretation of agglutination in horses. When autoagglutination is present or when no compatible units are available, transfusing the least incompatible unit if necessity. Without crossmatch testing, even a small volume of blood is unsafe practice and never recommended (Giger, 2009).

The basic reason for cross matching is to decrease risk of sensitizing patients. Sometimes transfusions reactions can occur even after prior transfusions cross matching because cross matches do not evaluate white blood cells or platelets, which are the main source of many immediate transfusion reactions such as pyrexia and acute pulmonary hypersensitivity (Sharma *et al*., 2009).

Cross matching technique

Collect the blood from the donor in purple top EDTA tube and the recipient in red top tubes non EDTA tubes (Lanevschi and Wardrop, 2001). Centrifuge the blood to separate plasma or serum from the erythrocytes. Separate the serum and store it in a sterile tube. Remove plasma from the EDTA tube.

Wash the RBCs collected from EDTA tube. Place the RBCs in a separate tube filled with normal saline and centrifuge for 1 minute. Repeat the process 5 times, removing the supernatant every time. Resuspended the cells to make a 2% to 4% solution (0.2 mL of blood in 4.8 mL of saline gives a 4% solution).

Label the tubes to make the following mixtures as Major Crossmatch (2 drops patient serum with 1 drop donor RBC suspension), Minor crossmatch (1 drop patient RBC suspension with 2 drops donor serum) and Control (1 drop patient RBC suspension with 1 drop patient serum). Incubate the mixtures for 15 to 30 minutes at 37°C and then centrifuge for 15 seconds. Donor is unsuitable if hemolysis or hemagglutination is observed macroscopically and agglutination is observed microscopically.

Transfusion therapy

Blood transfusion should be practised after proper blood grouping and cross matching the donor's group with the recipient's to prevent transfusion reactions (Kumar, 2017). Blood grouping for canine DEA 1.1 and for feline types A and B is generally practiced in veterinary medicine (Stieger *et al*., 2005).

The primary indication for blood transfusion is the treatment of severe anaemia caused by haemorrhage, hemolysis, ineffective erythropoiesis, immune-mediated hemolytic anaemia, chronic inflammatory or infectious disease, or neoplasia; thumb rule for the therapeutic management of anaemia is blood transfusion in the cases of lower packed cell volume (PCV) up to 10-15% (Divers, 2005).

Animals with acute-onset anaemia, however, usually require transfusion before their PCV decreases to 15%, which contrasts with the situation in animals with chronic anaemia. For cases of thrombocytopenia, the generally accepted trigger for platelet transfusion is platelet counts of 10,000/µL (Ogg, 2003). Other indication of blood transfusion comprises hypovolemia, hypoproteinemia and deficiency of either primary or secondary clotting factors. Collected blood should be labeled with all the details. Record keeping is crucial in all blood collection and administration cases and record keeping is crucial in all blood collection and administration cases.

Selection of donor

All donors should be healthy young adults that have never been transfused. Donors must have undergone routine physical, haematological and clinical chemistry evaluation examinations. Proper clinical history of the expected donor

should be collected by carefully interviewing the owner to minimize the risk of disease transmission through blood.

Donor should be vaccinated, free from blood parasites and any infectious diseases. Donors should have normal baseline PCV and total protein concentrations before any donation. Blood should be collected aseptically, usually *via* jugular vein puncture. To avoid interference with platelet function, donors should not be sedated with acepromazine (Hackett *et al*., 2006).

For the selection of suitable donors, small animals like dogs and cats must be screened for lyme disease, brucellosis, rocky mountain spotted fever, ehrlichiosis, dirofilariasis, haemobartonellosis, feline leukaemia and feline immunodeficiency diseases. For the selection of suitable donors, screening of large animals for the diseases like trypanosomosis, Filariasis, theileriosis, anaplasmosis, babesiosis, paratuberculosis, tuberculosis, brucellosis, mucosal disease complex (bovine virus diarrhoea), contagious bovine pleuropneumonia, cattle plague (rinderpest), haemorrhagic septicaemia, vibriosis (campylobacteriosis), Trichomoniasis and Candidiasis is essential (Sharma *et al*., 2009).

Dogs

Fifteen ml of blood per kg body weight may be collected from the dog at interval of 6 weeks (Wardrop, 2008). Dogs with a history of previous blood transfusion should not be used as donors (Giger, 2009). Dogs negative for DEA 1.1 can be considered universal donors for first-time transfusion recipients (Giger, 2009). A dog is regarded as a universal donor when negative for DEA 1.1, 1.2, 3, 5, 7 and positive for DEA 4 (Hohenhaus, 2004).

Dogs to be used as donors should be heavier than 25-30 kg well nourished with no iron deficiency. Donors should be checked for faecal and heartworm disease to ensure good health. Donors should be test negative for transmissible infectious diseases like babesiosis, leishmaniasis brucellosis, ehrlichiosis, anaplasmosis, trypanosomiasis, bartonellosis and hemoplasmosis and neorickettsiosis (Wardrop *et al*., 2005).

Cats

10-12 mL of blood/kg body weight can be collected for transfusion from the donor. Healthy adult cats can donate 45-60 mL every 6 weeks (Roux *et al*., 2008). Donor cats should be negative for feline leukaemia virus (FeLV), feline immunodeficiency virus (FIV), cytauxzoonosis, anaplasmosis, bartonellosis, ehrlichiosis and neorickettsiosis and hemoplasmosis (Wardrop *et al*., 2005). Cat blood donor should be more than 5 Kg and PCV should be 35%.

Horses

Adult horses may donate about 6-8 litre of blood safely. Whole blood can be collected every 15-30 days and plasma collected every 7 days if the erythrocytes are returned to the donor (Byars and Divers, 1981). Donor horse should be healthy, free from equine infectious anemia and have normal hematocrit and plasma protein concentration.

Cattle and sheep

Cattle can donate 8-14 ml of blood per kg of body weight. First transfusions are generally of low risk, but ideally, a donor would be negative for the J antigen (Hackett *et al*., 2006). Cases of transmission of Prion diseases by blood transfusion have been reported in sheep; therefore, screening should be done for prion disease before blood transfusion in ruminants (Wardrop *et al*., 2005).

Anticoagulant used for storage

Citrate-phosphate-dextrose-adenine (CPDA-1) and Acid-citrate-dextrose (ACD) are commonly used for blood storage. CPDA-1 is considered better anticoagulant because it maintains higher levels of 2, 3-disphosphoglycerate (2, 3-DPG) and adenosine triphosphate (ATP) in collected blood. Blood can be preserved in CPDA-1 for about 35 days and in acid citrate dextrose (ACD) for 21 days (Wardrop, 2008).

Preservation of 7 ml of blood requires 1 ml of anticoagulant (CPDA-1/ACD). Refrigeration of blood should be done in blood collection plastic bags. Heparin is not used for blood collection due to it activates blood platelets. With the increase in storage time and temperature, the survivability and functions of erythrocytes decrease due to the consumption of glucose and the decrease of ATP and 2,3-DPG. Blood should be stored in a latex-free plastic bag or plastic syringe to preserve platelets (Mudge *et al*., 2004).

Transfusion volume

As per Mudge (2014) volume of transfusion was calculated for normovolemic anaemia and for hypovolemic anaemia after the restoration of circulating blood volume:

Transfusion volume (mL) =

$$\frac{\text{Body weight of recipient (Kg)} \times 80 \text{ ml/kg} \times \text{Desired recipient PCV - Actual recipient PCV}}{\text{Donor PCV}}$$

Where,

80 ml/Kg = Normal circulating blood volume.

The volume of the transfused blood, also depends on the size of the animal, degree of anemia, platelet defect or coagulopathy. Volume could be adjusted by two general rules (Chakrabarti, 2016).

General rule 1

2 ml whole blood/kg to raise PCV by 1% (assume anticoagulated donor PCV=40% for dog and 30% for cat).

General rule 2

$$\left[\begin{array}{c}\text{Anticoagulated blood}\\ \text{required for transfusion}\\ \text{from doner (in ml)}\end{array}\right] = \left[\begin{array}{c}\text{Recipient}\\ \text{volume}\\ \text{(in ml)}\end{array}\right] \times \frac{\text{Desired PCV - Actual PCV of recipient}}{\text{PCV of anticoagulated donor blood}}$$

Recipient volume: 80 ml/kg in dogs and 60 ml/kg in cats.

Transfusion rate-1-2 ml/minute for cat and pups 3-6 ml/minute for adult dogs (Chakrabarti, 2016).

Transfusion process

At the time of blood collection for the transfusion process a complete aseptic procedures should be adopted. Blood must be filtered by nonlatex filters (150-170 µm) either before or during transfusion. To prevent hypothermia, blood should be maintained at 37°C before transfusion. Blood is transfused intravenously through I/V sets having filters.

Circulatory overload and cardiac failure occur due to excessive and fast blood or plasma transfusion. Blood transfusion should be intravenously at a rate less than 10 ml/kg/hour with an initially slow rate and then increase gradually. Hypovolemic patients may be transfused at rate of 20 ml/kg/hour, while patients with renal, cardiac or hepatic ailment or recumbent calf may require only 1 ml/kg/hour (Wardrop, 2008).

Fast and excessive blood transfusion sometimes results in vomiting, salivation and muscle fasciculation. The blood transfusion volume is determined based on the recipient's body weight, total blood volume, hematocrit of recipient and donor and the purpose for that therapy is used. A simple guideline for small animals is that 10-15 ml/kg of packed erythrocytes or 20 ml/kg of whole blood increases the PCV by 10% if the donor has a PCV of about 40% (Lichtenberger, 2004). Half-life of erythrocytes transfused after matching is about 21 days in dogs. In cats, the half-life of erythrocytes transfused after matching is approximately 30-38 days (Mario and Smith, 1983). In horses and cattle, the survival time of compatible transfused erythrocytes is only 2-4 days (Kallfelz *et al*., 1978).

Fresh whole blood Transfusion is done in case of acute haemorrhage, anaemia, coagulation disorders and thrombocytopenia. Stored whole blood can be given in anaemia but will not provide platelets or coagulation factors. Packed Erythrocytes Transfusion is done in anaemic animals, having a high risk of volume overload. Fresh or stored frozen plasma can be given in congenital or acquired deficiencies of coagulation factors and hypoproteinemia and Platelet-rich plasma is provided in case of severe thrombocytopenia.

Post transfusion complications

Blood transfusion is not always safe and reactions can occur due to improper compatibility, poor storage or faulty administration. In general immediate reactions occur within 2-4 hours post transfusions and delayed reactions may take days to weeks or even months. In most cases, delayed reactions are not noticed because only a few cases undergo long-term post transfusions follow up. The most common reaction is immune mediated destructions of RBCs due to the development of the allo-antibody or due to other red cell antibodies (Sharma *et al*., 2009).

Sequelae of blood transfusion may be acute or delayed. Acute intravascular hemolysis resulting to hemoglobinemia and hemoglobinuria may occur due to incompatible blood transfusion. Other complications besides erythrocyte antigen-antibody reactions comprise pyrexia, circulatory overload, allergic reactions, citrate toxicosis, ammonia toxicosis and infections (Harrell *et al*., 1997).

Potentially one of the most important adverse effects of blood transfusions is transmission of infectious diseases. Due to this reason it is necessary to screen the potential donors. The refrigerated cold blood component can causes hypothermia in severely debilitated neonates and patients undergoing anaesthesia. Dilution of coagulation factors and thrombocytopenia may occur if an excessive amount is transfused. Allergic reactions may occur with the manifestation of facial oedema, pruritus and urticaria (Sharma *et al*., 2009).

Pyrexia is the most common clinical manifestation after blood transfusion and may occur in response to leukocyte or platelet antigens or due to sepsis from bacterial contamination of the blood. Circulatory overload is the most possible sequel while whole blood is administered in patients with impaired cardiac functions. Citrate toxicity can be serious in hypocalcaemic cattle (Novaretti *et al*., 2004).

Post Transfusion Complications can be avoided by careful screening of the donor, performing cross matching and blood typing before transfusions and using an appropriate process for collection, storage and administration. Blood transfusion must be very slow in cardiac patients. Animals should not be allowed to eat just before or during transfusion to prevent vomition (Chakrabarti, 2016).

CONCLUSION

Blood transfusion may be a life saving modality in case of emergency or critically ill animals. An important concern in performing a blood transfusion is the risk of patients and patients should be appropriately screened with blood typing and cross matching before transfusions.

Conflict of interest

All authors declared that there is no conflict of interest.

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