Review On Blood Transfusion And Transfusion Reaction In Large Animal

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Abstract: Blood transfusion is a process of transfer of homogenous blood from one individual to another of same species and most common practice to save the critically ill patient having acute hemolysis or hemorrhage and/or chronic anemia. This review highlights indications of blood transfusion and also management of the associated complications in large animals. The needs to transfuse each blood components are depend on the patient's condition and their indication. Fresh whole blood (FWB) is indicated for excessive hemorrhage and bleeding disorders; packed red blood cell (pRBC) for treatment of anemia caused by hemorrhage, hemolysis, or ineffective erythropoiesis; fresh frozen plasma (FFP) for the treatment of a single or multiple clotting factor deficiency, vitamin K deficiency or antagonism, surgical bleeding or where a massive transfusion is required. Platelets correct thrombocytopenia, control associated hemorrhage, and prevent death from bleeding whereas granulocyte transfusion is used in patients with life threatening neutropenia caused by bone marrow failure or in patients with neutrophil dysfunction. However blood transfusion can result in as much harm reaction as benefit to the recipient so that appropriate donor selection, blood grouping, major and minor cross matching tests, and slow delivery at the first 10–20 minutes should be considered to prevent agglutinating and/or hemolytic reactions. Citrate-phosphate-dextrose-adenine (CPDA-1) and Acid-citrate-dextrose (ACD) are commonly used anticoagulants for storage of blood. Each component obtained from whole blood has optimal storage conditions, which permits to preserve its specific activities and functions. In conclusion, transfusion medicine is lifesaving modality in case of emergency or critically ill animals to balance and correct the circulatory abnormality; however, potential risks associated with transfusions do exist. Therefore patients should be appropriately screened with blood typing and cross matching before transfusion and intensive transfusion follow up and monitoring should be performed.

1. Introduction

Blood is a complex fluid medium of plasma having suspension of living cells, and is a very essence of life (Choudhary, 2017), and blood transfusion is a process of transfer of homogenous blood from one individual to another of same species. It is most common practice to save the critically ill patient having low blood parameters and has been used as an emergency and life-saving step since many years in human as well as animal medicine (Davidow, 2013). Richard Lower in 1665 transfused the blood in a dog for the first time in the history (Kumar, 2017). With the help of latest techniques and equipment developed after 1950, blood transfusion became more popular and has made considerable advancements in veterinary medicine in recent times (Mamak and Aytekin, 2012).

Transfusion medicine has gradually become more feasible practice, with improved access to blood products through collection and transfusion from on-site donors, and the recent advancement of storage facility for whole blood and blood constituents.

Separation of specific blood constituents from whole blood helped to increase the storage period and led to the use specific blood constituents for transfusion based on the requisite (Mamak and Aytekin, 2012).

The requirement for transfusion of blood and its components arise to sustain life of anemic animals by improving the reduced red cell mass, and other cellular and non-cellular components i.e., platelets, leucocytes, circulating hemoglobin level and blood volume that ameliorate most clinical signs (Choudhary, 2017). It's indicated in the treatment of anemia caused by hemorrhage, hemolysis, ineffective erythropoiesis, hemoparasites and gastrointestinal helminthes (Mudge, 2010).

Oxygen in blood is mostly carried by hemoglobin (Hb) because it is poorly soluble in plasma. However, in anemic patients, this function is highly compromised leading to inadequate tissue perfusion. Blood transfusions increase the oxygen-carrying capacity of blood, therefore, inadequate

delivery of oxygen to tissues with consequent tissue hypoxia are prevented or treated (Callan, 2010).

In emergency management of severe anemia, the decision to transfuse blood should be based on the prognosis of the underlying condition and the availability of a suitable donor (Ermilio and Smith, 2011). Although, the information and availability of blood or its component has accessible, transfusion therapy has become more complex due to the need of advanced screening facilities, blood group testing and techniques for cross matching. Advancement in techniques of separating the components of blood has given the clinician an opportunity to use the component as per the demand of the patient (Delobel *et al.*, 2010).

Blood transfusion forms an integral part of life-saving procedures in developed country veterinary practices, which are used in critically ill animals though in large animal not as common as in small animal practice (Weingart *et al*., 2004). In developing country like Ethiopia both on large animal and small animal transfusion medicine is not familiar practice. Since most of the veterinary practice in these developing countries centered on farm/large animals, this transfusion medicine can be important if it is practiced on these large animals.

Therefore the objective of this review is to provide compiled information about the indications, transfusion-reaction and management in large animal blood transfusion therapy. Thus this review would be helpful to guide the clinicians in decision making of blood therapy.

2. Blood Transfusion
2.1. Indications of Blood Transfusion
The need for blood transfusions is critical in case of acute hemolysis or hemorrhage. Transfusions are also appropriate in treatment of acute or chronic anemia. Animals with haemostatic disorders usually require repeated transfusions of blood or its component. Blood transfusions must be given with care because they have the potential for further compromising the life of recipient (Zambelli, 2009).

Whole blood is rarely the ideal product to be transfused. Plasma is principally useful as a substitute for whole blood in transfusions because the proteins in it give it the same osmotic pressure as blood. If the need is to replace the oxygen-carrying capacity of the blood, then packed RBC are more appropriate (Hohenhous, 2005). While replacement of circulatory volume is required, crystalloid or colloid solutions may be used to restore volume, with packed RBC added as needed. Platelet number rises rapidly after hemorrhage, so substitution therapy is rarely needed. Plasma is not needed except in massive hemorrhage (Brooks, 2010). Animals that require coagulation

factors benefit most from administration of fresh-frozen plasma or cryoprecipitate if the need is specifically for factor VIII, von-Will brand's factor or fibrinogen. Platelet-rich plasma or platelet concentrates may be of value in thrombocytopenia, although immune-mediated thrombocytopenia is refractory to administration of platelets because they are removed rapidly by the spleen (Dhupa, 2005; Freireich, 2011).

The decision to transfuse RBC is determined by clinical signs in the patient, and not by any pre-selected packed cell volume (PCV). Animals with acute anemia exhibit the signs of weakness, tachycardia and tachypnea at a higher PCV than animals with chronic anemia. The amount of RBC required to relieve clinical signs will generally increase the PCV above 20%. Not more than 25% of a donor animal's blood is collected at a time (Mudge, 2010).

2.2. Blood Groups
Inherited cell surface antigens located on the red blood cells (RBC) membrane are referred to as blood group antigens. Their detection and description are based on polyclonal or monoclonal antibody serology. The antigens are vary immunogenicity and, therefore, clinically significance. These antigens participate in recognition of self and in some case can serve as a marker of disease. In veterinary medicine the clinical significance of blood group antigens is usually in the area of transfusion reaction and neonatal isoerythrolysis (NI) (Mudge, 2010; Hohenhaus, 2012). In this section current transfusion significance and types of cattle, horse, sheep, goats, and pig, llama and alpaca blood groups is reviewed.

2.2.1. Methods of blood group identification
Hemolytic and agglutination techniques are used to assay blood group factors. The choice of procedure is largely determined by the characteristics of the RBCs of each species. Blood grouping assays for cattle, sheep, goat, llama and alpaca are hemolytic tests because the RBCs of these species are not prone to agglutination. Horse and pig blood groups factors are assayed by saline agglutination or by hemolytic tests. Some pig factors require an antiglobulin test (Combos" test) or addition of dextrans to facilitate agglutination and improve scoring of reactions (Hill, 2007; Andrews and Penedo, 2010).

Hemolytic Tests
Hemolytic tests are set up in round-bottom, 96-well micro titer plates. A standard procedure consists of combining, in order, 50μL of blood typing reagent with 25μL of a 2–2.5% saline suspension of washed, packed RBCs and 25μL of undiluted rabbit complement. After addition of complement, the plate is shaken in a vibrating plate mixer. Reactions are read twice to record degree of hemolysis: once 30–45

minutes after set - up and a second time 3 hours later. A concave mirror is used for visual determination of hemolysis which is graded as 0 (negative, no visible hemolysis), 1 (partial hemolysis), 2 (intermediate), 3 (strong, almost complete) and 4 (complete hemolysis). In negative reactions, RBCs remain intact and settle in a pellet at the bottom of the well, whereas with complete hemolysis intact RBCs are not visible and the reaction fluid is clear and 5 reddish in color. A complement control consisting of 50 μL of saline, 25 μL of RBC suspensions and 25 μL of complement is run in parallel with the test reactions (Andrews and Penedo, 2010).

Rabbit serum is the source of complement for hemolytic tests. Because rabbits lack the heterophile Forssmann antigen, their sera can have Forssmann antibodies I high titers. Cattle and camelids are Forssmann negative and thus hemolytic tests in these species are not affected by Forssmann antibodies. For the Forssmann positive horse, sheep, goat and pig, rabbit serum needs to be absorbed with RBCs from these species prior to use as complement. Two serial absorptions carried out at 4 °C, for 15–20 minutes each and a 1:2 volume ratio of washed, packed RBCs to rabbit serum are usually sufficient to remove heterophile antibodies without affecting complement function (Andrews and Penedo, 2010; Susan, 2016).

Agglutination Tests

Saline agglutination tests are set up in the same way as hemolytic tests, except that complement is omitted. Reactions proceed at room temperature for 2–3 hours after which time the plates are then shaken briefly to loosen cells from the bottom of the wells. Degrees of agglutination are recorded 5–10 minutes after suspension as 0 (no agglutination), 1 (partial clumping), 2 (intermediate clumping) and 3 (total clumping of red cells). A microscope can be used to distinguish between negative and weak positive reactions. Antiglobulin tests are used with incomplete antibodies that require the addition of rabbit antiglobulin serum to produce agglutination. This procedure is used to detect some blood group factors in pigs. Addition of dextran to a saline agglutination reaction at a final concentration of 1.5% has been used with some incomplete antibodies in pigs as an alternative to the antiglobulin test (Andrews and Penedo, 2010; Susan, 2016).

2.2.2. Source of blood typing reagents

Blood typing reagents (monospecific-antisera) for livestock species are not commercially available. They have been traditionally prepared in laboratories to provided blood typing services. Comparison tests sponsored by the international society of animal genetics for several decades provided a forum for standardization of blood factor specificities and nomenclature for each species. Blood typing

comparison tests are no longer held and production of blood typing reagents has virtually ceased worldwide with the advent of DNA typing methods and technologies in the late 1990s (Andrews and Penedo, 2010).

2.3. Blood Groups in large animal

The identification of blood group antigens and analysis of their pattern of genetic in heritance in farm animal species was the subject of intense investigation for about 50 years (Kumar, 2017). In contrast to humans and cats, naturally occurring antibodies are seldom found in sera of cattle, horse, sheep, goats, pig, llama and alpacas. The molecular nature and function of the RBC antigens in farm animal remains largely unknown (Andrews and Penedo, 2010). Six livestock species cattle, horse, sheep, goats, pig, and llama (and the related alpaca) blood group systems (or loci) will describe in this section.

2.3.1. Blood group systems in cattle

The internationally recognized blood groups in cattle are A, B, C, F, J, L, M, R, S, T and Z. out of these 11 groups, group B and J being the most clinically relevant. The B group itself has more than 60 antigens, thereby making closely matched blood transfusions difficult. The J antigen is not a true erythrocyte antigen but a lipid found in plasma of Cattle having anti-J antibodies with a small amount of adsorbed J antigen on erythrocytes but negative J blood group, can develop transfusion reactions when receiving J-positive blood (Kumar, 2017).

2.3.2. Blood group systems in horse and donkey

The seven blood groups in horses A, C, D, K, P, Q and U are internationally recognized with more than 30 erythrocyte antigens (Blackmer and Parish 2002; Forcada *et al.,* 2007). Universal donor horse is not possible because of various possible antigenic combinations. The cross matching must be performed although impractical to minimize transfusion reactions (Hurcombs *et al*, 2007). Aa and Qa alloantigens are hemolysins and are extremely immunogenic and most cases of NI are associated with anti-Aa or -Qa antibodies. In horses Blood group vary with breeds. Arabian breeds have high prevalence of antigens Aa or Qa whereas, Standard breeds lack the Qa antigen (Blackmer and Parish 2002; Wilkins, 2004). Donkey factor, a unique donkey and mule erythrocyte antigen is not found in the horse and is responsible for neonatal isoerythrolysis in mule pregnancies (Kumar, 2017).

2.3.3. Blood group systems in sheep and goat

A, B, C, D, M, R, X are the seven blood groups identified in sheep. The B group has over 52 factors present over erythrocytes (Blackmer and Parish 2002). The R system in sheep is similar to the J system in cattle (i.e., antigens are soluble and passively adsorbed to erythrocytes). The blood groups of the goat (A, B,

C, M, J) are closely similar to those of sheep with the B system equally complex. Many of the reagents used for blood typing of sheep also have been used to type goats (Kumar, 2017).

2.3.4. Blood group systems in pig

As Yamamoto in 2001 stated that, development and expansion of pig blood groups is largely due to work carried out in Denmark, Germany, Poland and Russia. The source of blood typing reagents is primarily from isoimmune sera with most antibodies behaving as agglutinins and a few as hemolysins. Sixteen genetic systems are internationally recognized: *A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P*. some of these, e.g. *E* and *M*, approach the *B* and *C* systems of cattle in complexity and diversity (Andrew and Penedo, 2010).

2.3.5. Blood group systems in llama and alpaca

Little is known about blood group variation in the two domestic South American camelids, llama and alpaca. From iso and heteroimmune sera developed for these animals, six blood group factors were identified and given alphabetical designations in order of discovery: A, B, C, D, E and F. Factors A and B are inherited asco-dominant alleles and assigned to blood group system *A*. Factors C, D, E and F were assigned to four separate systems as they appeared to be transmitted independently from each other and from the *A* system (Andrews and Penedo, 2010).

2.4. Applications of blood groupings

The greatest impact of blood group identification in farm animals was in the area of animal identification and parentage verification, because of the high level of individual discrimination that could be achieved and their classic Mendelian modes of inheritance. From a clinical perspective in large animal, knowledge of blood groups is highly significant in horse because of the risk of NI posed by maternal- fetal incompatibility for certain factors (Andrews and Penedo, 2010).

2.4.1. Animal breeding

Blood group determination or blood typing is performed within a species for management purposes of genetic variation, pedigree validation, forensics, and determination of taxonomic relationships. Accurate pedigree records are essential to many aspects of animal breeding, including selection of breeding stock, estimation of heritability, and breeding values based on progeny testing. Most breed registries throughout the world have mandatory parentage testing programs to validate pedigree records of registered animals (Andrews and Penedo, 2010).

2.4.2. Blood and its component transfusion

Medically, blood typing technique is the cornerstone of effective blood transfusion as it categorizes potential donors to reduce likelihood for donor–recipient mistransfusion (Giger, 2000; Stieger

et al., 2005). Clinically, knowledge of blood groups in cattle, sheep, goat, pig and llama/alpaca has not affected conventional practice in transfusion. Large animals are not commonly transfused, and matching of blood types for antigenic compatibility is not practical because of the high variability of blood groups between individuals and limited availability of donors (Mudge*,* 2010).

Blood transfusions in large animals are indicated for certain acute, life threatening conditions and for plasma transfusion when failure of passive transfer occurs. Single, unmatched whole blood transfusions are generally safe and well tolerated. A gross cross match is recommended and sufficient when repeated transfusions are required (Mudge, 2010). Matching is done with hemolytic and/or agglutination tests depending of the species and involves testing of the recipient's serum for antibodies against the RBCs of potential donors (major) and of the donors" sera for antibodies against the recipient's RBCs (minor) (Kumar 2017).

2.4.3. To screen neonatal isoerythrolysis in horses

Neonatal isoerythrolysis is a disease of newborn horse foals and mule foals that occurs within the first week of life (Boyle *et al.,* 2005). It is caused when the mare produces antibodies against the foal's red blood cells and transfers those antibodies to the foal through colostrums during the early stages of lactation and nursing. This syndrome may occur when the blood type of the mare is different than that of the stallion and the foal inherits the sensitizing red blood cell type from the stallion (Mc Cluke Blackmer, 2003; Andrews and Penedo, 2010).

Mares that are negative for red blood cell factors have the potential to develop antibodies against those factors. Mares may become sensitized as a result of exposure to blood of a fetus with incompatible blood type as a result of placentitis, difficult parturition, or from exposure to blood containing the foreign blood factors from a previous blood transfusion. In some cases, a mare may produce sufficient antibody during a first pregnancy which can cause NI in her foal (Giguere and Polke, 2005). Increased risk of developing NI occurs with subsequent pregnancies due to breeding to that stallion or another stallion with the same red blood cell factor. After ingestion of colostrums containing antibodies to red cell factors, the antibodies are absorbed into the foal's blood. The antibodies attach to the factors (antigens) on the foal's red blood cells, and through a series of reactions, cause the foal's red blood cells to rupture (erythrocyte lysis, which describes the syndrome's medical name, neonatal isoerythrolysis (Polke, 2003).

The reported incidence of NI in newborn mules is about 10%, which is higher than the incidence in

horses. All donkeys possess the red blood cell antigen known as donkey factor; therefore every donkey/horse breeding has potential for NI. Mules suffering from NI frequently manifest thrombocytopenia (low platelet count) as well as anemia, presumably because of the presence of anti-platelet antibody as well as anti-red cell antibodies. Alloimmune thrombocytopenia (platelet destruction due to anti-platelet antibody) may occur without NI as well (Boyle *et al*, 2005; Andrews and Penedo, 2010).

A serum sample taken about 3 weeks before a pregnant mare is due to foal can be screened for evidence of blood group incompatibility. If the test results are positive for hemolytic anti-blood group activity, it is strongly advised to withhold the foal from its dam's colostrums for 36 – 48 hours before putting it back to its dam's milk. An alternative colostrums and milk source must be provided to the foal during that period (Polke, 2003; Andrews and Penedo, 2010).

3. Blood Transfusion In Large Animals

Studies in the field of hemotherapy for large animal are scarce, particularly in relation to blood conservation and responses to transfusion. Even through the illnesses that require blood transfusion are known, this therapeutic measure is sometimes used without proper criteria and without considering the potential risks of transfusion reactions (Souse *et al.*, 2014). Blood product transfusion is an integral part of equine practice, both in referral institutions and in ambulatory practice. Blood products may be administered for conditions ranging from life–threatening acute hemorrhage to failure of transfer of passive immunity (FPT). Although parasitic gastro-enteritis, blood parasites and eperythrozoonosis are chronic diseases, they sometimes require hemotherapy for chronic anemia, weakness, emaciation and progressive weight loss. As a result of chronic anemia, oxygen carrying capacity of blood will reduce and significantly lead to circulatory or respiratory failure (Abdulah *et al., 2016*).

3.1. Indications of Blood component Transfusions

3.1.1. Whole blood

Fresh whole blood (FWB) provides red blood cells, plasma proteins, viable platelets and all clotting factors. Indications for the use of FWB include in excessive hemorrhage and bleeding disorders (related to platelet or clotting factor deficiencies). Stored whole blood (SWB) provides red blood cells, plasma proteins, stable clotting factors and fibrinogen. SWB has the same indications for use as fresh whole blood, but is less useful in the treatment of coagulation abnormalities because platelets and certain clotting factors (Factors V and VIII) are no longer viable (Dhupa, 2005). In cases of blood loss, the transfusion

serves to restore blood volume as well as oxygen carrying capacity. While there are no set variables that serve as "transfusion triggers," a combination of physical examination and clinicopathologic parameters can be used to guide the decision to transfuse (Mudge, 2010).

Stored blood is a blood which has more than 8 hours old. The length of storage depends on the anticoagulant/preservative solution used. It varies from 48 hours for 3.8% sodium citrate (no preservative) to 4 weeks for CPD-A1 (citrate, phosphate, dextrose, and adenine). Acid citrate dextrose (ACD) and citrate phosphate dextrose (CPD and CP2D), and citrate phosphate dextrose-adenine (CPDA-1) are mostly used as preservatives. The viability of RBCs is provided by the added dextrose, phosphate, and adenine. Due to the preservative used, the storage can extend up to 3 to 5 week (Lanevschi and Wardrop, 2001; Callan, 2010).

In cases of acute hemorrhage one should remember that the packed cell volume (PCV) may be normal for up to 12 hours because of the time required for fluid redistribution and the effects of splenic contraction. As the patient is rehydrated with intravenous fluids, serial monitoring of PCV and total protein (TP) can estimate the amount of blood loss. The transfusion decision is made by suspicion of large volume blood loss, together with tachycardia, tachypnea, pale mucous membranes, lethargy, and decreasing TP. During an acute bleeding episode when the PCV fall under 20%, blood transfusion is probably required. In acute severe cases, transfusion may be required before there is a significant fall in PCV. PVC shows the need for beginning of transfusion in chronic anemia better whereas in acute hemorrhage, with transfusions proposed for animal with demonstration of tissue hypoxia and a PCV less than 10-12% (Hrcumbs *et al.,* 2007).

Estimation of blood loss at surgery can be used to guide the decision to transfuse, with greater than 30% blood loss generally requiring transfusion. Anesthetized horses may have very stable heart rate and PCV despite massive blood loss; pale mucous membranes with prolonged capillary refill time, decreasing TP, hypotension, and hypoxemia are better indicators of blood loss (Mudge, 2010).

Oxygenation status can help to determine the need for blood transfusion in cases of both acute hemorrhage and chronic anemia. A rise in blood lactate concentration despite volume replacement with crystalloid or colloid fluids may indicate continued tissue hypoxia and a need for blood transfusion (Magdesian *et al*., 2006).

The oxygen extraction ratio is also a useful measure: $ERO2= (\ )$ where $ERo2$ is the oxygen extraction ratio, $Sao2$ the arterial oxygen saturation

and *S*vo2 the mixed venous oxygen saturation. A ratio greater than 40–50% in the context of blood loss may indicate a need for blood transfusion. Due to the short half-life of transfused red blood cells (RBCs), transfusion should be considered a temporary measure to restore oxygen-carrying capacity, relying on the patient erythropoeitic response or resolution of underlying disease to provide long-term resolution (Mudge, 2010).

3.1.2. Packed red blood cells

Indications of red blood cell transfusions include mainly anemic patients as a result of hemorrhage, hemolysis, or ineffective erythropoiesis. Oxygen is poorly soluble in plasma. Because of this oxygen in blood is mostly carried by hemoglobin (Hgb). In anemic patient, RBC transfusions increase the oxygen-carrying capacity. Therefore inadequate deliveries of oxygen to tissues with consequent tissue hypoxia are prevented or treated by packed red blood cell transfusion (Callan, 2010).

The treatment of severe anemia caused by hemorrhage, hemolysis, ineffective erythropoiesis, auto-immune hemolytic anemia, or neoplasia is primary indication for blood transfusion. Lethargy and altered mentation, increased respiratory effort, pale mucous membranes and tachycardia are the clinical signs of anemia. The body carries out a number of adaptive responses physiologically, to maintain carrying of oxygen to the tissues (Hebert *et al*., 2004; Barffield *et al.*, 2011). The solution of oxygen in plasma is weak because of this hemoglobin (Hgb) carries approximately whole oxygen in blood. The decision to conduct a RBC transfusion is generally based on a measurement of the patient's packed cell volume (PCV), hematocrit (Hct) or Hgb concentration (Hgb) and especially on clinical evaluation of the patient (Callan, 2010).

Generally when the hematocrit is less than 10%, the treatment of anemia is transfusion. However, animals with acute-onset anemia usually require transfusion before their hematocrit decreases to 15%. This contrasts with the situation in animals with chronic anemia. Other indications for transfusion are hypervolemia, thrombocytopenia, clotting factor deficiency, and hypoproteinemia (Brown and Vap, 2006). Electrocardiographic signs of myocardial ischemia are similar to those identified in human patients with myocardial infarction. It can occur with anemia (Michael *et al.*, 2007).

3.1.3. Plasma

The usage of administration of FFP are indicated for the treatment of a single or multiple clotting factor deficiency, vitamin K deficiency or antagonism, surgical bleeding or where a massive transfusion is required (Roux, *et al.*, 2008). Hypoalbuminaemia and coagulopathies especially due to liver disease are the main reported indications for FFP transfusions in cats (Castellano *et al.*, 2004).

In patients that are hypothermic or receiving large volumes of blood, refrigerated RBC products should be pre warmed to temperatures between 22°C and 37°C immediately before transfusion. In the routine practice, transfusion of refrigerated RBC products to normovolemic anemic patients does not need warming to body temperature. Warming may accelerate the deterioration of stored RBCs and may cause rapid growth of contaminating microorganisms (Mamak and Aytekin, 2012).

3.1.4. Platelet transfusion

Freshly collected platelets correct thrombocytopenia, control associated hemorrhage, and prevent death from bleeding. Hemorrhagic diathesis is prevented by platelet replacement for thrombocytopenia (Freireich, 2011). Sever thrombocytopenia or thrombopathia result in bleeding. Platelet transfusion is used for the control of this bleeding. In veterinary medicine platelet transfusion has been used rarely compared to red blood cell (RBC) and plasma transfusion. In dogs, reports related to platelet transfusion are generally associated with experimental hematopoietic stem cell transplantation. Platelet-rich blood products consist of fresh whole blood (FWB), platelet rich plasma (PRP) and platelet concentrate (PC). They are used for aggressive anticancer therapy and treating complex hematologic disorders. Centrifugations of whole blood constitute platelet-rich plasma (PRP) and centrifugation of platelet-rich plasma constituted platelet concentrates (PC). Platelet activation is induced by centrifugation so that the resuspension of the platelet pellet during PC preparation from dogs is difficult (Mamak and Aytek, 2012).

At room temperature (RT) (20-24°C), PRP and PC can be stored for 5-7 days with continuous or intermittent agitation. At RT FWB can be stored for up to 8 hours. The interest in freezes (4°C) storage of platelets is increasing because of the increased risk of bacterial proliferation at RT storage. Platelet transfusions as with RBC and plasma components should be performed with 170 μm filters standard blood administration sets. Transfusion sets which can bind platelets should be exempt from latex. The most common reaction to PC is febrile reactions. The frequency is decreased by prestorage leukoreduction. Leukocyte reduction and ultraviolet B irradiation are recently accepted methods for preventing the development of platelet alloimmunization (Abrams-Ogg, 2010).

Recently platelet cryopreservation is used to provide long-term storage and immediate availability of platelet products for transfusion. When fresh platelets are unavailable cryopreserved platelets can be

activated in vitro and provide therapeutic benefit (Mamak and Aytekin, 2012).

3.1.5. Granulocyte transfusion

Granulocyte transfusion can be used as supportive therapy. It is used in patients with life threatening neutropenia caused by bone marrow failure or in patients with neutrophil dysfunction. A granulocyte transfusion is shown to be useful in treatment of infections in patients post-treatment with high-dose chemotherapy. It is helpful especially in the chemotherapy associated with conditioning for hematopoietic stem cell transplant. By using granulocyte colony-stimulated factors higher doses of granulocytes for transfusion are produced. Thus recently the use of therapeutic granulocyte transfusion has been increased. The outcomes of transfusion are affected by the type of infection being treated, the likelihood of recipient marrow recovery, and recipient alloimmunization (Harris 2009).

In small animals therapeutic granulocyte transfusions have been used especially in experimental models of myelosuppression and neonatal sepsis. In clinical veterinary medicine they have been used rarely. Granulocytes can be used to identify the site of inflammation. Besides leukapheresis, centrifugation of FWB, with or without colloid facilitated sedimentation, may be used to isolate canine and feline buffy coats. Only sedimentation may also be used in the cat. At RT granulocytes are stored immobil for 24 hours. The dose for beginning is 1 x 1011granulocytes/kg in a volume of 15mL/kg. It is used once to twice in a day (Mamak and Aytek, 2012).

3.1.6. Oxyglobin

Oxyglobin ® (Biopure Corp., Boston, MA), a hemoglobin based oxygen-carrying solution, has been used experimentally in ponies with normovolemic anemia. Oxyglobin improved hemodynamic and oxygen transport parameters; however, one pony did have anaphylactic reaction. The use of Oxyglobin was also reported for treatment of a pony mare with chronic hemorrhage and a history of acute transfusion reactions. Although Oxyglobin is currently commercially available, the cost and volume (125 mL) per bag limit its utility for equine treatment (Mudge, 2010).

3.2. Blood Donor Selection

Blood grouping should be performed to select permanent blood donors. All donors should be healthy young adults that have never been transfused. In addition, donors must have undergone routine physical, hematological and clinical chemistry evaluations 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. In the veterinary medicine, it is usually the cost that restricts to test

individual units. Therefore, a combination of careful interview and blood screening of the donor is used to minimize the risk of infectious disease transmission (Wardrop *et al.*, 2005).

Donor should be properly vaccinated and should be tested free of blood parasites and other infectious diseases. In 2005, the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on infectious disease testing for blood donors was published. Since publication, polymerase chain reaction (PCR) assays have become more readily available. Several veterinary diagnostic laboratories offer donor screening PCR panels (Davidow, 2013). Donors should have normal baseline PCV and total protein concentrations prior to any donation. Blood should be collected aseptically usually via jugular venipuncture. To avoid interference with platelet function, donors should not be sedated with acepromazine (Hackett *et al.,* 2006).

3.3. Red Blood Cell Donors for Foals with NI

Appropriate management for a severely anemic NI foal may be a RBC transfusion to alleviate the anemia and prevent death (Whiting, 2003). The best blood donor is one whose RBCs lack the factor to which the mare is making antibodies. The sire of the foal is the worst possible donor since he has the factor to which the mare's immune system has responded. The best immediate RBC donor is the mare. The mare's RBCs should be administered to the foal in a suitable transfusion solution, but first they must be separated from the plasma (Polke, 2003; Andrews and Penedo, 2010).

3.4. Blood Typing and Cross matching

Major and minor cross matching tests are done for agglutinating and/or hemolytic reactions between donor and recipient. In equines agglutinating and hemolytic tests are required because of presence of agglutinating as well as hemolytic antibodies in equines. For cattle, sheep and goats test for hemolytic antibodies and complement is necessary (Divers, 2005).

The major cross match evaluates for the presence (positive findings) or absence (negative findings) of detectable levels of antibodies, whether naturally occurring or induced, in the recipient against donor erythrocyte antigens. A major cross match should always be performed in animals that have strong naturally occurring antibodies, as in those that may have induced antibodies as from prior transfusions (Kumar, 2017).

The latter is true even if the same donor blood is intended for repeated transfusion beyond a span of several days. The minor cross match procedure follows the same steps as the major cross match 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 in comparison to the recipient and is diluted in the recipient particularly in case when only erythrocytes are transfused (Giger, 2000).

Administration of packed erythrocytes may contain sufficient antibodies against recipient erythrocytes to induce adverse reactions in horses (Hurcombe *et al.*, 2007). An ethylene diamine tetra acetic acid (EDTA) tube and a clot tube from the recipient are preferred for use in cross match testing. The EDTA plasma should not be used in place of serum because this contributes to increased rouleaux formation and difficult interpretation of agglutination, particularly in the horse. Preferably, samples should be free of auto-agglutination, hemolysis and lipemia to aid in the interpretation of the reactions. When auto agglutination is present, or when no compatible units are available, transfusing the least incompatible unit may be a necessity, albeit not without significant risk (Giger 2009).

Cross matching technique

Collect the blood from the donor as well as recipient in purple top and red top tubes i.e. EDTA tube and non EDTA tubes respectively (Lanevschi and Wardrop, 2001). Centrifuge the blood and allow separating plasma and serum from the RBCs. Remove the serum and save it in a separate sterile tube. Discard the plasma from the EDTA tube. Wash the RBCs collected from EDTA tube. Place the RBCs in a spate tube filled with normal saline and centrifuge for 1 minute. Repeat the process 5 times removing the supernatant every time. Resuspend 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 Cross match (2 drops patient serum with 1 drop donor RBC suspension), Minor cross match (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. If cross matching shows either hemolysis or hem agglutination macroscopically or microscopically, the donor is not a good match for the recipient (Kumar, 2017).

3.5. Collection Techniques

Blood is collected from the jugular vein of the donor animal. Up to 20 – 25% of total blood volume can be removed from the donor animal, usually via needle cannulation or jugular catheterization, with total blood volume estimated at 80 mL/kg. For this purpose two way used; direct needle cannulation or catheterization. When a large volume of blood is required, a 10 or 12 gauge catheter is recommended. A 14 gauge catheter is also sufficient. Plastic bags and vacuum collection glass bottles in sizes ranging from 450 mL to 2 L are suitable for blood accumulation. Anticoagulation with 3.2% sodium citrate is enough when blood is received for immediate transfusion. In saline-adenine-glucose-mannitol solution red blood cell concentrates stored and they can be used for transfusion for up to 35 days after blood accumulation (Niinisto *et al.,* 2008; Mudge, 2010,).

Fresh frozen plasma is obtained by separation of erythrocytes and plasma. Both of them can be used individually. RBC survival evaluation should be done in vivo. To allow separation of red blood cells by gravity sedimentation the blood is stored in a refrigerator at 5 °C for 48 hours in an upright position. Then the plasma is decanted into a sterile 3-L bag with sterile plastic connecting tubing using gravity. 3-L bags contain a constant weight of plasma (3.4 kg). The red cell fraction is thrown out. The plasma bags are sealed, labeled with the horse's name and the date of decantation. They are stored at -20 °C until needed for plasma transfusion (Wilson *et al.,* 2009).

3.6. Anticoagulants Used for Storage

Two anticoagulants namely Citrate-phosphate-dextrose-adenine (CPDA-1) and Acid-citrate-dextrose (ACD) are commonly used for storage of blood. 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. In CPDA-1 blood can be stored for approximately 35 days. Acid-citrate-dextrose (ACD) allows storage of blood for 21 days (Wardrop, 2008; Lucas, 2004). Use 1 mL of anticoagulant (CPDA-1/ACD) for every 7 mL of blood. Blood should be refrigerated in plastic blood collection bags. Heparin is not recommended for blood collection because it activates platelets, but if still used 5 U of heparin per mL of `blood is sufficient. Blood collected in heparin as anticoagulant must be used immediately. Because of glucose shortage and depletion of ATP and 2, 3-DPG, Survival and functional usefulness of erythrocytes decrease with increased storage temperature and time. Blood should be collected into latex free plastic bags or plastic syringes to preserve platelets (Mudge *et al.*, 2004).

Plasma processing can be performed by gravity sedimentation, centrifugation using a double - bag system, or plasmapheresis. Plasmapheresis is the preferred technique as it is more rapid than WB collection and processing, and results in plasma with minimal RBCs and leukocytes. Since bovine blood does not readily separate, a centrifuge is needed to process WB into plasma and pRBC components. Immunoglobulins are well - maintained for at least 1 year in FFP; however, coagulation factor activity may decrease after 2 – 4 months of storage. Platelet - rich plasma has been prepared from fresh WB (Mudge, 2010).

Each component obtained from whole blood has optimal storage conditions, which permits to preserve its specific activities and functions. The temperature is a particularly important storage parameter regarding the viability and the quality of products intended for transfusion. Supplemented with an additive solution, generally a saline-adenine-glucose-mannitol (SAGM) solution, RBCs can be stored for up to 42 days from +2 °C to +6 °C, in order to preserve the functionalities of erythrocytes (Delobel *et al.,* 2010). On the contrary, PLT are stored from +20 °C to +24 °C up to 5 days, with sufficient agitation to permit a good oxygenation and to prevent platelet aggregation. Storage at room temperature promotes bacterial proliferation, and thus increases the risk of transmitted bacteria. The dilemma is that if platelets are transfused after refrigeration at 4 °C, they are rapidly cleared from the recipient circulation (Snyder and Rinder, 2003). Finally, as indicated by its name, FFP has to be frozen, for an optimal storage, at least at −25 °C, for up to 36 months (Delobel *et al.,* 2010).

3.7. Blood Administration

The volume of blood to be transfused depends on estimated blood loss, estimated total blood volume, and donor PCV (Abdullah *et al.,* 2016):

Volume required (mL) = Body weight (kg) ×Blood volume (mL/kg) × (desired PCV-actual PCV/donor PCV).

In cases of acute blood loss, PCV is often not useful for estimates of volume to be transfused since it does not accurately reflect blood loss. Instead, estimates of blood loss and evaluation of clinical parameters are used to determine the volume of blood needed. Between 25% and 50% of the total blood lost should be replaced by transfusion since much of the circulating volume will be replaced by fluid shifts. It is important to remember that up to 75% of RBCs lost into a body cavity (example hem peritoneum) are auto transfused back into circulation within 24–72 hours (Sellon, 2004). The lower percentages of blood volume replacement may be needed in cases of intracavitary hemorrhage. Blood and plasma products should be delivered with an in - line filter to remove small clots and fibrin (Mudge, 2010).

Volumes of plasma for treatment of hypoproteinemia can be estimated by TP or albumin concentrations, although the use of plasma to normalize severe hypoproteinemia can be prohibitively expensive in the adult horse.

Plasma transfusion volume (mL) =Body weight (kg) ×45(mL/kg) (desired TP-actual TP/donor TP) Volumes of plasma given for treatment of hypoprotenemia or coagulopathy is often determined by clinical and clinicopathological response. The volume of plasma needed in a foal with FPT can be determined if the IgG concentrations of the foal and the plasma are known. A dose of 20 mL/kg of plasma (IgG approximately 1200 mg/dL) will generally raise the foal"s IgG concentration by 200 – 300 mg/dL. A larger volume of plasma may be needed to achieve a similar rise in IgG in clinically ill foals (Abdullah *et al.,* 2016).

In order to monitor for transfusion reactions, blood should be delivered at a rate of approximately 0.3 mL/ kg over the first 10–20 minutes, while monitoring heart rate, body temperature, and respiratory rate. Patient should also be monitored for signs of muscle fasciculation, piloerection, and urticarial, adverse reactions reported in animals receiving blood transfusions include urticarial, hemolysis, and acute anaphylactic reactions. The rate of adverse reaction to WB transfusion has been reported as 16%, with 1 of 44 horses (2%) having a fatal anaphylactic reaction. If no signs of reaction are seen, the rate of administration can be increased to 5 mL/ kg/h for normovolemic patient and up to 20 – 40 mL/ kg/h for hypovolemic patient (Mudge, 2010).

4. Transfusion Reaction And Its Managements

Blood is a complex biologic product which, like any tissue transplant, can result in as much harm as benefit to the recipient. The term transfusion reaction denotes any adverse event associated with transfusion of blood or a blood component. The reaction may occur during or within hours to weeks after administration of a blood product. Understanding how to prevent a transfusion reaction and recognizing the potential clinical and clinicopathologic signs of an adverse reaction should one occur are key to good transfusion medicine practice (Kumar, 2017).

Transfusion reactions have been classified using various terminologies in both the human and veterinary literature but are most often characterized by immunologic and non - immunologic mechanisms. There have been several reviews in the veterinary literature on blood transfusions in cats, dogs, and horses, with the incidence and type of transfusion reactions varying between institutions and species but ranging from 3 – 13% (Hurcombe *et al.,* 2005). Reports of adverse reactions in large animal blood transfusion are underscoring and needs for further education on their prevention and identification (Weinstein, 2010).

4.1. Immune Complications

4.1.1. Hemolytic transfusion reactions

Hemolytic transfusion reactions (HTR) jeopardize the health of an already compromised patient. A HTR is the result of naturally - occurring or induced antibodies present in the recipient plasma which can destroy donor red blood cells (RBCs) immediately upon transfusion or within hours to weeks. These reactions are classified as type 2

hypersensitivity and are mediated by antibodies directed against antigens present on the surface of RBCs (Abbas *et al.*, 2005). After reacting with the RBC surface antigen, IgG or IgM antibodies activate the complement system, culminating in the formation of a membrane attack complex which disrupts the lipid bilayer of the RBC membrane, causing intravascular hemolysis. Also, antibody or complement fragments, primarily C3b or C4b, can adhere to the RBC surface (opsonization), enhancing RBC susceptibility to phagocytosis by leukocytes expressing receptors for these proteins. Either intravascular or extravascular hemolysis can result, depending on whether the leukocytes recognize the opsonized RBCs while in circulation or within the reticuloendothelial system. The severity of a HTR is influenced by the concentration of recipient alloantibody, the immunoglobulin type, whether the antibody is warm or cold - reacting, the amount of blood transfused, and the condition of the recipient (Weinstein, 2010).

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions (AHTRs) present within 24 hours of a RBC transfusion (Davenport and Mintz, 2007). Preformed antibodies in the recipient react with transfused donor RBCs. The recipient has previously formed an alloantibody against an antigen present on the donor's RBCs which is not present on the recipient's RBCs. Within seconds to a few minutes of receiving as little as 1 mL blood, the patient may exhibit restlessness, vocalization, vomition, urination, salivation, and recumbence (Weinstein, 2010). Bradycardia, cardiac arrhythmias, decreased pulse strength, pale mucous membranes, and prolonged capillary refill time are also expected in the initial phase. If the reaction is recognized and the transfusion stopped, hemoglobinemia and hemoglobinuria will follow, as these reactions are IgM and complement - mediated with obvious intravascular hemolysis (Giger, 2009).

First transfusions in cattle are of low risk, whereas transfusing J-positive erythrocytes to J-negative cattle recipient can result in transfusion reactions. In J-antigen mismatched second transfusion within four days of first transfusion can result in hemolytic reactions (Divers, 2005). Neonatal isoerythrolysis is the destruction of erythrocytes in the circulation of offspring by alloantibodies of maternal origin that are absorbed from colostrums. Nearly all cases of NI in foals are caused by factor Aa in the A system and factor Qa in the Q system (Blackmer and Parish, 2002). Signs of transfusion reactions usually develop 24- 36 hours after suckling like anemia, liver failure and kernicterus (bilirubin encephalopathy) being the primary causes of death in foals (Polkes *et al*, 2008).

A cross match test can identify preformed alloantibodies against a blood group antigen, thus preventing an AHTR (Hurcombe *et al.*, 2005).

Delayed Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reactions (DHTRs) are defined as those occurring more than 24 hours following a transfusion, but the time of onset can vary to 48hours post - transfusion depending on the reference (Weinstein, 2010). DHTRs are often the result of an anamnestic response to a RBC antigen that the recipient lacks, with the previously produced reactive alloantibody weak or present in very low concentrations. Pre-transfusion cross match testing may not identify the potential incompatibility if the test is insufficiently sensitive. Alternatively, DHTRs may be a result of primary alloimmunization to a RBC antigen, with hemolysis occurring weeks later after sufficient time for alloantibody production (Davenport and Mintz, 2007).

DHTR should be suspected if there is a more rapid decline than expected in PCV in the weeks following a blood transfusion, based on the patient's underlying disease. Additional clinicopathologic signs to support a diagnosis of DHTR include hyperbilirubinemia, bilirubinuria, or hemoglobinuria: fever can develop but often goes unnoticed. Diagnosis of a DHTR requires documentation of development of antibodies by the recipient against the donor (s) RBCs. Regardless of the designation of acute versus delayed, the majority of HTRs can be prevented through proper blood typing and cross match testing (Davenport and Mintz, 2007; Weinstein, 2010).

4.1.2. Non - hemolytic transfusion reactions

Febrile and Allergic Reactions

Febrile and allergic reactions are two of the most common types of transfusion reactions reported in veterinary medicine, comprising 60 – 90% of reported reactions (Divers, 2005). Febrile, non-hemolytic transfusion reactions (FNHTRs) are defined in human medicine as a rise in temperature of either 2 ° F or 1 ° C during or within 4 hours post-transfusion without an obvious other cause for the rise in temperature (Weinstein, 2010). Additional clinical signs can include vomiting and tremors: the vomiting will often resolve without treatment, but a decreased transfusion rate may help to alleviate this symptom (Wardrop, 2008). Febrile, non - hemolytic transfusion reactions are frequently attributed to recipient alloantibodies which react with histocompatibility leukocyte antigens or other antigens present on donor lymphocytes, granulocytes, or platelets. Cytokines released from leukocytes and platelets within stored blood are also implicated as causes for FNHTRs and some allergic type reactions. Pre - storage leukoreduction has been shown to decrease, but not eliminate, FNHTRs (Hurcombe *et al.*, 2007).

Allergic reactions are more often associated with transfusion of plasma products and are triggered by exposure to a substance, likely a protein, present in donor plasma to which the recipient has been sensitized (Weinstein, 2010). Signs of an allergic reaction typically start within the first 15 minutes of a plasma transfusion but can occur during or within a few hours of administration. Clinical signs include mild to sometimes dramatic urticaria, pruritis, and erythema. Additional signs can include vomiting, nausea, diarrhea, and/or abdominal pain. Treatment of an allergic reaction to a plasma product includes stopping or, at least, decreasing the rate of transfusion, as well as administering an antihistamine such as diphenhydramine (1–2 mg/kg IM). Although pretreatment to prevent these types of immune reactions has been previously advised, administration of diphenhydramine to humans prior to leukoreduced platelet transfusions did not decrease the frequency of allergic-type urticarial reactions (Davenport and Mintz, 2007).

Uncommon Immune Reactions

Post-transfusion purpura (PTP) is a relatively un-common transfusion reaction in humans and has been described once in veterinary medicine. Thrombocytopenia develops 1–2 weeks post transfusion due to recipient - produced anti - platelet antibodies. These antibodies are most often directed against a platelet specific antigen (e.g. in humans, HPA-1a) which the recipient lacks: platelets targeted for destruction are typically those of the donor but targeting of recipient/patient platelets have also been documented (Weinstein, 2010).

PTP must be differentiated from worsening underlying disease or development of a concurrent disorder. Anaphylaxis secondary to IgA deficiency has been reported in a single dog. Anaphylaxis results from patient anti - IgA antibodies reacting to IgA antibodies in the donor plasma. Clinical signs vary from facials welling, urticaria, and erythematous skin to respiratory distress, vomiting, diarrhea, and shock. An IgA -deficient patient who previously demonstrated a severe anaphylactic reaction would require future transfusions that are free of IgA (Lanevschi and Wardrop, 2001).

4.2. Non-Immune Complications

4.2.1. Infectious disease transmission

Transmission of infectious agents to a blood transfusion recipient, though a relatively infrequent complication in both human and veterinary transfusion medicine, is not a true transfusion reaction but is obviously an avoidable and potentially devastating complication of transfusion (Aleman *et al*.,2005; de Freitas*, et al*.,2006). Although WB and pRBCs carry a greater risk of in factious disease transmission, plasma is not without risk; recently, herpes virus was

inadvertently transmitted to horses receiving commercially prepared plasma (Wardrop, 2008).

Documentation of a transfusion- acquired infection requires testing of pre–transfusion recipient blood, in addition to testing the donor; unfortunately, pre-transfusion recipient samples are not always available. Proper transfusion records will allow for easy identification of the suspected infected donor, removal of any remaining blood units from that donor, and appropriate treatment of the donor (Weinstein, 2010).

4.2.2. Transfusion-associated sepsis

Bacterial contamination of a blood unit can result in transfusion-associated sepsis. Clinical signs associated with transfusion of a contaminated blood unit include fever, vomiting, diarrhea, hypotension, and hemolysis (Davenport and Mintz, 2007). Contamination can occur at the time of collection from inadequate preparation of the venipuncture site or contamination of materials used in collection. Once contamination of a unit occurs, bacterial numbers tend to increase with storage time, even when the unit is refrigerated. Storage at room temperature, which is necessary to preserve the post - transfusion survival of platelets in fresh WB and platelet rich preparations, can also lead to bacterial proliferation in contaminated units. It has been documented that units of human pRBCs stored for longer than 21 days are more likely to contain proliferating bacteria. The severities of a reaction will ultimately depend on the bacterial species, the number of bacteria present, and the clinical condition of the recipient/patient (Hillyer *et al.,* 2003).

Reports of bacterial contamination of blood products and transfusion - associated sepsis are infrequent in veterinary medicine. This report illustrates the importance of bacterial culture of materials other than the unit and demonstrates the steps necessary to identify the source of contamination. Contaminated WB or pRBC units are typically discolored (dark brown, purple, or black), and clots and air bubbles may also be present (Abrams-Ogg, 2000). The discoloration associated with bacterial contamination indicates deoxygenation, hemolysis, and the formation of methemoglobin. Blood units with such an abnormal appearance should not be used, and an investigation to confirm bacterial contamination and identify the source of contamination should be pursued. Lastly, administration of a blood component unit should ideally take no longer than 4 hours to reduce the potential for bacterial proliferation (Weinstein, 2010).

Once a unit is opened, even if refrigerated, it should be used within 24 hours. If bacterial contamination is suspected after the transfusion has been started, the transfusion should be stopped

immediately and the unit submitted for a Gram stain and bacterial culture. Blood culture of the recipient may also be warranted (Weinstein, 2010).

4.3. Uncommon Non - immune Complications
4.3.1. Citrate toxicity
Citrate is the anticoagulant used in most standard blood collection systems. Plasma and WB have the greatest concentrations of citrate when compared to pRBCs. Patients most at risk for citrate toxicity include those receiving large volumes of blood products, such as in cases of massive transfusion and, potentially, patients with severe liver disease since citrate is metabolized by the liver. Ionized hypocalcaemia and hypomagnesaemia result from chelation of these cat ions by citrate, and associated clinical signs include muscle tremors, vomiting, cardiac arrhythmias, ear twitching, hypotension and/or tetanic seizures (Jutkowitz *et al.,* 2002). Intravenous calcium can be administered to treat clinically significant transfusion-related hypocalcaemia (Weinstein, 2010).

4.3.2. Circulatory overload
Patients with chronic anemia and a compensatory expanded plasma volume or patients with compromised pulmonary and/or cardiac function may be at risk for circulatory overload. Expected clinical signs include respiratory distress and, in some cases, congestive heart failure; signs may be seen during or soon after transfusion. Management of fluid overload with diuretics is advised. Slowing the transfusion rate and using pRBCs rather than WB in anemic patients can help to decrease the risk of circulatory overload (Mudge, 2010).

4.3.3. Non-immune hemolysis unrelated to bacterial contamination
Hemolysis unrelated to a blood group incompatibility or bacterial contamination may occur in vitro due to improper storage or handling of blood units, including use of a hot water bath, inadvertent freezing, use of pumps not approved for administration of blood products, and concurrent administration of incompatible fluids, such as 5% dextrose or hypertonic saline through a shared intravenous line. Warmed blood has been demonstrated to have decreased survival in the patient which could mimic a delayed transfusion reaction (Hohenhaus, 2005; Wardrop *et al.,* 2005; Weinstein, 2010).

4.4. Prevention and Recognition of Transfusion Reactions
Prior to blood product administration, baseline values of temperature, heart rate, and respiratory rate should be determined and pre - transfusion PCV should be recorded. Pre - transfusion WB and serum samples should be collected from the recipient, if not already submitted for other routine testing. These samples can be invaluable in cases of HTRs and in documentation of infectious disease transmission (Barfield *et al*., 2011; Chiaramonte, 2004). Transfusion of any blood product is ideally started at a slower rate for the first 15 minutes while monitoring for signs of any adverse reactions. Clearly, in cases of severe, ongoing blood loss, rapid administration from the start may be necessary. Transfusion monitoring should be performed every 15 minutes for the first hour, with serial measurement of temperature, heart and respiratory rates. If there is any concern about an AHTR, evaluation of plasma and/or urine for the presence of hemoglobin is indicated. Lack of an expected increase in PCV post - transfusion may also be suggestive of an AHTR (Hackett *et al.*, 2006; Wardrop, 2008).

If signs of anaphylaxis are present, epinephrine (0.01 – 0.02 mL/kg IV of 1:1000 solutions) should be administered immediately. More mild transfusion reactions, such as urticaria, fever, and tachypnea, may be treated with an anti-inflammatory (e.g. flunixin meglumine 1.1 mg/kg IV) or an antihistamine (e.g. tripelennamine 1.1 mg/kg IM) (Mudge, 2010).

4.5. Evaluation of Patients with a Suspected Transfusion Reaction
Investigation of hemolytic and febrile reactions should include inspection of the patient's plasma for evidence of hemolysis or icterus. Evaluation of the blood product unit administered including unit labels, the administration set, Gram stain and blood culture of the transfused product; comparison of patient bilirubin both pre–and post-transfusion; retesting of patient and donor blood type, especially for reactions involving RBC–containing units; and post- transfusion cross match testing of recipient-donor compatibility (Lanevschi and Wardrop, 2001).

Adequately screening potential blood donors, transfusing patients only when clinically indicated, selecting the most appropriate blood component, properly administering blood products, and carefully monitoring transfusion recipients will greatly diminish the risk of a transfusion reaction (Weinstein, 2010).

5. Conclusion And Recommendations
Transfusion medicine is a lifesaving modality in cases of emergency or critically ill large animals similar to that of small animals and humans. The appropriate use of transfusion medicine can balance and correct the circulatory abnormality associated with hemolysis, hemorrhage, ineffective erythropoiesis and coagulopathy disorders. Blood transfusion is safe in large animals if performed with established standard protocol. However, it may result in disease transmission from donor to recipient if the donor is not screened for diseases, in addition to blood compatibility tests.

Therefore based on the above conclusion the following recommendations are forwarded:

➢ Clinicians should consider and use blood as therapeutic option during hematological abnormalities.

➢ The donor animal should be appropriately screened with cross matching to patients'' blood to prevent transfusion reaction.

➢ The donor animal should be free from diseases that may be transmitted through blood transfusion.

➢ Transfusion monitoring should be performed carefully by frequent measuring vital parameters.

➢ Further studies are required for the documentation of adverse reactions in large animal blood transfusion.

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References
1. Abbas, A.K. (2005): Diseases of immunity. In: Kumar, V., Abbas, A.K. and Fausto, N. (Eds): Robbins and Cotran Pathologic Basis of Disease, 7th ed. Philadelphia: Elsevier Saunders, Pp. 193 – 267.
2. Abdullah, F. F. J., Chung, E. L. T., Sabrina, L.,2 Abba, Y., Sadiq, M. A., Mohammed, K., Hambali, I.U., Bitrus, A.A., Haron, A.W., and Lila, M.A.M. (2016): Clinical Case of Severe Anaemia in a Sheep Due to Parasitic Gastro Enteritis (PGE) Infection Concurrent with Eperythrozoonosis. *Journal of Livestock Research International,* 4(2):75-78.
3. Abrams-Ogg, A. C.G. (2010): Plalet and Granulocyte Transfusion. In: Weiss, D.J. and Wardrop, K.J. (Eds): Schalm''s Veterinary Hematology. 6th ed. USA: Blackwell Publishing Ltd, Pp.751-756.
4. Aleman, M., Nieto, J.E. and Carr, E.A. (2005): Serum hepatitis associated with commercial plasma transfusion in horses. *Journal of Vet Intern Med*, 19:120–122.
5. Andrews, G.A, and Penedo, M.C. (2010): Erythrocyte Antigens and Blood Groups. In: Weiss DJ and Wardrop KJ (Eds.): Schalm''s Veterinary Hematology. 6th ed. USA: Blackwell Publishing Ltd, Pp.711-724.
6. Barfield, D. and Adamantos, S. (2011): Feline Blood Transfusions. *Journal of Feline Medicine and Surgery,* 13: 11-23.
7. Blackmer, J. and, Parish, S. (2002): Diseases caused by allogeneic incompatibilities. In: Smith, B.P. (Ed.), Large Animal Internal Medicine. 3rd ed, Mosby Elsevier Science, St. Louis, USA, Pp. 1604-1613.
8. Boyle, A.G., Magdesian, K.G. and Ruby, R.E. (2005): Neonatal Isoerythrolysis in horse foals and a mule foal: 18 cases. *Journal of AVMA*, 227(8):1276–83.
9. Brooks, M.B. (2010): Transfusion of Plasma Products. In: Weiss, D.J. and Wardrop, K.J. Eds. Schalm''s Veterinary Hematology. 6th ed. USA: Blackwell Publishing Ltd, Pp.744-745.
10. Brown, D. and Vap, L. (2006): Principles of Blood Transfusions and Cross-Matching, In: Thrall, M.A., Baker, D.C., Campbell, T.W., DeNicola, D., Fettman, M.J., Lassen, 33
11. E.D., Rebar, A., and Glade, W. (Eds.) Veterinary Hematology and Clinical Chemistry. USA: Blackwell Publishing, Pp.197-202.
12. Callan, M.B., (2010): Red Blood Cell Transfusion in the Dog and Cat. In: Weiss, D.J., Wardrop, K.J. (Eds): Schalm''s Veterinary Hematology. 6th ed. USA, Blackwell Publishing Ltd, Pp 738-743.
13. Castellanos, I., Couto, C.G. and Gray, T.L. (2004): Clinical use of blood products in cats: a retrospective study (1997–2000). *Journal of Vet Intern Med*, 18:529–532.
14. Chiaramonte, D. (2004): Blood-component therapy: selection, administration and monitoring. *Journal of Clin Tech Small Anim Pract*, 19:63–67.
15. Choudhary, S.S., Jacob, A., Varan, S.S., Khatti, A., Yadav, P.J., Singh, K.S. and Jaiswal, K.R. (2017): Review on Blood Transfusion in Small Animals: A Lifesaving Modality in Veterinary Practice. *Journal of International Science, and Environment Technology,* 6(1):893–898.
16. Da Freitas, E., Melo, M.N. and da Costa-Val A.P. (2006): Transmission of *Leishmania infantum* via blood transfusion in dogs: potential for infection and importance of clinical factors. *Journal of Vet Parasitol*, 15: 159–167.
17. Davenport, R.D. and Mintz, P.D., (2007): Transfusion medicine. In: McPherson, R.A., Pincus, M.R. (Eds): Henry''s Clinical Diagnosis

and Management by Laboratory Methods. 21st ed. Philadelphia, WB Saunders, Pp. 669–684.

18. Davidow, B., (2013): Transfusion medicine in small animals. *Journal of Vet Clin Small Anim,* 43(4): 735-756.

19. Delobel, J., Rubin, O., Prudent, M., Crettaz, D., Tissot, J.D. and Lion, N. (2010): Biomarker Analysis of Stored Blood Products: Emphasis on Pre-Analytical Issues. *Journal of Int. Mol. Sci.*, 11:4601-4617.

20. Dhupa, N. (2005): Clinical Use of Component Therapy Vs. Whole Blood. In the Proceeding of the North American Veterinary Conference (NAVC), Jan, 8-12, 2005, Orlando, Florida, Published in IVIS, Pp. 377-379.

21. Divers, T., (2005): Blood component transfusions. *Journal of Vet Clin North Am Food Anim Pract*, 21: 615-622. 34

22. Ermilio, E.M. and Smith, M.C. (2011): Treatment of emergency conditions in sheep and goats. *Journal of Veterinary Clinics of North America-Food Animal Practice*, 27(1):33–45.

23. Forcada, Y., Guitian. J. and Gibson, G. (2007): Frequencies of feline blood types at a referral hospital in the South East of England. *Journal of Small Anim Pract*, 48(10):570-573.

24. Freireich, E.J. (2011): Origins of Platelet Transfusion Therapy. *Journal of Transfusion Medicine Reviews*, 25(3):252-256.

25. Giger, U. (2009): Transfusion medicine. In: Silverstein, D. and Hopper, K. (Eds): Small animal critical care medicine, St. Louis, MO: WB Saunders, Pp. 282-286.

26. Giger, U. (2000): Blood typing and crossmatching to ensure compatible transfusions. In: Bonagura, J.D. (Ed.): Kirk"s Current Veterinary Therapy XIII, Philadelphia: WB Saunders, Philadelphia, USA, Pp. 396-399.

27. Giguere, S. and Polkes, A.C. (2005): Immunologic disorders in neonatal foals. *Journal of Vet Clin Equine,* 21:241–72.

28. Hackett, T.B., Jensen, W.A., Lehman, T.L., Hohenhaus, A.E. and Crawford. P.C. (2006): Prevalence of DNA of Mycoplasma haemofelis, Candidatus Mycoplasma haemominutum, Anaplasma phagocytophilum and species of Bartonella, Neorickettsia and Ehrlichia in cats used as blood donors in the United States. *Journal of Am Vet Med Assoc,* 229(5):700-705.

29. Harris, D.J., (2009): The Resurgence of Granulocyte Transfusions. *Journal of Infusion Nursing;* 32(6):323-329.

30. Hebert, P.C., Van der Linden, P., Biro, G. and Hu, L.Q. (2004): Physiologic aspects of anemia. *Journal of Crit Care Clin*, 20:187–189.

31. Hill, E. (2007): Immunology, Serology, and Molecular Diagnostics. In: Sirois, M., and Hendrix, C., (Eds): Laboratory procedures for veterinary technicians. 5th ed. St. Louis, MO: Mosby Elsevier health science, Pp. 264-286.

32. Hillyer, C.D., Josephson, C.D. and Blajchman, M.A. (2003): Bacterial Contamination of Blood Components Risks, Strategies, and Regulation Hematology. American Society of Hematology, Pp. 575 – 589. 35

33. Hohenhaus, A. (2005): Transfusion reactions. In: Feldman, B.F. & Zinkl, J.G. (Eds.): Schalm"s Veterinary Hematology. 5th ed. Lippincott, Williams & Wilkins, Philadelphia, USA, Pp. 864-868.

34. Hohenhaus, A. (2012): Blood transfusion Blood substitutes. In: DiBartola, S.P., (Ed). Fluid, electrolyte, and acid-base disorders in small animal practice. 4th ed. St. Louis, M.O. Mosby Elsevier health science; Pp 593-594.

35. Hurcombe, S., Mudge, M. and Hinchcliff, K. (2007): Clinical and clinicopathologic variables in adult horses receiving blood transfusions: 31 cases (1999–2005). *Journal of Am Vet Med Assoc*, 231(2): 267-274.

36. Jutkowitz, L.A., Rozanski E.A. and Moreau, J.A. (2002): Massive transfusion in dogs: 15 cases (1997-2001). *Journal of Am Vet Med Assoc*, 220: 1664-1669.

37. Kumar, R. (2017): Blood Transfusion in Veterinary Medicine. *Journal of Hematology & Transfusion*, 4(4):2-8.

38. Lanevschi, A., and Wardrop, K.J. (2001): Principles of transfusion medicine in small animals. *Journal of Can Vet,* 42(6):447-454.

39. Lucas, R., Lentz, K. and Hale, A. (2004): Collection and preparation of blood products. *Journal of Clin Tech Small Anim Pract,* 19(2):55-62.

40. Magdesian, K.G., Fielding, C.L. and Rhodes, D.M. (2006): Changes in central venous pressure and blood lactate concentration in response to acute blood loss in horses. *Journal of Am Vet Med Assoc*; 229:1458–1462.

41. Mamak, N. and Aytekin, I. (2012): Blood Cell and Overview of studies in haematology. doi.org/10.5772/48332. http://www.intechopen.com/books/blood-cell-an-overview-of-studies-inhematology/principles-of-bloodtransfusion, Accessed on 27 08-2017.

42. Mc-Clure Blackmer, J. (2003): Strategies for the prevention of neonatal isoerythrolysis in horses and mules. Equine vet Educ Manual 6: 6–10.

43. Michael, M.A., Masry, H., Khan, B.R., and Das, M.K. (2007): Electrocardiographic signs of

remote myocardial infarction. *Journal of Prog Cardiovasc Dis*, 50:198–208.

44. Mudge, M.C., MacDonald, M., Owens, S. and Tablin, F. (2004): Comparison of 4 blood storage methods in a protocol for equine preoperative autologous donation. *Journal of Vet Surg,* 33(5):475-486. 36

45. Mudge.M..C. (2010): Blood Transfusion in Large Animals. In: Weiss, D.J, and Wardrop, K.J. (Eds.): Schalm''s Veterinary Hematology. 6th ed. USA: Blackwell Publishing Ltd. Pp.757-762.

46. Niinisto, K., Raekallio, M. and Sankari, S. (2008): Storage of equine red blood cells as a concentrate. *Journal of the Veterinary*, 176:227–231.

47. Polkes AC (2003) Neonatal Isoerythrolysis: overview, management strategies and longterm outcome. ACVIM Forum Proceedings 21: 248–50.

48. Polkes, A.C., Giguere. S., Lester, G., and Bain, F. (2008): Factors associated with outcome in foals with neonatal isoerythrolysis (72) Cases, (1998-2003). *Journal of Vet Intern Med* 22(5):1216-1222.

49. Roux, F.A., Deschamps, J.Y., Blais, M.C., Welsh, D.M., Delaforcade- Buress, A.M. and Rozanski, E.A., (2008): Multiple red cell transfusions in 27 cats (2003–2006): indications, complications and outcomes. *Journal of Feline Med Surg*, 10:213–218.

50. Sellon, D.C. (2004): Disorders of the hematopoietic system. In: Reed, S.M., Bayly. W.M. and Sellon, D.C. (Eds): Equine Internal Medicine. 2nd ed. St. Louis Elsevier, Pp. 728-742.

51. Snyder, E.L. and Rinder, H.M. (2003): Platelet storage-time to come in from the cold. *N. Engl. Journal of Med*., 348:2032–2033.

52. Sousa, R.S., Minervino, A.H.H., Araújo, C.A.S.C., Rodrigues, F.A.L.M., Oliveira,F.L.C., Mori,C.S., Zaminhan, J.L.R., Moreira, T.R., Sousa, I.K.F., Ortolani, E.L. and Júnior, R.A.B. (2014): Clinical Response and Transfusion Reactions of Sheep Subjected to Single Homologous Blood Transfusion. In: Blanco, B.S., (Eds). Hindawi Publishing Corporatio. Pp, 1-7.

53. Stieger, K., Palos, H., Giger, U., (2005): Comparison of various blood typing methods for the feline AB blood group system. *Journal of Am Vet Res*, 66(8):1393-1399.

54. Susan, M. (2016): Blood Typing. In: the Merck veterinary manual. Available at http://www.merckvetmanual.com/circulatorysystem/bloodgroupsandbloodtransfusions/bloodtyping. Accessed on 5/8/2017.

55. Wardrop, K. (2008): Transfusion medicine. In: Morgan, R.V. (Ed.), Handbook of Small Animal Practice. 5th ed. Saunders Elsevier, St. Louis, USA, Pp. 707-713. 37

56. Wardrop, K.J., Reine, N., Birkenheuer, A., Hale, A. and Hohenhaus, A. (2005) Canine and feline blood donor screening for infectious disease. *Journal of Vet Intern Med,* 19(1): 135-142.

57. Weingart, C., Giger, U. & Kohn B. (2004): Whole blood transfusions in 91 cats: a clinical evaluation. *Journal of Feline Medicine and Surgery*, 6(3): 139–148.

58. Weinstein, N.M., Blais, M.C. Harris, K., Oakley, D., and Aronson L (2007): A newly recognized blood group in domestic shorthair cats: the mik red cell antigen. *Journal of vet intern med,* 21(2): 287-292.

59. Whiting. J.L. (2003): Current Therapy in Equine Medicine 5th ed. Elselvier Publishing, Pp. 636–40.

60. Wilkins, P. (2004): Disorders of foals. In: Reed, S.M. & Bayly, W.M. (Eds.), Equine Internal Medicine. (2nd edn), Saunders Elsevier, St. Louis, USA, Pp. 1402-1431.

61. Wilson, E.M., Holcombe, S.J., Lamar, A., Hauptman, J.G. and Brooks, M.B. (2009): Incidence of Transfusion Reactions and Retention of Procoagulant and Anticoagulant Factor Activities in Equine Plasma. *Journal of Vet Intern Med*, 23:323–328.

62. Yamamoto, F.M. (2001): Molecular genetic basis of porcine histo-blood group AO system. *Journal of Blood,* 97:3308 –3310.

63. Zambelli, A.B. and, Leisewitz, A.L. (2009): A prospective, randomized comparison of Oxyglobin (HB-200) and packed red blood cell transfusion for canine babesiosis. *Journal of Veterinary Emergency and Critical Care*. 19(1):102-112.

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