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COMPLICATIONS OF BLOOD TRANSFUSION AND MANAGEMENT: DEFINITIONS AND HISTORY OF BLOOD GROUP SYSTEMS

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ABSTRACT: *International Society of Blood Transfusion recently recognized thirty-three (33) blood group systems. Apart from ABO and Rhesus system, many other types of antigens have been noticed on the red cell membranes. Blood grouping and cross-matching is one of the few important tests that the anaesthesiologist orders during perioperative period. Therefore, a proper understanding of the blood group system, their clinical significance, typing and cross-matching tests and current perspective are of paramount importance to prevent transfusion-related complications. Nevertheless, the knowledge on blood group system is necessary to approach blood group-linked diseases which are still at the stage of research. This review addresses all these aspects of the blood groups system.*

KEYWORDS: ABO blood groups, antibody typing, blood group system, Rhesus blood group screening.

INTRODUCTION

A blood group system is defined as a group of antigens that encoded by alleles at a single gene locus or at gene loci so closely linked that cross over and is very rare (Daniel, 2016). An antigen collection is a group of antigens that are phenotypically, biochemically or genetically related, but the genes bring them together have not been identified (Reid, 2017). Placement of a blood group antigen into a system or collection follows a natural progression (Anstee, 2011). Sometimes an antibody is discovered, usually in the serum of a pregnant woman that has two or more pregnancies or a woman that has multiple transfusions and is found to have unique pattern of reactivity (Enosolease, 2008). By the use of traditional serological methods, antibody can be used to study basic biochemical properties of the corresponding antigen, in order to enable recognition of the pattern of inheritance of the antigen in families and populations, to identify red blood cells (RBCs) that lack the antigen and to search for an antithetical antigen. A newly recognized antigen can be evaluated by the use of biochemical and molecular genetics methods (Dean, 2017). Identified characteristics, such as prevalence of positive reactions or sensitivity or resistance of specific enzymes are compared to known systems and collections (Miller, 2010). Red blood cells (RBC) blood group antigens are

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inherited carbohydrate or protein structures located on the outside surface of the RBC membrane (Logberg, 2011). Almost all of the protein group antigens are carried on integral transmembrane proteins; but, few are carried on glycosyl phosphatidylinositol (GPL) linked proteins (Anstee, 2018). Some of the antigens are in form of carbohydrates attached to proteins or lipids, some are require a combination of a specific portion of protein and carbohydrates but, few of the antigens are carried on proteins that are adsorbed from the plasma (Denomme, 2016). Some of the transmembrane proteins interact with other transmembrane proteins Rhesus (Rh) and Rhesus antigen (RhAg), lipids and proteins in the membrane skeleton for example band 3, ankyrin and glycophorin C (GPC) (Owen, 2018). Most of the components of blood group carrying antigens are assigned different numbers in cluster (Daniels, 2016). In human blood grouping system, agglutination of red blood cells (RBCs) indicate the type of blood group of the person, the ability of detecting and identifying blood group antigens and antibodies has been contributed to safe blood transfusion practices and have reduce the numbers of death from blood transfusion (Daniels, 2016).

ABO BLOOD GROUP SYSTEM

The ABO blood group system was the first system blood group system that was identified and remains the most significant used for transfusion medicine (Golassa, 2017). A wrong transfusion of ABO blood group will lead to a death of the recipient, this may occur because antibody A and antibody B are usually present on the blood of adults lacking the corresponding antibodies. These antibodies are stimulated by the ubiquitous distribution of the antigen that forms part of the membrane structure of many bacteria, plants and animals (Agarwal, 2013). As a result of this problem all blood donors has to be tested for blood group before donation, the four main ABO blood groups are blood group A, B, AB and O, there is no antigen A and B on the surface of blood group O (Kobayashi, 2017). The sugars defining A and B antigens are added to carbohydrate chains carrying the H antigen (fucose) and it is "hidden" by the A or B sugar. Thus group A or B erythrocytes happen to have smaller antigen than group O cells, still H antigen is present on every human erythrocytes except those individuals with (Bombay) phenotype (Agarwal, 2013). Transfusion of incompatible ABO blood group can cause intravascular haemolysis to the recipient this is because antigen A and B are expressed on most tissue cells (Zhang, 2012). ABO compatibility is a significant consideration in solid organ transplantation; however ABO incompatibility mostly causes clinical haemolytic disease of the new born (HDN) this is because antibodies directed against antigen A and B are predominantly immunoglobulin (IgM) which does not cross placenta, because antigen A and B are not fully developed on red blood cells (RBCs) from the fetus (Eweidah, 2018).

ABO blood group system has only four phenotypes and more than ninety (90) alleles have been identified by DNA analyses. The ABO gene was cloned in 1990 following purification of A transferase (Miller, 2016). A and B transferase have only four amino acid differences in the catalytic domain two out of four amino acid are primarily responsible for substrate specificity (Ammaria, 2017). Group O phenotype result from mutations in A or B alleles that causes loss of glycosyltransferase activity, the most common group O result from a single nucleotide deletion near the 5' end of the gene that causes a frame shift and early termination with no active enzyme

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production (Logdberg, 2017). The ABO gene have exons and A and B subgroups with only small exceptions result from a variety of mutations in exon 7 that cause alteration in the catalytic domain of the glycosyltransferases (Rao, 2016). AB phenotype expresses both A and B antigens results from variant glycosyltransferases that have a combination of A and B specific residues. In addition to single point mutation, recombination and gene rearrangements can result in hybrids with unexpected activity transferase, this makes ABO typing by DNA analysis difficult to interpret (Eweidah, 2018).

RHESUS BLOOD GROUP SYSTEM:

The Rhesus blood group system is the second most important blood group in transfusion medicine because antigen positive red blood cells (RBCs) frequently immunize antigen negative individuals through transfusion and pregnancy (Golassa, 2017). Inheritance of Rhesus antigens is determined by a complex of two closely linked genes: one encodes the protein carrying D antigen (Rhesus D); the other encodes the protein carrying C or c and E or e antigen (Rhesus CE) (EL Wafi, 2016). Red blood cells (RBCs) from Rhesus positive people have both Rhesus D and Rhesus CE, where as Rhesus negative red blood cells (RBCs) have only Rhesus CE. In the Rhesus system eight common antigen combinations or haplotypes are possible Dce (Ro, Rho), DCe (R1, Rh1), DcE (R2, Rh2), DCE (Rz, Rz), ce (r,rh), cE (r", hr"). The letter ''d'' is commonly used to designate the lack of D, but there is no d antigen or anti-d (Wagner, 2016).

Different nomenclatures can be used to describe Rhesus genes and antigens. The Fisher Race nomenclature which uses Rhesus designations is favoured for haplotypes and gene complexes and the Rosen field and Rubinstein nomenclature which uses numerical designations was introduced to allow analyses without bias (Weiner, 2016). The Rhesus blood group system has 48 antigens and ABO blood group system has four (4) antigens (Denomme, 2016). The most important and immunogenic antigen is antigen D Rhesus o (Rho) weiner terminology, referring to Weiner's discovery that a Rhesus monkey injected wiyh human red blood cells (RBCs) would produce antibody that agglutinated 85% of blood cells from New York people (Owen, 2018). For most clinical purposes, testing individuals for the D antigen and classifying them as Rhesus D positive and those that didn't antigen D is tested as Rhesus D Negative, approximately 85% of the Caucasian population are Rhesus D positive and 15% are Rhesus D Negative (Mack, 2016). Every Rhesus Negative recipients produce antigen D if they receive Rhesus D positive blood and this can cause haemolysis in an individual following transfusion of Rhesus D positive blood and it will cause haemolytic disease of the new born (HDN) if antibodies were raised in the form of transfusion or pregnancy (Urbaniak, 2017). The risk of antigen D sensitization by transfusion is eliminated by cross matching and the risk of sensitization in pregnancy is minimized by passive immunization of mothers at risk against antigen D therefore, donors and recipients are routinely typed and cross matched for antigen D (Touinssi, 2018).

The antigens C, c, E and e are less immunogenic and become important in patient care only after the corresponding antibody develops or when the basic Rhesus haplotype must be determined (Avent, 2016). The remaining forty (40) positive antigens are other Rhesus protein epitopes whose

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corresponding antigen is rarely encountered; some are encoded by diverse Rhesus alleles and appear as antithetical antigens to C, c or e as related "extra" antigens (Cantan, 2018). Others compound specificities include Ce (rh), cE, CE, V (ce5) and Ce5, still some Rhesus antigens are related to the complex "mosaic" nature of D and e antigens. If immunized, individuals who lack a part of the D or e and make antibody to the portion they lack can present with challenging serologic picture for example, the antigen D positive person who lacks part of the D epitope and makes an antibody to the missing portion appears to make alloantibody D because normal antigen D positive red blood cells (RBCs) carry all antigen D epitope and form an antibody to the missing portion appears to make alloantibody D this is because normal antigen D positive carry all antigen D epitopes (Scott, 2016). Some of the individuals who lack part of the antigen D or have weak expression of antigen D on their red cells that can only detected by antiglobulin test, having a C gene in transposition to a D gene for example Dce/Ce or DCe/Ce genotypes also can weaken expression of antigen D in some individuals. The third type of weak D expression results from inheriting a D gene that encodes all epitopes of D, but in less than normal quantity (EL Wafi, 2016).

BLOOD TRANSFUSION:

The first person that brought about blood transfusion was Andreas Libavius from Italy in 1615; however the recorded successful blood transfusion was in 1666 by lower, who exsanguinated a dog almost completely before resuscitating the dog with blood from another dog (Reid, 2016). There are several attempts to transfuse human being with animal blood but failed until in 1818 when Blundell reported the first successful human blood transfusion (Yamamoto, 2017). The common factor in blood transfusion within the ABO system is the existence of naturally occurring antibodies, which means that the first choice of blood to be transfused for a patient should be a blood of the same ABO blood group and Rhesus blood group of the patient (Enosolease, 2008). In standard blood transfusion practice always avoid transfusing blood group O to those who are not blood group patient until after a standard cross matching with the patient serum this is because some of the blood group O contains dangerous immune antigen A and antigen B haemolysin (Eweidah, 2018). Process of blood selection for transfusion as shown in the table below

Patient's group	1st	2nd	3rd	4th
Group A	Group A	Group O	-	-
Group B	Group B	Group O	-	-
Group O	Group O	-	-	-
Group AB	Group AB	Group A	Group B	Groupp O

NB: When transfusing patient blood group AB start with blood group AB, blood group A, blood group B, blood group O.

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BLOOD GROUPING, CROSS- MATCHING AND COMPATIBILITY TESTING BEFORE TRANSFUSION:

To ensure that the donor's red cells survive for the expected length of time and function effectively in the circulation of the recipient, standard grouping and test to be performed in vitro for compatibility. The following grouping method and cross- matching have to be carried out on the recipients and donors blood.

1. Cell grouping in which the red cells are tested for antigen A and antigen B using anti- sera A, anti-sera B and Rhesus D.
2. Serum grouping (reverse grouping) in which the serum is tested for A antibodies and B antibodies using known A and B red cells.
3. Tile, micro-titre and tube grouping.
4. Cross-matching for compatibility before transfusion.

CELL AND SERUM GROUPING USING A TILE METHOD:

Anti-sera A	Anti-sera B	Blood cells A	Blood cells B	Rhesus D	Control	Blood groups
+	-	-	+	+	-	A Rh. D positive
-	+	+	-	-	-	B Rh.D Negative
+	+	-	-	+	-	AB Rh. D positive
-	-	+	+	-	-	O Rh. D Negative

Protocol:
+ = positive
- = Negative

COMPLICATIONS OF BLOOD TRANSFUSION:

In every blood transfusion services a standard have to design to make blood transfusion safe, in order to achieve a desire goal for saving lives without any complications as a result of blood transfusion reactions of various degrees (Miller, 2010). Atypical antibodies can develop reactions to foreign proteins that come across, for the fact that numbers of red cells as compared to those of leucocytes or platelets, antibodies to red cell antigens are more important and cause more severe reactions than those associated with leucocytes or platelets (Guilliams, 2016).

These are some that causes complications in blood transfusion:

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ACUTE HAEMOLYTIC TRANSFUSION REACTION (AHTR):

ABO in compatibility is the most common cause of acute haemolytic transfusion reaction. Antibodies against blood group antigens other than ABO can also cause acute haemolytic transfusion reaction (AHTR), mislabelling the recipient's pre- transfusion sample at collection and failure to match the intended recipient with the blood product immediately before transfusion are the usual causes (Daniel, 2010). Haemolysis is intravascular, causing haemoglobinuria with varying degrees of acute kidney injury and possibly disseminated intravascular coagulation (DIC). The severity of acute haemolytic transfusion depends on the degree of incompatibility, amount of blood given, rate of administration and integrity of the kidneys, liver and heart.

An acute phase usually develops within one hour of initiation of transfusion, but it may occur late during transfusion or immediately after transfusion. The patient may complain of discomfort and anxiety. Dyspnea, fever, chills, facial flushing and severe pain may occur more especially in the lumber area. Shock may develop, causing a rapid, feeble pulse; cold, clammy skin; low blood pressure; nausea and vomiting (Silver, 2017).

IMMUNOLOGICAL COMPLICATIONS:

a. Haemolytic transfusion reactions: This is the most serious issue that causes complications in blood transfusion resulting from interactions between antibodies in the recipient's plasma and surface antigens on donor's red blood cells, although more than 250 red blood cells group antigens have been described but differ in their potential in causing immunization, the ABO and Rhesus D blood groups account for the most of the reactions and of clinical significance (Urbaniak, 2017). Blood group antibodies are either naturally occurring or immune in origin. Naturally occurring antibodies are present in the plasma of individuals who lack the corresponding antigens. The most important are antigen A and antigen B, they belong to IgM class, immune antibodies develop after exposure to red blood cells expressing antigens which is not present on the red cells of an individual, this is as a result of previous blood transfusion or transplacental passage during pregnancy, they are mostly IgG in origin haemolytic transfusion reactions may either be immediate or delayed.

Immediate reactions: This will occur as a result of incompatibility between donor red blood cells antigen and recipient plasma antibody produces an antigen- antibody complex causing complement fixation, intravascular haemolysis and ultimately destruction of the transfused blood. The severity of the reaction depends on the recipient's antibody titre; severe reactions are cause as a result of ABO incompatibility and can be precipitated by transfused small quantities.

Delayed reactions: The donor red blood cells antigen-plasma antibody interaction responsible for this subset of transfusion reaction more commonly result from incompatibility with minor blood groups such as Rhesus and Kidd, on pre-transfusion antibody screening the patients will commonly test negative because their antibody titres are too low for detection (Kobayashi, 2018).

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GRAFT-VS-HOST DISEASE (GVHD):

Transfusion associated graft-host-disease and graft rejection is usually caused by transfusion of products containing immunocompetent lymphocytes to an immunocompromised host. The donor lymphocytes attack host tissues because host immune system cannot destroy donor lymphocytes. Graft-vs-host disease can occur occasionally in immunocompetent patients if they receive blood from a donor usually a close relative who is homozygous for a human leukocyte antigen (HLA) haplotype for which they are heterozygous. The recipients will present with fever, rash, vomiting, watery and bloody diarrhea, lymphadenopathy and pancytopenia as a result of bone marrow aplasia, Jaundice and elevated liver enzyme levels are also common. Graft-vs-host disease occurs within 4 to 30 days after transfusion and is diagnosed base on clinical suspicion and skin and bone marrow biopsies.

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD:

Although transfusion-associated circulatory overload is under recognized and under reported, recently it has been recognized as the most common cause of transfusion-related deaths. The high osmotic load of blood products draws volume into the intravascular space over the course of hours, which can cause transfusion-associated circulatory overload in susceptible patients for example those with cardiac or renal insufficiency. The patients should be observed if signs of heart failure occur, the transfusion should stopped and the patient is to given a treatment for heart failure with a diuretic such as furosemide 20 to 40 mg intravenous (IV).

COMPLICATIONS OF MASSIVE TRANSFUSION:

Massive transfusion this is a transfusion of blood greater than or equal to one pint of blood within 24 hours for example 10 pints in a 70 kg adult. When the patient receives standard resuscitation fluids of packed red blood cells colloid plus crystalloid (Ringer's lactate or normal saline)in such large volume, the plasma clotting and platelets are diluted, causing a coagulopathy (dilutional coagulopathy). This coagulopathy worsens the consumptive coagulopathy due to major trauma that is, as a result of extensive activation of the clotting cascade and can leads to a deadly triad of acidosis, hypothermia and bleeding.

Although recently protocols for massive transfusion of blood have been written in which fresh frozen plasma and platelets are given earlier in resuscitation before coagulopathy occurs. Such protocols have been shown to decrease mortality. Recent trial showed no significant mortality difference between giving one pint of plasma and one pint platelet concentrate to two pints of red blood cells versus giving one pint of plasma and one pint of platelet concentrate to one pint of red blood cells (Holcomb, 2015).

ALLERGIC TRANSFUSION REACTIONS:

Allergic reactions to unforeseen component in donor blood are common, usually due to allergens in donor plasma or less often to antibodies from an allergic donor. These reactions mostly are mild and include urticaria, edema, occasional dizziness and headache during or immediately after the

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transfusion. Sometimes anaphylaxis occurs more especially in recipients with IgA-deficiency. In a patient with a history of allergies or an allergic transfusion reaction, a histamine maybe given prophylacically before or at the administering the transfusion for example diphenhydramine 50 mg intravenous (IV), if the allergic reaction occurs the transfusion should stopped, an antihistamine for example diphenhydramine 50 mg IV mostly controls mild urtcaria and itching and transfusion may resumed. However, a moderate allergic reaction generalized urticaria or mild bronchospasm also requires hydrocortisone 100 to 200 mg IV and a svere anaphylactic reaction requires additional treatment with epinephrine 0.5 mL of 1:1000 solution sc and 0.9% saline IV along with investigation by the blood bank.

INFECTIOUS COMPLICATIONS:

i. Transmitted Transfusion Infectious (TTIs) in another word viral complications in blood transfusions: The incidence of transfusion related viral infection has greatly reduced since the mid 1980s when pre-donation questionnaires to identify groups with high risk behaviour was implemented, since then the intended donors have to be screened for hepatitis B, hepatitis C, HIV 1 and 2, syphilis. However, disease transmission may occur in the window period that is the time after infection and the person have tested negative.

ii. Bacterial complication: Bacterial contamination of blood components is an infrequent complication of transfusion, however, if it occurs the potential for fulminant sepsis in the recipient is associated with high mortality. This is as a result from contamination during blood collection from the donor, symptom occur during or shortly after transfusion of the contaminated blood and these include high fever, rigors, erythema and cardiovascular collapse. There are no screening tests currently available for detection of bacterial contamination therefore visual inspection of the bag before transfusion is important, contaminated bags may seem usually in colour or contain gas bubbles. Diagnosis rest with culture of the same organism from both the patient and the blood from the bag.

iii. Parasitic complications: plasmodium falciparum is one of the most dangerous of the malarial parasites and is the most commonly encountered one. Unexplained fever after transfusion maybe as a result of blood from such donors and the affected recipients should be treated with anti- malaria, other species of malaria parasites are plasmodium vivax, plasmodium ovale and plasmodium maleriae. Since these parasites are specifically affect red cells it can also contaminate blood components such as platelets, they can also be transmitted through platelets transfusion (Novotna, 2008).

MANAGEMENT OF COMPLICATIONS IN BLOOD TRANSFUSION:

1. Medical officers prescribing transfusion should carefully select patients who will benefit from transfusion therapy according to established criteria. Document the indication for transfusion in the medical record.

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2. Patients should be monitored closely especially at the beginning of the transfusion.
3. Staff should follow hospital procedures for the collection of pre transfusion samples and for blood administration and adhere to all steps in the process.
4. The patient and relatives should be informed of the possible adverse effects that may occur.
5. Stop the transfusion if there is sign for transfusion reaction.
6. Check vital signs and rapid review if indicated and continue to take vital signs as possible.
7. Check if the right pack has been given to the right patient.
8. Immediately notify medical laboratory scientist in charge of blood bank to consult with haematologist whether to continue with the transfusion.
9. The reacting blood bag unit, urine of the patient, pre- transfusion sample and post-transfusion sample should send to the blood bank for necessary test to be carried out.

SUMMARY

Currently, our knowledge on blood groups goes beyond the usual tests of agglutination and transfusion to the better understanding of red blood cell antigens in light of their association with multiple diseases and the scope of use of this knowledge to modulate the disease processes. In this context, the role of adequate understanding of screening, typing and cross-matching apart from awareness on evolving trends, for every clinician, may not be overemphasized.

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