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TRANSFUSION PRACTICES IN OBSTETRICS AND GYNAECOLOGY

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ABSTRACT Blood transfusion plays a vital role in Obstetrics and Gynaecology and appropriate transfusion practices can prove as a boon to patient with minimal adverse reactions. Several diseases in obstetrics like, Obstetric haemorrhage, especially postpartum haemorrhage and antepartum haemorrhage, severe anaemia, ectopic pregnancy, molar pregnancy requires immediate transfusion of blood to reduce maternal mortality. In gynaecological practice, certain conditions like fibroids, cervical cancer, endometrium cancer, ovarian cancer, hysterectomy requires transfusion of blood mostly to recover operative loss of blood. Written informed consent and pre-transfusion testing is very important before start of transfusion. For this purpose, role of transfusion medicine specialist is equally important e.g. from the selecting of appropriate blood and blood components to the pre-transfusion testing and antibody screening of patient's sample. Though, blood transfusion is a lifesaving process in critical conditions but it is not without side effects and risks. Therefore, some strategies have been designed to avoid blood transfusion. In conclusion, we can say that before every transfusion risk benefit ratio must be kept in mind and appropriate transfusion practices should be adopted for every blood transfusion.

KEYWORDS : Obstetric haemorrhage, Pre transfusion testing, Feto-maternal haemorrhage, Transfusion transmitted infection, Iron-deficiency anaemia, Recombinant factor VIIa (rFVIIa), Acute normovolemic haemodilution, Intraoperative cell salvage.

INTRODUCTION:

Blood transfusion is an integral part of patient management in Obstetrics and Gynaecology. Blood transfusion is performed as a lifesaving measure to replace blood cells or blood components lost through bleeding. Postpartum haemorrhage is a condition which accounts for 25% of all pregnancy-related deaths [1]. Various pregnancy complications and disorders of labor present as risk factors for extra blood loss during pregnancy and cause severe hemodynamic instability. This along with complications due to abortion and ruptured ectopic pregnancy show up as conditions needing transfusion in the day-to-day practice of obstetrics. The rates for transfusion vary at different centres and show regional variation, different practices at different hospitals and different clinicians [2-3].

Blood transfusion must be done only after due diligence to the situation and adhering to guidelines. All possible strategies to be applied to minimize transfusion in patients to reduce the risk of transfusion transmitted infection (TTI). The decision to perform blood transfusion should be made on both clinical and haematological grounds. The necessity of blood transfusion arises at the time when haemoglobin falls down to 6 gm% and it is rarely required when haemoglobin is more than 10 gm%. Clinical evaluation of the patients is necessary to estimate the need for blood transfusion because some patients with acute haemorrhage can have normal haemoglobin [4,5]. Obstetric and gynaecologic conditions associated with the need for blood transfusion often leads to morbidity and mortality, hence, strategies should be implemented to increase the haemoglobin level at delivery and decrease the blood loss. In this review we have focused on diseases that require transfusion in obstetrics and gynaecology. We have also highlighted the importance of informed consent, pre transfusion testing, risk associated with blood transfusion and strategy to minimize blood transfusion.

DATA SOURCES:

MEDLINE database (http.ncbi.nlm.nih.gov/PubMed/) were used to conduct a simple literature search to identify relevant articles according to the subject of the review article from January 1997 to December 2019. Inclusion criteria were original articles, review articles, case series and case reports published in English were taken in the study. Exclusion criteria were article published in language other than English and commentary and letter to editors were not taken.

Diseases that require transfusion in Obstetrics and Gynaecology:

In the last decade with the advancement in medical and surgical treatment and the implementation of new and aggressive surgical and therapeutic methods with increasing number of oncology, and more referred cases from periphery, there is increase in the number of transfusions requiring large quantities of blood and blood products. Diseases in which blood transfusion is indicated can be divided in two broad groups: Diseases in Obstetric and Diseases in Gynaecology.

Diseases in Obstetric:

1. Anaemia in pregnancy
2. Abortions or ectopic pregnancy
3. Molar pregnancy
4. Obstetric haemorrhage (Antepartum, postpartum haemorrhage)
5. Caesarean delivery

6. Hepatic disorders and HELLP syndrome
7. Haematology Factor deficiency, all thrombocytopenia

Diseases in Gynaecology:

1. Fibroids – Myomectomy
2. Hysterectomy - AUB/ Prolapse/ Fibroids Adenomyosis/ Endometriosis/ PID
3. Abnormal Uterine Bleeding
4. Cancer cervix
5. Carcinoma endometrium
6. Carcinoma ovary

(A) Diseases in Obstetric:

1. Anaemia in pregnancy: Anaemia is one of the common causes of blood transfusion in pregnancy. According to WHO, anaemia in pregnancy is present when the haemoglobin concentration in the peripheral blood is 11g/100 ml or less [6]. Blood transfusion is usually needed to treat severe anaemia (Hb <7g %) in third trimester or women in labour and if any anaemic pregnant women presents with heart failure. Packed red cells should preferably be transfused slowly with administration of furosemide to maintain negative fluid balance. Blood transfusion is mostly required when the Hb is less than 70 g/l and it is rarely required when the Hb is more than 100 g/l.

2. Abortions or ectopic pregnancy: Abortion is the condition of extraction or expulsion of an embryo from its mother and when the fetus weight is less than or equal to 500 g, as it is not able to survive independently. Sometimes miscarriage can present with excessive bleeding, so it requires blood transfusion. Even ruptured ectopic pregnancy can be present with shock requiring blood transfusion. These are the conditions which may result in acute blood loss leading to haemodynamic instability. Packed cell transfusion can be lifesaving along with definitive treatment of the condition.

3. Molar pregnancy: It is an abnormal condition of the placenta where there are partly degenerative and partly proliferative changes in the young chorionic villi. Abnormal vaginal bleeding is the commonest presentation and it can complicate in to haemorrhagic shock. Blood transfusion is required if the anaemic patient present with excessive bleeding.

4. Obstetric haemorrhage (Antepartum, postpartum haemorrhage): Obstetric haemorrhage is most feared complication of pregnancy. It is also commonly associated with massive blood transfusion. It may be antepartum or postpartum haemorrhage. Antepartum haemorrhage is defined as bleeding from or into the genital tract after the 28th week of pregnancy but before the birth of the baby [7]. Two most common cause of antepartum haemorrhage are placenta previa and abruptio placenta. Postpartum haemorrhage (PPH) is defined as blood loss of greater than 500 ml following vaginal delivery and loss of 1500 ml following C section or blood loss sufficient to cause hypovolemia, a 10% drop in the haematocrit or requiring transfusion of blood products or any amount of bleeding following the birth of the baby which adversely affects the general condition of the patient evidenced by rise in pulse rate and falling blood pressure [8]. Complications like placenta previa, placenta abruption and PPH are associated with significant maternal morbidity and mortality. Major obstetrics hemorrhage is defined as blood loss of >1500 ml or a fall in hemoglobin of more than 4 g/dl after acute blood loss in a parturient or need transfusion of four or more units of blood [9]. In major obstetric hemorrhage, blood component management should follow a similar pathway as massive transfusion protocol in non-pregnant patient except that meticulous attention should be paid to fibrinogen levels and consideration given to the early use of fibrinogen supplementation when fibrinogen levels are <2 g/l [9]. Consideration should be given to using tranexamic acid. Massive transfusion protocol provides early access to red blood cells, plasma, and Platelets (6:4:1) for patients experiencing severe postpartum hemorrhage [10].

5. Caesarean delivery: It is an operative procedure whereby the fetus after the end of 28th weeks are delivered through an incision on the abdominal and uterine walls. The incidence of caesarean section is steadily rising. Caesarean delivery is performed when labour is contraindicated and vaginal delivery is not possible. Blood is usually kept ready if patient is anaemic or bleeding is anticipated.

6. Hepatic disorders and HELLP syndrome: HELLP syndrome is an acronym of Haemolysis (H), Elevated Liver Enzyme (EL) and Low Platelet count (LP). This is a rare complication of preeclampsia. Platelet transfusion should be given if platelet count less than 50,000/ ul and blood transfusion is required during caesarean section or excessive bleeding during delivery due to thrombocytopenia.

7. Haematology Factor deficiency, all thrombocytopenia: Coagulation factor deficiency and thrombocytopenia in pregnancy due to any cause should be treated by fresh frozen plasma (FFP) and platelet concentrate (PC) respectively.

(B) Diseases in Gynaecology:

1. Fibroids – Myomectomy: Abnormal uterine bleeding due to fibroids may result into anaemic state. Fibroids are the most common benign solid tumours in females. Myomectomy is the enucleation of myomata from the uterus leaving behind a potentially functioning organ capable of future reproduction. In some cases, if the patient is having severe anaemia and heavy bleeding during fibroid surgery, blood transfusion is needed.

2. Hysterectomy - AUB/ Prolapse/ Fibroids Adenomyosis/ Endometriosis/ PID: Hysterectomy is the surgical removal of the uterus. A history of abnormal uterine bleeding and haemoglobin level should be identified to anticipate requirement of blood transfusion pre or post operatively.

3. Abnormal Uterine Bleeding: Abnormal uterine bleeding can be defined as any uterine bleeding outside the normal volume, duration, regularity or frequency. This is a common problem among women in the reproductive age group which includes oligomenorrhoea, polymenorrhoea, hypomenorrhoea, menorrhagia, metrorrhagia and dysfunctional uterine bleeding. Some emergency conditions like acute uterine bleeding, may necessitates immediate treatment to decrease the risk of anaemia for which blood transfusion is required.

4. Cancer cervix: Cervical cancer is one of the common gynaecological malignancy. The most common symptom of cervical cancer is irregular vaginal bleeding and deep pelvic pain. And the management of cervical cancer can be surgery and radiation therapy. Radical hysterectomy which is performed as a surgical treatment of cancer cervix needs extensive dissection of surgical planes and may lead to increased blood loss sometimes, requiring blood transfusion.

5. Carcinoma endometrium: Endometrial cancer mostly affects women in the post-menopausal age group (peak incidence occurs from 55 to 70 years). Endometrial cancer is a cancer that arises from the endometrium (the lining of the uterus or womb). The most initial sign is irregular vaginal bleeding not associated with a menstrual period. In the vast majority of cases, diagnosis of endometrial cancer does not necessitate immediate treatment but some patients present with heavy bleeding and anaemia require transfusion.

6. Carcinoma ovary: Ovarian cancer has emerged as one of the commonest malignancies affecting women in India. The risk of ovarian cancer is high in women who never had children, those who begin ovulation at a younger age and those who reach menopause at an older age. The treatment of ovarian carcinoma include surgery, chemotherapy, radiation therapy, hormonal therapy and immunotherapy. Tranexamic

acid can be administered prior to surgery to reduce the need for blood transfusions due to blood loss during the surgery. Blood transfusions have been associated with worse survival in ovarian cancer patients.

General principles of blood transfusion in Obstetrics and Gynaecology:

(A) Consent for blood transfusion: Blood and blood components are categorized as 'drug', as per the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945, therein as amended from time to time [11]. A written valid consent should be taken before administering a blood or blood components. It is a regulatory requirement. Valid consent requires the provision of information to patient about risks and benefits along with alternatives available, with clear documentation in the clinical records. Written consent should be taken in the language of patient or patient's attendant understands best only after providing information. For minors and unconscious patients, the next of kin should sign the informed consent. In the clinical records of the patient, the decision process leading to transfusion including indication for transfusion and obtaining valid consent should be documented. As there are some evidences showing that, when the indication leading for blood transfusion is documented there is a lower rate of inappropriate transfusion. Ideally consent form should be available in the patient's file itself. In one of the judiciary verdict it was mentioned that blood transfusion without consent is assault.

(B) Requirements of blood grouping, antibody screening and cross-matching: Blood group and antibody status of all the pregnant women should be checked at booking and at 28 weeks of gestation [12]. Maternal red cell antibodies are relatively common in some pregnant women which may cause haemolytic disease of the fetus and new-born (HDFN) and will also have implications for the selection of blood for transfusion in the mother to avoid the risk of haemolytic transfusion reactions. If red cell antibodies are detected in the booking sample of any pregnant female, further testing of maternal blood should be performed to determine the specificity and the titer of antibodies to assess the likelihood of HDFN [13]. Maternal red blood cell alloimmunization results from the production of immunoglobulin G (IgG) maternal antibodies against erythrocyte surface antigen that she lacks (primary immune response). Immunization is most often secondary to fetal-maternal haemorrhage and more rarely to transfusion [14]. Some particular situations, such as miscarriage, abortion, trauma, invasive prenatal diagnosis, childbirth, may contribute to fetal-maternal haemorrhage (FMH) but FMH may also occur spontaneously. On re-exposure to antigen, usually during a subsequent pregnancy, a secondary immune response occurs with rapid synthesis of IgG antibodies. IgG antibodies cross the placental barrier, bind to the fetal red blood cells – if they have the corresponding antigen – and are therefore responsible for progressive fetal haemolytic anaemia. HDFN is associated with more than 50 red cell antigens however most common antigens are RhD, Kell and Rhc. Some other antibodies also associated with severe HDFN but lesser frequency e.g. anti-Rh-e/E (Rhesus), Kidd (Jka), Fy(a)/Fy(b) (Duffy blood group), and anti-M (MNS system) [15,16].

(C) Selection of blood in pregnancy: Reproductive women or pregnant women with Rh D negative blood group must receive only Rh D negative blood to avoid the risk of Rh D alloimmunisation [17]. Similarly, unless a woman is known to be K positive, only K-negative blood should be used for transfusion in reproductive women [17]. All of the major obstetric haemorrhage protocols must include the provision of emergency blood with immediate issue of group O, Rh D-negative and K-negative units, with a switch to group-specific blood as soon as feasible [18]. The aim of antibody screening is to identify the presence of atypical red cell antibodies of likely clinical significance. In case, antibody screen is positive, further testing is required to detect the relevant antibody or antibodies and red cell units must be selected negative for the relevant antigen for cross-matching [17].

Blood, blood components and its uses:

In India blood and blood components intended for transfusion are routinely collected in anticoagulated whole blood either 450 ml or 350 ml blood bags. Most commonly used anticoagulant is CPDA 1 (citrate phosphate dextrose adenine). By using CPDA blood bags we can store PRBC up to 35 days. CPDA is called anticoagulant preservative solution. 49ml and 63 ml of anticoagulant preservative is required for 350ml and 450 ml of whole blood respectively. By using additive solution, we can extend self-life of PRBC up to 42 days. SAGM (saline, adenine, glucose, mannitol) most commonly used additive solution for PRBC in blood bank. Donated whole blood can be separated in blood components: packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelet concentrate (PC), cryoprecipitate. There are many other modifications of blood components e.g. SAGM PRBCs, Leucoreduced PRBCs, irradiated PRBCs, washed PRBCs, pool platelets. Component is separated on principal of differential centrifugation and different specific gravities of blood components. Advantage of component separation is that one blood donation can be used in multiple patients depending on the need of the patient. Leucoreduced PRBCs is used to prevent HLA alloimmunization, prevention of cytomegalo virus (CMV) transmission and prevention of febrile non haemolytic transfusion reaction (FNHTR). Leucoreduced and irradiated PRBCs is used in intra uterine blood transfusion (IUTs). Now a day's apheresis technology is used for the collection of specific components. By apheresis technology we can collect PRBCs, plasma, apheresis platelet, granulocytes and stem cells. Single donor apheresis platelet (SDAP) contains equal to at least 6 units of random donor platelets.

Risk Associated with blood transfusion:

Transfusion of blood has decreased from last many years as blood for transfusion is a limited, costly resource, and its use has specific risks [19]. 1% of all transfusions cause an immediate and delayed adverse reaction, despite the measures taken to reduce risks [20]. Internationally, this has led to increased efforts to reduce unnecessary blood use across many disciplines. Innovation of better pharmacological, surgical and mechanical techniques, to reduce blood loss and iron supplementation for high risk people has also affected blood transfusion practice in obstetrics and gynaecology [21]. Transfusion-transmitted infections or immunological sequelae such as red cell alloimmunisation may develops in recipients after transfusion. There is a risk of transmission of transfusion transmitted infection (TTI) like hepatitis B, hepatitis C, HIV, especially in centres where nucleic acid test (NAT) testing is not available [22].

There are some major and minor side effects of blood transfusion: Minor side effects include headache, fever, rash or itchiness. Major side effects like difficulty in breathing, severe headache, low blood pressure which can be life-threatening. These side effects are called transfusion reaction which can be acute or delayed and immunological or non-immunological. Acute transfusion reaction can be haemolytic or non-haemolytic, allergic, transfusion-related acute lung injury (TRALI). Delayed transfusion reaction can be alloimmunization, graft versus host disease (GVHD), post transfusion purpura, delayed haemolytic transfusion reaction. Major obstetric haemorrhage where massive transfusion is required, are associated with multiple complications. These complications include: [23]

- Hypothermia
- Hyperkalaemia – electrolyte imbalance involving low potassium levels

- Hypocalcaemia – decreased calcium levels
- Dilutional coagulopathy– clotting factors are diluted leading to weakened or impaired coagulation
- Acidosis-
- 2, 3-DPG depletion – depletion of a blood component that regulates how easily oxygen is moved from haemoglobin into tissue
- Jaundice
- Infection
- Alloimmunization
- Immunosuppression
- Transfusion Reactions

Strategies to minimise blood transfusion:

1. Detection of anaemia and its treatment:

A complete blood count (CBC) be obtained to screen for anaemia at booking and at 28weeks, as well as at any time during pregnancy if symptoms of anaemia are present. In a woman with microcytic or normocytic anaemia, iron deficiency (ID) should be confirmed by a trial of oral iron or serum iron studies.

Oral Iron: Oral iron is given in prevention as well as treatment of iron deficiency anaemia. Iron is best absorbed in the ferrous form through oral tablets or capsules or syrup and dietary iron like red meat, fish and poultry. Some rich sources of dietary iron provide haem iron that is more easily absorbed than non-haem iron. Absorption of non-haem iron is boosted with Vitamin C, whereas tea and coffee inhibit iron absorption from food [24]. In areas with a high prevalence of anaemia in pregnancy, daily administration of 200 mg of ferrous sulphate (containing 60mg of elemental iron) along with 1mg folic acid supplementation should be given as part of routine antenatal care to reduce the risk of maternal anaemia and infant low birthweight [25]. For the treatment of mild to moderate iron-deficiency anaemia (IDA) (Hb≥8 g/dl) in early pregnancy (first and second trimesters) oral ferrous iron (80–100mg/day elemental iron) and folic acid (400 µg/day) should be given. Once the Hb concentration is in the normal range, we recommend that iron supplementation be continued for at least three months to replenish iron stores. According to Cochrane review of studies on comparison of iron supplementation with no iron or placebo found that iron supplementation decreased the incidence of low birthweight babies and prevented maternal anaemia and iron deficiency anaemia [26]. Another Cochrane review comparing intermittent versus daily iron supplementation showed that intermittent supplementation produced a similar risk of anaemia at term, prematurity and low birth weight babies, but was associated with fewer side effects [27].

Iron infusion: Iron infusion is a procedure in which iron is delivered to body intravenously. This method of delivering medication is also known as Intravenous (IV) iron infusion. It is needed to increase iron levels fast to avoid medical complications or blood transfusion. Intravenous (IV) iron infusion therapy offers a shorter duration of treatment and a quicker response than oral therapy [28]. Indications of IV iron infusion are intolerance to oral iron and severe anaemia in advance pregnancy. It is invasive and expensive to administer; though severe allergic reactions are even possible with all iron preparations. Intravenous iron therapy should only be administered when staff is well trained to evaluate and manage anaphylactic or anaphylactoid reactions, as well as resuscitation facilities, are available immediately.

2. Active management of obstetric haemorrhage:

Acute blood loss in obstetric hemorrhage may be due to placenta previa, abruptio placentae, post-partum hemorrhage or surgery related. Management involves a multidisciplinary approach involving obstetrics and gynaecology specialist, anaesthetist, transfusion medicine specialist and paediatrician. Active management of third stage of labour should be routinely followed in all labour wards. Atonic uterus to be managed by oxytocin, methergine, misoprostol and carboprost. Uterine tamponade and surgical methods should be followed if medical management fails. If the patients' blood group is not known , blood group O RhD-negative packed red cells are to be given.

3. Recombinant factor VIIa (rFVIIa) therapy:

Recombinant factor VIIa (rFVIIa) is required for the treatment of inherited bleeding disorders. Factor VIIa has a central role in initiating the process of blood coagulation. In the absence of FVIII and FIX, rFVIIa induces hemostasis likely by enhancing thrombin generation on activated platelet surfaces. At concentrations much higher than normal circulating concentrations mediate a tissue-factor-independent conversion of factor X to its activated form on a phospholipid surface. Dosing is typically 90 g/kg with repeated dosing every 2–3 hours until hemostasis is achieved followed by increasing intervals thereafter [29].

4. Fibrinogen concentrate therapy:

Fibrinogen is significant endogenic component of haemostasis, and its plasma level increases during pregnancy [30]. Coagulopathy and reduction in fibrinogen levels happens due to blood loss. Massive transfusion can itself result in dilutional coagulopathy in the treatment of haemorrhage. As a matter of fact, fibrinogen is the first coagulation factor to decrease to a critically low level during major blood loss and replacement with RBC [31]. Observational studies of patients with post-partum haemorrhage (PPH) reveals that a less fibrinogen concentration in the initial stage of post-partum haemorrhage (PPH) is linked with excessive bleeding and blood transfusion [32]. Fibrinogen concentration therapy as the first-line agent can reduce the risk of massive transfusion complications [33]. Fibrinogen levels should be maintained above 1g/L by the use of FFP or cryoprecipitate.

5. Antifibrinolytics:

The main antifibrinolytic agent used is tranexamic acid. Tranexamic acid is a synthetic derivative of the amino acid lysine that reversibly binds to the lysine-binding sites of the plasminogen molecule. In doing so, it prevents activation of plasminogen to plasmin, leading to inhibition of fibrinolysis. The CRASH-2 study showed that tranexamic acid reduces mortality in bleeding trauma patients without an increase in the rate of venous thromboembolism [34].

6. Management of preoperative anaemia:

Preoperative anaemia is the most important predictor of perioperative transfusion. Depending on the comorbidity, it is found in 5% to 75% of elective surgical patients. The mechanism of the anaemia is best elucidated and treated appropriately before any elective surgery. Treatment options:

a. Recombinant erythropoietin
b. Oral or intravenous iron.

7. Management of intraoperative and post-operative anaemia:

Acute normovolemic haemodilution (ANH) and autologous Blood Recovery and reinfusion are technique to manage intraoperative blood loss. ANH is the immediate preoperative removal of whole blood and its replacement with an acellular fluid (in general, a combination of crystalloid and colloid) in order to maintain a normovolemic state [35]. Potential benefits of ANH included a reduction of red cell loss, because the hematocrit of the blood shed during intraoperative procedures is less and it eliminate the need for allogeneic blood transfusion.

Intraoperative cell salvage (IOCS) is a technique used to decrease the need for blood transfusion. Intraoperative cell salvage (IOCS) is an efficacious technique for blood replacement in which red blood cells lost during surgery are recovered, washed and re-infused to the patient [36]. Cell salvage is indicated when anticipated intraoperative blood

loss 1 litre or 20% of blood volume, preoperative anaemia or increased risk factors for bleeding, patients with rare blood group or antibodies and patient refusal to receive allogeneic blood transfusion.

Traditionally, cell salvage has been avoided in the obstetric population because of the perceived risk of amniotic fluid embolism or induction of maternal alloimmunization. The available literature on the use of IOCS in obstetrics demonstrates that there is limited evidence to support or refute the use of IOCS at caesarean section [37,38].

CONCLUSION:

Blood transfusion is a lifesaving procedure in obstetrics and gynaecology, but few transfusions can cause immediate and delayed adverse reaction. Despite best measure to avoid blood transfusion, many diseases of obstetrics and gynaecology required blood transfusion. Data from estimation of blood requirement shows that out of 14 million of total clinical demand of blood, 22% (3 million) blood are required for obstetrics and gynaecology [39]. If measures are taken to reduce this utilization, both the pressure on resource allocation as well as the risks associated with allogenic transfusion could be reduced. In this review we highlighted diseases that require transfusion in obstetrics and gynaecology. Every transfusion is associated with few risks. In this regard a valid informed consent must be taken to safeguard our self. Role of transfusion medicine specialist is equally important e.g. from the selecting of appropriate blood and blood components to the pre transfusion testing and antibody screening of patient's sample. Every transfusion reaction should be reported to blood bank and a comprehensive work up should be done to find out the cause of reaction. So, in this review we could conclude that before every transfusion risk benefit ratio must be kept in mind and must focus on strategies to reduce blood transfusion.

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