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Review Article

Obstetrics and Gynaecology Section

Intrauterine Blood Transfusion for Haemolytic Disease of Foetus: Current Indications, Intrauterine Transfusion Methods, Complications and Outcome

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ABSTRACT

Foetal anaemia remains a serious complication in pregnancy which can lead to hydrops and perinatal death. It is important to detect it timely in order to prevent formation of hydrops and improve the long term outcome. Foetal anaemia can be successfully treated by Intrauterine Transfusion (IUT), if it occurs due to red cell alloimmunisation. Management involves a multidisciplinary approach involving foetal medicine specialist, transfusion medicine specialist, obstetrics and gynaecology specialist and paediatrician. This review article focuses on current IUT indications, methods, complications and outcome.

Keywords: Alloimmunisation, Blood modification, Foetal anaemia, Foetal therapy, Middle cerebral artery, Peak systolic velocity

INTRODUCTION

Intrauterine blood transfusion is considered to be the most successful treatment for foetal anaemia during pregnancy [1]. Haemolytic Disease of Foetus and New-born (HDFN) is still a serious complication during pregnancy and it is also associated with perinatal mortality and morbidity [2]. In 1960s, Liley AW introduced intrauterine treatment of foetal anaemia due to red cell alloimmunisation by percutaneous intraperitoneal transfusion [3,4]. In 1981, Rodeck Ch et al., described intravascular IUT into the umbilical cord, using the guidance of the needle by fetoscopy [5]. Ultrasound-guided cordocentesis and blood transfusion directly into the umbilical vein performed by Bang J and Daffos F et al., [6,7]. In 1990 Nicolini U et al., described first time IUT into the umbilical vein [8]. With the beginning of 1987, intravascular technique became the method of choice [9]. After that, IUT continued to be the keystone of treatment for foetal anaemia for a various cause.

HDFN is caused by the demolition of foetal or neonatal Red Blood Cells (RBCs) all through maternal RBC alloantibodies that are specific against the inherited paternal RBC alloantigen of the foetus and new-born. The primary prevention of HDFN includes the antenatal and postnatal administration of anti-D immunoglobulin for Rhesus (Rh) D-negative mothers, while secondary prevention is achieved via antenatal screening for Red Blood Cell (RBC) antibodies [10]. In skillful hands, IUT is consider to be a secure procedure. However, complications, even foetal loss, do still occur. The treatment of foetal anaemia using IUT has been associated with survival rates that exceed 90% in specialised centres [1,2,11]. In previous reviews of this topic [1,2] importance of transfusion specialist was not discussed. However, for the preparation of IUT blood, selection of blood, pre-transfusion testing, blood modification (leukoreduction and irradiation) and quality control is upmost important and which cannot be ensure without a transfusion medicine specialist. This review article, summarises IUT current indications, methods, complications and outcome.

DISCUSSION

Data Sources

MEDLINE database (http.ncbi.nlm.nih.gov/PubMed/) was used to conduct a simple literature search to identify relevant articles according to the subject of the review article from January 1961 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 articles published in language other than English and commentary and letter to editors were not taken.

Indications

IUT is indicated in moderate to severe foetal anaemia [2]. Foetal anaemia occurs due to various causes like degradation or haemolysis of normal red cells, impaired red cell production,

haemoglobinopathies and erythrocyte membrane or enzymatic disorders. Intrauterine blood transfusion should be considered in any foetal disease with severe anaemia. Foetal anaemia which occurs due to to red cell alloimmunisation remains the most common indication for intrauterine blood transfusion. In non-immune aetiology, such as human parvovirus B19 infection, Feto-Maternal Haemorrhage (FMH), twin-twin transfusion syndrome, placental/foetal tumours and other uncommon diseases success of IUT has been documented [1].

Now-a-days foetal anaemia is determined by serial Doppler determinations of the Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) [12,13]. MCA-PSV can be initiated as early as from 16 to 18 weeks of gestation. The reliability of MCA-PSV decreases after 35 weeks of gestation [14]. MCA-PSV is also very useful in detecting foetal anaemia in other cases like non-immune hydrops, FMH, chorioangioma, α-thalassemia and Monochorionic (MC) twins [15]. IUT should be performed if MCA-PSV Doppler exceeds 1.5 Multiples of the Median (MoM) and if signs of hydrops are present, as both correlates strongly with moderate to severe foetal anaemia [12].

Timing of subsequent IUTs can be done by calculating the expected decline in haematocrit and by MCA-PSV Doppler measurements [16]. In some centres further IUT were decided after assessing continuing foetal anaemia, shows by decrease of 0.3 g/dL per day from post-transfusion Hb following the second IUT procedure [17]. However, the degree of foetal anaemia, assessed by the Hb concentration in the pre-transfusion foetal blood sample is conclusive IUT indication. IUT should be performed in case of moderate to severe anaemia, usually defined as Hb concentrations of four to five standard deviations below mean/median for gestational age [18,19] or a Hb deficit of 5 g/dL or more [20]. In most centres foetal transfusions is performed only up to 35 weeks of gestation and delivered at 37-38 weeks of gestation. IUT treatment in late pregnancy is considered to be safer than procedures performed in early gestation [21]. Though, IUT procedure carries a risk of procedure-related complication like asphyxia, especially in a compromised foetus.

Red Cell Alloimmunisation: Maternal RBC alloimmunisation results from the production of immunoglobulin G (IgG) maternal antibodies against erythrocyte surface antigen that maternal lacks (primary immune response). Immunisation is most often secondary to foetal-maternal haemorrhage and more rarely to transfusion [22]. Some particular situations, such as miscarriage, abortion, trauma, invasive prenatal diagnosis and childbirth, may contribute to 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 foetal RBCs-if they have the corresponding antigen- and are therefore responsible for progressive foetal haemolytic anaemia. HDFN is associated with more than 50 red cell antigens however, most common antigens are Rh D, 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) [23,24]. Recently, a large follow-up study (LOTUS study) discovered alloimmunisation was due to RhD in 80%, Kell in 12% and Rhc in 5% of the cases [25]. In anti-Kell alloimmunisation, the mechanism leading to foetal consequences was more complex. Foetal haemolysis is worsened by direct inhibition of erythropoiesis by the anti-Kell antibodies [26]. Outcome can be improved by early detection and timely treatment. High survival rate confirms the success of IUT for alloimmune anaemia.

IUT Methods

In most of the centres, patient's obstetrics history was determined and any bad obstetric history, history of previous IUT or exchange transfusion and patient with known Rh D negative group is send to blood bank for antibody screening. In some higher centres, antibody screening is done for all antenatal women irrespective of the blood group. If antibody screening is found to be positive, then antibody identification and titre used to be done. If titre is found to be above the critical level, foetal MCA-PSV was measured. Positive titre of more than 1:16 was considered critical level when the foetus was at risk of anaemia [27]. IUT is typically designed, if the foetus had MCA-PSV values of ≥1.5 multiples of the median and/or signs of hydrops foetalis were found via ultrasonography. During IUT, cordocentesis is usually performed and blood is collected for haemoglobin, haematocrit and blood group-ABO and Rh. IUT used to be carried out at the same setting, if foetal Hb is less than 10gm% or haematocrit is less than 30. If there is foetal hydrops on ultrasound, the condition categorised as severe foetal anaemia requiring IUT [27].

Setting: IUTs can be operated using a 20-22-gauge needle under the guidance of ultrasound/Doppler in aseptic conditions [9,11,28].

Pre-medication: Paralytic agent administered intramuscularly (or intravenously) routinely before the IUT procedure to prevent movement of foetus during IUT and lower frequency of complications were reported when paralytic agent used before procedure [9,18]. Most commonly used paralytic agents are atracurium (0.4 mg/kg), vecuronium (0.1 mg/kg) or pancuronium (0.1 mg/kg) [29-31]. First-line paralytic agents are atracurium or vecuronium because of short half-life and give sufficient paralysis during IUT procedure. Furthermore, pancuronium is associated with several cardiovascular side effects [32].

Transfusion Volume: Rodeck CH et al., described a method to calculate transfusion volume [5], using estimated fetoplacental volume (V), foetal haematocrit in pre-transfusion sample (Ht1),

donor blood haematocrit (Ht2) and the aimed foetal haematocrit post transfusion (Ht3):

Transfusion volume = V (Ht3-Ht1)/Ht2

Calculations for computing the V are:

• 1.046+(ultrasound estimated foetal weight in grams) x 0.14 [33]

• 0.1 mL volume/g of ultrasound estimated foetal weight [34], or

• 0.15 mL volume/g of ultrasound estimated foetal weight [35], or

To simplify these formulas, Giannina G et al., [34] introduced a simple formula [33]:

Transfusion volume = 0.02 × target increase in foetal Ht per 10% × g of estimated foetal weight,

Target foetal haematocrit should be around 45% [9,30,35].

Selection of Blood for IUT:

• According to British Committee for Standards in Haematology (BCSH) guidelines [36], IUT transfusions are usually carried out with the red cells of group O, D negative, K negative, extended Rh phenotype matched with mother and should be Indirect Coombs Test (ICT)-cross-match compatible with maternal serum and negative for the relevant antigen(s) determined by maternal antibody status. Blood should be <5 days old and in Citrate Phosphate Dextrose (CPD) anticoagulant and within seven days old blood can be used according to American Association of Blood Banks (AABB) guidelines [37].

• Saline Adenine Glucose Mannitol (SAGM), RBC should be avoided and if used SAGM should be removed before transfusion. Haematocrit {Packed Cell Volume (PCV)} of red cells should be up to, but not more than 0.75. Leukoreduced, Cytomegalo-Virus (CMV) negative and Transfusion Transmitted Infection (TTI) non-reactive. All RBC units used were tested for human immunodeficiency virus (HIV-1 and 2), hepatitis C virus, hepatitis B virus, malaria and syphilis.

• Red cells should be irradiated before use to prevent transfusion associated graft-versus-host disease (TA-GvHD) [37]. The RBC units were irradiated using a Cesium-based irradiation method to a minimum target dose of 25 Grays, as per existing recommendations [38]. Red cells should be transfused within 24 hours following irradiation.

IUT Complications

Now-a-days, IUT is considered safe method in experienced hands to treat foetal anaemia. However, procedure related complication may occur.

Acute Complications: Some of the common complications during or following IUT are: bleeding from the puncture site, brady-or tachycardia, cord occlusion and Preterm Premature Rupture Of Membranes (PPROM) or preterm emergency delivery [39]. In some of the cases infection may also occur. In severe cases foetal distress or foetal death is also reported [27,28]. Foetal distress during or post-procedure is the most serious complication and may result in foetal death or emergency delivery with the risk of prematurity, neonatal asphyxia or death.

Long-term Complications: Foetal erythropoiesis suppression occurs due to frequent IUT during pregnancy, required more RBC transfusions during the first six months of life [40]. There is a risk of transmission of TTI like hepatitis B, hepatitis C, HIV, especially in centres where Nucleic Acid Test (NAT) testing is not available [41]. IUT transfusions have a minimal but theoretical risk for anaphylactic reactions.

Following the IUT procedure additional antibody formation may also occur due to FMH after IUT. Additional maternal red cell antibodies formed in 19-26% cases and may complicate subsequent transfusions and next pregnancy [42]. The presence of additional antibodies can cause problems in finding compatible RBCs for foetal and maternal transfusions, and the antibodies are capable of inducing delayed haemolytic transfusion reactions and increase anaemia.

Outcome

With the advancement of technology, better knowledge of subject and use of high-resolution ultrasound to guide procedure, IUT rapidly became safer in experience hand. Many centres have reported IUT result in recent years and overall survival vary from 93-100%. Survival reported in studies by Sainio S et al., Zwiers C et al., Pasman SA et al., Deka D et al., and Potdar O et al., are 96.2%, 97%, 100%, 93.1%, and 77.5%, respectively [10,18,19,28,43].

Foetal hydrops is the main prognostic factor affecting survival after IUT therapy [44-46]. In addition, foetal hydrops is a major risk factor for long-term neurodevelopmental impairment [25]. In recent study, descending aorta PSV also found useful in diagnostic after two IUTs other than MCA-PSV [47].

In last few years, red cell alloimmunisation due to D antigen has reduced significantly because of Anti D given to Rh-negative women. Still red cell alloimmunisation are more common in India compared to western country because of many reasons e.g., Anti D not given to all women, insufficient dose, hiding history of miscarriage due to social stigma and poor socio-economic status. In our country only few centres perform IUT because of non-availability of foetal medicine and transfusion medicine specialist, non-availability of O negative blood, poor infrastructure. In our centre, almost 200-250 IUT were performed yearly because it is a tertiary care referral centre with a mandate for teaching, research and patient care and receives referred patients from all over the country. In our centre, IUT is preferred by simple transfusion because of more complication

by intrauterine exchange transfusion. There is a limited role of TPE and IVIG in foetal anaemia due to alloimmunisation compared to IUT because of fewer evidence of benefit by TPE and IVIG, high cost of these therapy [44,48,49]. IUT is safer at our centre and very few complications reported in published study [27,28].

Limitation(s)

The present review was limited by the fact that indications of IUT is not describe in full length because it was described in earlier review article and other modality of treatment e.g., Therapeutic Plasma Exchange (TPE), Intravenous Immunoglobulins (IVIG) was not discussed because of limited role.

CONCLUSION(S)

The study can conclude this review that IUT is a safe and effective procedure in the treatment of foetal anaemia. Most common indication for IUT is red cell alloimmunisation. Besides the role of foetal medicine specialist, role of transfusion medicine specialist is equally important in volume calculation, selection of blood and its modification (leukoreduction and irradiation). Acute complications are rare in experience hand and to avoid long term complication associated with TTI, NAT tested blood should be given. In India there is no universal screening program for early detection of red cell alloimmunisation due to resource constraint. To prevent red cell alloimmunisation, anti D is given to all Rh-negative mothers. Red cell antibody screening of all pregnant woman must be done in first trimester to detect red cell alloimmunisation at earliest.

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