Intrauterine Fetal Blood Transfusion (IUBT) for Rh Incompatibility – 12 Years' Experience from Pakistan

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ABSTRACT

Objective: To determine the perinatal outcome of pregnancies complicated by Rh-alloimmunisation, requiring intrauterine blood transfusion.

Study Design: Observational study.

Place and Duration of Study: Feto-maternal Unit of Gene Tech Laboratory, Lahore, from 2007 to 2019.

Methodology: A retrospective analysis was done on the data of cases of intrauterine, intravascular blood transfusion given to at-risk foetuses to correct foetal anaemia due to Rh-alloimmunisation or *parvovirus* B19. All cases, who were eligible to receive IUBT were included in the study. Cases where historic data was not available have been excluded.

Results: A total of 305 intrauterine blood transfusion (IUBT) procedures were performed on 127 foetuses. The gestational age ranged from 18-32 weeks at the time of referral. Infra-hepatic part of umbilical vein was preferred for transfusion, but in some cases of anterior placenta, the cord insertion was approached with exception of only two cases where intra-cardiac route was employed. In this study, 71.6% of the babies survived, 14.2% were loss to follow and 14.2% died.

Conclusion: IUBT is a safe procedure, especially when performed by experienced hands, and helps save the foetuses at risk. Mothers with Rh-alloimmunisation should be referred before developing *hydrops fetalis* for better outcome.

Key Words: *Red cell alloimmunisation, Intrauterine intravascular blood transfusion, Foetal anaemia.*

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INTRODUCTION

Rhesus (Rh) incompatibility or Rh-disease is a condition when an Rh-negative woman is exposed to Rh-positive foetal blood cells, leading to development of Rh-antibodies during the course of pregnancy or delivery. It may also occur if an Rh-negative female receives an Rh-positive blood transfusion. The immunological system in the woman is stimulated to produce antibodies against Rh-antigen. These IgG antibodies persist for life and may cross the placenta freely when pregnant; and it adversely affect an Rh-positive child. They form antigen antibody complexes with Rh-positive foetal RBCs causing haemolysis leading to severe haemolytic anaemia.[1] This can cause *hydrops foetalis* and demise of foetus, if left untreated.[2]

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Currently, the prevention and treatment of Rh-incompatibility is successful in most modern obstetric practices worldwide. Prevention include the antenatal and postnatal administration of anti-D immunoglobulin for Rh D-negative mothers following a sensitising event and prophylactic anti-D administered in the third trimester.[3]

The treatment of foetal anaemia by intrauterine blood transfusion (IUBT) is associated with survival rate more than 90% in specialised centres.[3] IUBT is performed mainly for foetal anaemia due to Rh-isoimmunisation, but it also improves fetal outcome for other causes of anaemia associated with antibodies and infection with *parvovirus* B19.[3] The risk of foetal loss is about 1:3 per procedure and it can increase up to 20% in *hydrops foetalis.*[4] Other complications, including miscarriage/preterm labour, foetal bradycardia, cord hematoma, vessel spasm, bleeding from the puncture site, and foetal death are reported. These complications can be minimised by a multidisciplinary approach between foetal medicine interventionist, blood transfusion laboratory, obstetricians, and neonatologists as the multidisciplinary approach helps in timely addressal of the complications. There is no reported foetal outcome after IUBT, representing the results of intrauterine treatment for red cell alloimmunisation in Pakistan.

Table I: Gravidity and parity of mothers.

Gravidity			Parity		
Gravida	**Frequency**	**Percentage**	**Para**	**Frequency**	**Percentage**
Upto 2	3	2.4%	Upto 2	26	20.5%
3-5	54	42.5%	3-5	36	28.3%
6 or more	70	55.1%	6 or more	65	51.2%

Table II: Frequency of IUBTs per case and post natal transfusions per case.

Number of IUBTs per case			Post-natal transfusions per case		
Number of IUBTs	**Frequency (Number of cases)**	**Percentage**	**Post natal transfusions**	**Frequency (number of cases)**	**Percentage**
One	127	41.6%	One	32	25.2%
Two	96	31.5%	Two	35	27.6%
Three	60	19.7%	Three	38	29.9%
Four	22	7.2%	Four	22	17.3%

The objective of this study was to determine the perinatal outcome of pregnancies complicated by Rh-alloimmunisation, and identify factors affecting results of intrauterine blood transfusion (IUBT) for such cases.

METHODOLOGY

It is an observational study and data was analysed retrospectively from clinic records from 2007 to 2019.[4] All cases, which were medically eligible to receive IUBT, were included in the study; while cases where historic data was not available, were excluded. Cases with missing information in the clinic records were also excluded.

The past obstetrical and paediatric experience was reviewed in detail and cases were selected for IUBT. Each mother was investigated for her blood group, haemoglobin (Hb) level, hepatitis B and C screening, Rh-antibody titre, and Doppler ultrasonography for peak middle cerebral artery velocity for foetal anaemia. Ultrasound (USG) was performed at each visit for the general foetal growth, hyperplacentosis, liquor volume, foetal cardiac activity and movements and any signs for foetal hydrops. Fetal anomaly scan was performed at the first visit. The father was tested for Rh-genotype. All the treated cases had Rh-isoimmunisation, except two, which were due to *parvovirus* B19. *Hydrops foetalis* was graded into mild, moderate, and severe. Mild cases had a thin rim of ascitic fluid under abdominal skin; moderate had fluid in abdominal cavity with or without pleural and pericardial effusion; and severe case was labelled when there is abundant amount of fluid in abdominal cavity with or without pleural and pericardial effusion.

The pre- and post-transfusion foetal Hb were measured by Sysmex. The donors were Hep B and C negative with blood group O negative. The blood was leuco-depleted and collected 24 hours before transfusion. The blood was concentrated with a haematocrit of 75-80%, and irradiated at least 6 hours before administration.

The operating team comprised of a feto-maternal consultant, perinatologist, ultra-sonographer, nurses and laboratory technologist. Lignocaine (2-3mL) was injected for local anaesthesia into the maternal abdominal wall under aseptic condition. A 20-gauge special needle was inserted into the umbilical vein under continuous ultrasound guidance. The umbilical vein at the insertion site of placenta was preferable site to be approached for blood transfusion. If this seemed technically difficult then second choice was the intrahepatic part of the umbilical vein; and as a last choice, the foetal heart was approached. In the operating room immediate assessment of haematological parameters was performed on the first foetal pretransfusion blood sample. The volume of the blood to be transfused was calculated by using the formula aiming at a post-transfusion haematocrit of 40-50%.[5]

Foetal heart rate tracings were obtained before and after transfusion. During procedure, foetal condition was monitored by frequent ultrasound observation of foetal heart rate and contractility. Post-transfusion foetal blood sample was taken to assess the haematological parameters. Foetal condition was evaluated before discharge by means of ultrasound and foetal heart rate tracing. The interval between successful transfusion was 1-4 weeks, depending upon the post-transfusion Hb concentration and post-transfusion MCA velocity. The intrapartum and postpartum data were collected from referring obstetricians and neonatologists. The data was analysed using SPSS version 23.0 and results were expressed as frequencies and percentages.

RESULTS

In this 12-year period, 127 foetuses received 305 intrauterine blood transfusions. The descending frequency of blood groups of foetuses was O+ (41.7%), A+ (21.3%), B+ (28.3%), AB+ (7.1%) and B- and O- (0.8% each), respectively. Gravida and para status of the mothers is given in Table I. Majority of the women were gravida 3 or above (55.1% more than 6 and 42.5% between 3 and 5). Similar trend was noted for parity.

In this study, out of the 127 cases, majority (64%) were interahepatic and 34% were umbilical. Two cases required foetal heart approach. The number of IUBTs received by a single foetus ranged from one to four. Forty-three foetuses received IUBT before 26 weeks gestation and remaining foetuses after 26 weeks of gestation. If additional IUBTs were required, these were planned according to post transfusion foetal Hb level (Table II). The decision of giving the first IUBT and gestational age was dependent upon MCA velocity, Rh-antibody titre, *hydrops fetalis* in current pregnancy or in previous preg-

nancies, previous history of IUDs, icterus neonatorum and requirement of postnatal exchange transfusion. Variable number of foetuses required post-natal transfusion (Table II). The overall status of alive children at follow up was 71.6% (n = 91), death in 14.2% (n = 18) of the cases; the status of similar number (14.2%, n = 18) infants was unknown.

DISCUSSION

The blood groups were discovered in 1900 by Landsteiner; and later in 1940, he discovered the Rh factor, the Rh (D) antigen as the cause of hemolytic disease.[6] The CDE genes are located on the short arm of chromosome 1 and inherited as a group, independent of other blood group genes. Frequency of Rh-negativity is higher in Whites 15% then in Blacks 5%, Hispanics 8%. It is rare in Native Americans, Japanese, and Eskimoes.[7] According to www.rehuses.net, the Rh-negative population is about 4.28% in India and 10.85% in Pakistan.[8] Approximately 1.7% of Rh D negative pregnant women develop Rh-antibodies with the greatest risk in the first pregancy. The foetal loss in severe cases of Rh-isoimmunisation may be 80%-100%. The introduction of Rhesus (D) immunoprophylaxis in 1965 dramatically decreased the incidence of perinatal Rhesus Haemolytic disease. Some of the Rh-negative women do not receive antenatal & postnatal anti D-immunoglobulin; and some women develop isoimmunisation in spite of receiving anti D immunoglobulin.

Haemolytic anaemia became the first treatable foetal disease after Lilly successfully transfused affected foetuses intraperitoneally with adult RBC in 1961.[3] Rodeck achieved a high survival rate in 1981 by using intrauterine intravascular transfusion.[4,9] Management of Rh-isoimmunised pregnancies is based on regular monitoring of increasing Rh- antibody titre and ultrasound examinations. Middle cerebral artery peak systolic velocity increases with the severity of foetal anaemia. The measurement of MCA PSV has become the standard technique for diagnosis of foetal anaemia. This can predict moderate to severe foetal anaemia with 88% sensitivity and a false positive rate of 18%.[7]

Similar experiences, as in this current study, have been reported from other countries where IUT procedures have been done.[10-16]

The overall survival rate in Finland was 94.2%.[10] The survival rates reported by Tiblad *et al.* in a study conducted in Stockholm are 91.8%.[11] The overall survival rate reported in a similar study from Netherlands was 86% over a period of 11 years;[12] while the survival rate was reported as 93% by Deka *et al*.[13] A longitudinal study done over 27 years, reported 1,678 procedures with an improvement of survival rate from 88.6% to 97%.[14] A similar study by Pasman *et al.* explained 14 years of experience in Leuven, where 135 IUTs were conducted for 56 fetuses, and no mortality was observed in any of the case; however, adverse effects were reported.[15] Klumper *et al*. reported that the benefits of transfusion were more if treatment was done both before and after 32 weeks of pregnancy as well, as 100% results were obtained for such cases while the results were 91% for those who received treatment after 32 weeks, and 48% for those who received only before 32 weeks.[16]

Late referral of patients, leading to delays in accessing IUBT services, results in a high rate of *hydrops fetalis*, which in turn contributes to adverse outcomes after IUBT, and also impacts the survival rates negatively.[3,17]

Overall mortality and morbidity, due to complications, noted in this study from Pakistan were comparable with similar other researches done in other countries. It ranged from 75% in cases where *hydrops fetalis* was present when treatment was initiated, to over 90% in cases of non-hydropic fetuses.[18] Among the cases included in this study, the majority of the cases were those with *hydrops fetalis,* therefore, mortality was higher compared to other studies. Overall, the fetal loss rate due to the procedure is 1–2%.[12,19] The mortality rate is higher at gestational age of <22 weeks, due to the technical difficulties encountered when the procedure is performed very early in gestation.[12] The presence of *hydrops fetalis* is a major contributor to adverse outcomes. The rate of fetal death at <20 gestational weeks is higher (5.6%).[12,20,21]

In the current study, most of the deaths occurred among fetuses of <30 gestational weeks. This outcome is to be expected given the higher rate of prematurity related complications in this group.

This study presents the 12 years' experience with IUT as a life-saving pioneer procedure in Pakistan. Limitation of the study was that the data against many variables was not available as historic data from 12 years were used. Therefore, some of the analyses which could have been made part of the study had to be omitted. However, despite this limitation, this study presents the success rate of IUBT in Pakistan, giving a hope that lives of neonates can be saved in cases of Rh-incompatibility. Overall, this procedure appears safe and effective when carried out by a multidisciplinary team of individuals with extensive training and experience. However, access to a high-quality blood bank is necessary to ensure the availability of the required blood components, among other specialised services.

CONCLUSION

IUBT is a safe procedure when performed by experienced hand to save the foetuses at risk. Mothers with Rh-alloimmunisation should be referred before developing *hydrops fetalis* for better outcome through early identification, which can be achieved through appropriate awareness of the healthcare providers.

ETHICAL APPROVAL:
Ethical approval was taken from the Ethical Committee of the Gene Tech Lab.

PATIENTS' CONSENT:

Informed consents were taken from all patients before the procedure was conducted. The consent also covered the clause to use data for research purposes, ensuring anonymity of the patients.

CONFLICT OF INTEREST:

No conflict of interest to be declared.

AUTHORS' CONTRIBUTION

YR, AA, YE: Clinical work, study design, interpretation, drafting of work and final revision.

HJ: Clinical work, study design, interpretation, drafting of work and final revision.

IW: Clinical work, drafting of work and final revision.

GM: Clinical work, study design, drafting of work and final revision.

NM: Study design, analysis, interpretation, drafting of work and final revision.

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