

Complications of intravascular intrauterine transfusion for Rh alloimmunization

Asma Alkhaibary,^a Mohannad Ali,^a Maha Tulbah,^a Maha Al-Nemer,^a Rubina M. Khan,^a Maisoon Al Mugbel,^a Nada Al Sahan,^a Marwah Mazen Hassounah,^b Waleed Alshammari,^b Wesam I. Kurdi^a

From the ^aDepartment of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; ^bDepartment of Family and Community Medicine, King Saud University, Riyadh, Saudi Arabia

Correspondence: Dr. Mohannad Ali · MBC 52 Department of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia · dr.mohannadali@yahoo.com · ORCID: <https://orcid.org/0000-0003-2139-0370>

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BACKGROUND: Intravascular intrauterine transfusion (IUT) is considered a safe procedure, but complications still occur, including fatalities.

OBJECTIVE: Review the outcomes of Rh alloimmunization, including indications and possible complications.

DESIGN: Retrospective cohort (medical record review).

SETTING: Tertiary care center.

PATIENTS AND METHODS: We retrieved the records for all mothers who had an IUT for Rh alloimmunization between January 2009 and August 2019. We collected data on complications, post-transfusion hemoglobin and antibody combinations.

MAIN OUTCOME MEASURE: Complications of IUT.

SAMPLE SIZE: 119 mothers with 154 fetuses (154 different pregnancies).

RESULTS: The 154 fetuses had 560 intrauterine transfusions. The median pre-IUT hemoglobin was a median of 8.0 g/dL while the median post-IUT hemoglobin 16 g/dL. Immediate procedure-related complications included fetal bradycardia in 2.7%, significant bleeding from the cord puncture site (for more than 2 minutes in 0.9%), and contractions in 0.9%. Eight (5.2%) were delivered by cesarean delivery due to IUT-specific complications such as post-procedure fetal bradycardia. Intrauterine fetal death complicated 8.4% of the pregnancies (13 fetuses). Phototherapy was required in 76 (49.4%), postnatal blood transfusions in 17 (11%), and exchange transfusion in 11 (7.1%). Neonatal death occurred 8 (5.2%). Data were insufficient to assess associations of complications with antibody combinations.

CONCLUSIONS: Intrauterine transfusion is an effective treatment with high survival rates (around 90% for cases of Rh alloimmunization).

LIMITATIONS: Case series.

CONFLICT OF INTEREST: None.

With the introduction of anti-D immunoprophylaxis, the number of cases of Rh alloimmunization has decreased in current practice; remaining cases are usually due to failure to receive antenatal or postnatal prophylaxis or receiving lower than required dose usually related to a higher volume of fetomaternal hemorrhage. On the other hand, fetal anemia due to other red cell antigens (c, E, or Kell) or infectious causes, especially parvovirus B-19, has increased in incidence.¹ In the early 1960s, Liley introduced percutaneous intraperitoneal transfusion for the intrauterine treatment of fetal anemia due to red cell immunization.² The most commonly used technique of intravascular intrauterine transfusion (IUT) into the umbilical cord was first described by Rodeck et al in 1981.³ IUT into the intrahepatic portion of the umbilical vein was first described by Nicolini et al in 1990.⁴ This method is a safe alternative for umbilical cord transfusion especially in selected cases such as a posterior placenta.⁵ From 1987, the intravascular technique became the method of choice.⁶ IUT continues to be the cornerstone of treatment for fetal anemia for a variety of causes. In experienced hands, IUT is now considered a relatively safe procedure. However, complications, even fatal ones, do still occur. We reviewed the management of Rh alloimmunization cases over a period of 10 years.

PATIENTS AND METHODS

The patients included in this study were all mothers who had an IUT at at King Faisal Specialist Hospital and Research Center, Riyadh, one of the largest tertiary hospitals in the region, from January 2009 to August 2019. Medical record numbers were retrieved from the data warehouse services to enable collection of data on all patients in the integrated clinical information system, using the search term "intrauterine transfusion." The initial search retrieved more than 780 records. We excluded duplicated orders, IUT for non-immune hydrops fetalis, and canceled procedures (which nevertheless appeared in the search results). All complications encountered during the procedure were documented, including fetal bradycardia, bleeding, uterine contraction, needle dislodge, and cases where post-transfusion hemoglobin was unobtainable. Only IUTs for Rh alloimmunization were included. IUTs for any other indication were excluded. For missing information, we checked the medical paper files, especially for procedures done between 2009-2016. Details of the procedures, including ultrasound findings, were collected from the ultrasound database (ViewPoint, GE Healthcare).

Blood for the IUT transfusion was 50-150 mL (based on the gestational age, with lower volume in earlier pregnancies) of packed RBCs, leuco-reduced and irradiated, O Rhesus D-negative or cross-matched against the mother's blood. The blood was obtained from cytomegalovirus-negative donors and collected within 72 hours of the procedure. The hematocrit of the blood was assessed using a Sysmex 9001 (Sysmex NV Belgium) and concentrated to a hematocrit between 75% and 80%. All IUTs were intravascular, inserted into the placental umbilical cord when possible; no intraperitoneal transfusions were performed. Before starting the procedure, the middle cerebral artery peak systolic velocity was measured, and the first transfusion was performed once the velocity was ≥ 1.5 multiples of the median for the gestational age. Using a 20-gauge spinal needle, pre-transfusion hemoglobin was measured. Before commencing the transfusion, the amount of blood required was calculated based on the estimated fetal weight and the pretransfusion hemoglobin. A mid-transfusion sample was obtained to assess the hemoglobin level and decide on the final required volume for transfusion. All complications encountered during the procedure were documented, including fetal bradycardia, bleeding, uterine contraction, needle dislodge, and whenever post-transfusion hemoglobin was unobtainable.

For the statistical analysis, we used IBM SPSS statistics version 21. We started with descriptive statistics using frequencies and percentages for categorical variables and median and interquartile range for continuous numerical variables. For mothers with a record of more than one IUT procedure, we used the maternal age and gravida from the latest procedure. We used the median to substitute missing data for numerical variables. We categorized missing data as "not mentioned" for categorical variables. We created a variable for antibody combinations to calculate their frequency. We used Pearson's chi-squared test with adjusted standardized residuals for testing associations between the antibody indication for the procedure (exposure) and intrauterine fetal death (IUFD), exchange transfusion, and blood transfusion, respectively (the outcome), at a $P < .05$ level of significance. The null hypothesis was no association between antibody combination and outcome (IUFD, exchange transfusion, and blood transfusion).

RESULTS

The study population included 119 mothers with a median age of 34 years (Table 1). Gravidity for this population was a median of 6. The median gestational ages

were 29 weeks at IUT and 35 weeks at delivery. The 154 fetuses had 560 intrauterine transfusions. The median for the number of IUTs was 3.5, with a frequency range from 1 to 8 (in the 40 hydropic fetuses the median was 4). The pre-IUT hemoglobin was a median of 8 g/dL compared with 16 g/dL for post-IUT (Table 1). IUT was given urgently for 40 fetuses (26%) that were hydropic upon first presentation. Immediate procedure-related complications included fetal bradycardia in 2.7%, significant bleeding from the cord puncture site (for more than 2 minutes in 0.9%), and contractions in 0.9%. Seventy-nine (51.3%) were delivered by cesarean delivery, including 8 (5.2%) due to IUT-specific complications such as post-procedure fetal bradycardia. Thirty-three (21.4%) emergency cesarean deliveries were due to multiple previous cesarean deliveries, breech presentation, and intrapartum fetal distress. Thirty-eight (24.7%) were delivered by elective cesarean delivery. Intrauterine fetal death (IUFD) complicated 13 (8.4%) of the pregnancies with a survival rate of 91.6%, which is comparable to other reports (around 95.1%).⁷ The mode of delivery was unknown in 18 (11.7%) patients as they delivered outside our hospital. Fetuses who received IUTs usually require postnatal interventions. Phototherapy alone was required in 76 (49.4%)

fetuses, postnatal blood transfusions in 17 (11%), and exchange transfusion in 11 (7.1%). Neonatal death occurred in 8 (5.2%).

We found 21 different antibody combinations among the study population (Figure 1). The three most common antibodies/combinations were: anti-D and anti-C in 57 (37%) patients, anti-D in 34 (22.1%), and anti-D/anti-C/anti-E in 12 (7.8%) patients. Cell counts

Table 1. Characteristics of mothers (n=114) and fetuses (n=154) undergoing intrauterine transfusion procedure.

Maternal age (years)	34.5, 31-38
Gravidity	6, 4.0-7.3
Procedure	
Gestational age at IUT (weeks)	29, 25-32
Hemoglobin (g/dL), pre-IUT	8.0, 5.2-10.0
Hemoglobin (g/dL), post-IUT	16.0, 14.2-17.0
Fetus	
Gestational age at delivery (weeks)	35, 33-36
No. of intrauterine transfers	3.5, 2-5

Data are median, interquartile range

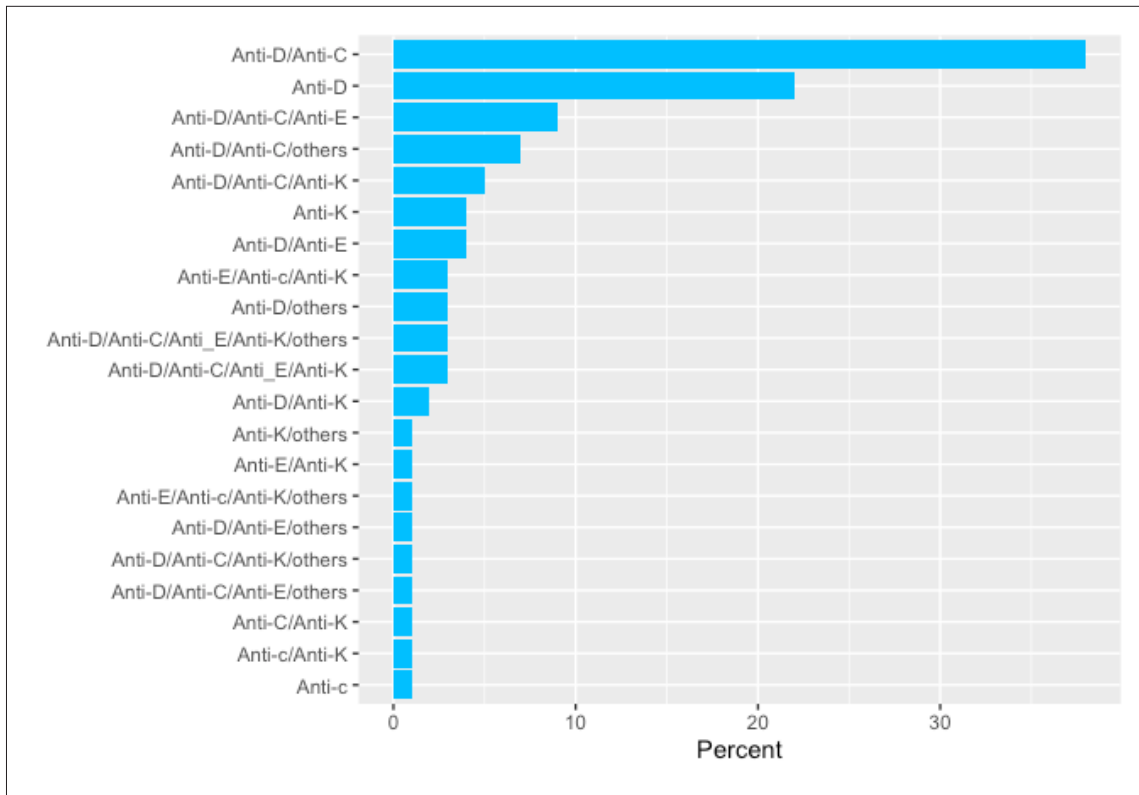


Figure 1. Percentage of antibody combinations requiring intrauterine transfusion.

were insufficient to estimate any statistical association between the types of antibodies and pregnancy outcomes, such as the need for blood transfusion, exchange transfusion, or IUFD, but data for non-zero or more than one case are presented in **Table 2**. For top-up blood transfusion the top three prevalent antibody combinations were anti-D/anti-C in 35.3% (n=6), anti-D in 29.4% (n=5), and anti-C/anti-D/anti-K in 11.8% (n=2). In exchange transfusion, both anti-D, as well as the anti-D/anti-C combination, were equally prevalent (27.3%, n=3 each).

DISCUSSION

Our center is a tertiary care center with long experience in maternal-fetal medicine, specifically in intrauterine transfusion and other different fetal interventions. Most cases were referred to us from other centers, and sometimes late referral can render some of the fetuses hydropic on presentation. Forty fetuses (26%) were hydropic upon the first presentation, and IUT was arranged for them urgently. The outcome for hydropic fetuses is likely to be worse than non-hydropic fetuses, with a need for more transfusions and an increased risk of IUFD.

Our study found that immediate procedure complications, including fetal bradycardia, prolonged bleeding after needle retraction, and uterine contractions comprised 4.5% of all cases, which is lower than that reported in other studies. In the study reported by Pisman and colleagues, the rate of mild adverse outcome (including bleeding from the puncture site) was 5.2%, uterine contractions (rarely required tocolysis) was 3%, and if fetal distress was added, the overall complications were more than 10%.⁸

In our experience, the mode of delivery for fetuses who received IUT is usually determined by factors such as prior cesarean deliveries, Bishop score, fetus post-IUT, the number of IUT received, and many other factors. Procedure-related emergency cesarean delivery in our study group occurred in 5.2% of mothers; 44.2% of the deliveries were elective at a mean gestational

age of 35-36 weeks (24.7% by induction of labor, and 19.5% by elective cesarean delivery). In the study by Tiblad and colleagues, up to 24% of the neonates were born before 34 weeks gestation. In the same study, the survival rate was 91.8%, which is similar to our study (90.7% survival with 4.5% IUFD and 4.8% neonatal death). It is noteworthy that 53% of IUFD were for non-hydropic fetuses, but most of the IUFDs were linked to a specific type of antibodies discussed below.⁹

More than 20 different antibodies were identified in the maternal serum in this study; these antibodies were encountered in different combinations. We noted that the most prevalent antibody combinations were anti-D and anti-C. The significant finding was that among the 13 cases of IUFD in the study, this combination was found in 12 cases (92.2%), either anti-D and anti-C alone or combined with other antibodies like anti-E, anti-K, and other types. One case of IUFD was linked to anti-D alone (7.6%) This indicates that the combination of anti-D and anti-C is potentially associated with more severe prenatal illness. The postnatal interventions ranged from bilirubin follow-up, phototherapy, immunoglobulin (IVIG), top-up transfusion, and the need for exchange transfusion. Twenty-four percent of babies eventually required exchange transfusion despite intensive phototherapy and IVIG. Most of these cases were linked to the combination of anti-D and anti-C mixed with other types. It is essential to remember that the presence of multiple antibodies is a challenge to the blood bank facilities to identify suitably packed cell units for the IUT procedure.

The limitation of this study includes few mothers with multiple procedures, resulting in a smaller maternal sample size in relation to the variables; hence there is not enough power to conduct multivariate analysis and control for possible confounders. Upon the review of IUT experience in our facility, intrauterine transfusion continues to be an effective treatment that yields high survival rates of around 90% for cases of Rh alloimmunization. This study is one of few studies that looked in-depth into all possible antibody combinations and their fetal and neonatal impact. The anti-D and anti-C combination of antibodies were linked to many adverse outcomes, including more than 90% of IUFD. This antibody combination was also the most prevalent among the study population. This relationship between different antibody combinations and pregnancy outcome deserves further assessment in larger studies. This study also managed to review the standard practice of management of patients suffering from Rh isoimmunization in Saudi Arabia, which does not differ from the worldwide standard of care.

Table 2. Antibodies and antibody combinations with adverse outcomes.

	Intrauterine fetal death	Blood transfusion	Exchange transfusion
anti-D	1 (7.7)	5 (29.4)	3 (27.3)
anti-D, anti-C	7 (53.8)	6 (35.3)	3 (27.3)
anti-D, anti-C, anti-E	1 (7.7)	0	2 (18.2)

Data are number (%). Statistical comparisons not feasible because of insufficient data.

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