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MATERNAL-FETAL MEDICINE

Perinatal survival and procedure-related complications after intrauterine transfusion for red cell alloimmunization

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Abstract
Objectives To study the perinatal survival and procedure-related (PR)complications after intrauterine transfusions in red cell alloimmunization.
Methods Prospective data of 102 women with Rh-alloimmunized pregnancy undergoing intrauterine intravascular transfusion for fetal anemia, from January 2011 to October 2014 were analyzed. Main outcome measures were perinatal survival and procedure-related (PR) complications.
Results A total of 303 intrauterine transfusions were performed in 102 women. Of 102 fetuses, 22 were hydropic at first transfusion. The mean period of gestation and hematocrit at first transfusion was 26.9 ± 3.3 weeks (range 19.7–33.8 weeks) and 17 ± 7.82 % (range 5.7–30 %), respectively. Average number of transfusions was 2.97 (range 1–7) per patient. Overall survival was 93 % and mean period of gestation at delivery was 34.5 ± 1.94 (range 28.3–37.4) weeks. Mean hematocrit at delivery was 36.9 ± 8.77 % (range 10–66 %). Fetal death occurred in four cases (3PR), neonatal death occurred in three cases (2PR). Emergency cesarean delivery after transfusion was performed in four pregnancies. The total PR complication rate was 2.97 %, resulting in overall PR loss in 1.65 % per procedure.
Conclusion Our results compare favorably with other studies published in the literature. Intravascular transfusion is a safe procedure improving perinatal survival in fetuses with anemia due to Rh-alloimmunization.

Keywords Fetal anemia · Red blood cell alloimunization · Intrauterine transfusion · Fetal therapy

Introduction

The treatment of fetal anemia, using intravascular intrauterine transfusion (IUT) of packed red cells, has been one of the biggest success stories in fetal medicine. A better understanding of the pathophysiology of the disease, along with an improved ability to predict anemia and the availability of in utero treatment have all contributed to the significantly improved outcomes. Advanced and meticulous neonatal care has also been the cornerstone of management of such pregnancies.

Treatment for fetal anemia has evolved from intraperitoneal transfusion by Liley (1963) [1] to intravascular transfusion using fetoscopically cannulated vessel on placental surface by Rodeck (1981) [2]. The final breakthrough came when Bang (1982) described ultrasound (USG)-guided fetal intravascular transfusions [3]. Ultrasound-guided intravascular transfusion is now the standard of care to treat fetal anemia. In one of the largest cohorts, the overall survival for fetuses treated with intravascular transfusion was 86 % [4]. A recent review by Lindenburg et al., has summarized that the survival rates after IUT for red cell alloimmunization exceeded 80 % in specialized centers all over the world. [5]. Untreated fetal anemia may result in cardiac failure, hydrops, hypovolemic shock and fetal or neonatal death.

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The procedure, however, is not without complications. Fetal distress during procedure remains the most serious complication and may result in preterm emergency delivery or fetal death.

Despite the availability of anti-D for many decades its usage is still not very widespread in our country because of lack of awareness, the cost of the injection and the logistics of the availability of such treatment in the remote areas. Consequently, Rh isoimmunization is still a major problem in our country, with few centers equipped to manage the afflicted pregnancies. Department of Obstetrics at All India Institute of Medical Sciences, a tertiary referral hospital, is the largest center in the country managing about 50–60 pregnancies complicated by maternal red cell alloimmunization per year. Of which at least one-third would require an intrauterine transfusion for fetal anemia. Our center has been performing intrauterine transfusions since 1985. The aim of present study is to look at the perinatal survival and procedure-related complications after fetal intravascular transfusion and compare them with published literature. This is the largest series to be reported from a developing country.

Materials and methods

This prospective cohort study included all women undergoing intrauterine intravascular transfusion for fetal anemia due to red cell alloimmunization from Jan 2011 to Oct 2014. Two experienced operators performed all the procedures. We identified 122 singleton pregnancies that underwent intrauterine transfusion in this period. Twenty women were excluded from analysis as the details regarding neonatal outcome were not available. Data were taken from database in the Fetal Medicine unit. Ethical clearance was obtained from Institutional Ethics Committee.

The main outcome measures were fetal and neonatal survival, procedure-related complications, gestational age at delivery and admissions to Neonatal Intensive Care Unit (NICU). Procedure-related complications were defined as fetal bradycardia during procedure requiring immediate delivery, delivery within 24 h of procedure for fetal distress; fetal intrauterine death within 1 week of procedure; neonatal death; intrauterine infection; rupture of membranes.

Procedure

Women with Rh-alloimmunized pregnancy included in the study were either booked with us and monitored for fetal anemia by middle cerebral artery-peak systolic velocity (MCA-PSV) from 18 weeks onwards or were referred with diagnosis of fetal anemia or hydrops. Value of MCA-PSV $\geq$ 1.5 multiples of median (MOM) was used for fetal intervention. Second and subsequent intrauterine transfusions were timed by MCA–PSV equal or more than 1.5 MOM or expected fetal anemia calculated by rate of fall in hematocrit of 1 % per day after first and 0.8 % after subsequent transfusions.

Fresh (less than 5 days old), O-negative, irradiated blood cross-matched with maternal blood and with hematocrit (Hct) of 70–80 % was used for intrauterine transfusion. The procedure was carried out in close proximity to operating theater with facility for emergency cesarean section if required.

Standard techniques for intravascular transfusions were used. The procedure was carried out under asepsis, under continuous ultrasound guidance with a free-hand technique. The fetus was paralyzed using 0.3 mg/kg pancuronium injected in fetal thigh. A 20-gauge needle was used to enter the umbilical vein preferably at cord insertion. If the cord insertion was not accessible, free loop was used. Before starting transfusion 1 ml of fetal blood was taken for hemoglobin and hematocrit. The target was to raise fetal hematocrit to 45–50 %. The volume to be transfused was calculated as Volume transfused (mL) = Volume of fetoplacental unit (mL) $\times$ (final $-$ initial hematocrit) divided by the hematocrit of the transfused blood.

The fetoplacental volume (mL) is calculated from the ultrasound estimate of the fetal weight according to the formula (1.046 + fetal weight in grams $\times$ 0.14). A post-transfusion sample was taken, if possible, at end of procedure. In hydropic fetuses, the calculated volume was given over two transfusions 3–4 days apart. After the procedure, all fetuses >28 weeks were monitored with fetal heart rate tracing for 1 h. All women received single dose of intravenous cefazolin 1gm.

The last transfusion was generally given at 33–34 weeks of gestation. If the procedure deemed to be difficult by the operators, these women were electively delivered after giving steroids for pulmonary maturity.

Statistical analysis

Data analysis was carried out using SPSS software of IBM version 19.0. Shapiro–Wilk W test was used for testing normality of continuous variables. Descriptive statistics such as mean, median, standard deviation and range values were calculated for the continuous variables. Percentage values were computed for frequency variables. Testing of two samples means was done using Student *t* independent test for normal distributed data. Frequencies by category were compared using Chi-square/Fisher's exact test as appropriate. Logistic regression analysis with backward elimination was carried out to identify risk variables for

procedure-related complication per pregnancy. Overall fitting logistic regression equation was assessed by log likelihood test and test of significance for coefficient of each variable was done using Wald statistics. Adjusted odds ratios and 95 % confidence limits were calculated. A probability of $p < 0.05$ was considered for statistical significance.

Results

During the 4-year period, 122 women underwent intrauterine transfusions. Pregnancy outcome was available for 102 women, who were included in the study. A total of 102 women underwent 303 in utero transfusions. Of these 22 fetuses were hydropic at first transfusion. In 101 women, the fetal anemia was the result of maternal RhD sensitization, there was one case of RhD plus RhC sensitization.

Most of the women were multiparous with history of one or more affected pregnancies. Forty-seven of the 102 (46.1 %) women had history of intrauterine death (IUD) or hydropic baby due to fetal anemia. One of the patient, a primigravida, was sensitized after blood transfusion. About half of these women had received postpartum anti-D, data regarding antepartum anti-D were not available.

A total of 303 technically successful procedures were performed (mean 2.97 procedures per patient with a range of 1–7 procedures). The mean gestational age at first transfusion was 26.9 weeks and the mean hematocrit (Hct) and hemoglobin at first transfusion were 17 % ± 7.82 and 5.67 ± 2.6 g/dl, respectively. Characteristics of intrauterine transfusions are summarized in Table 1. The overall survival for fetuses undergoing IUT was 93.1 %.

On comparing fetuses with and without hydrops, there was no statistical difference in the mean period of gestation (POG) at first transfusion, but there was significant difference between the two groups in terms of hematocrit at first transfusion and number of transfusions.

The survival of hydropic and non-hydropic fetuses was comparable (90.9 vs 93.8 %; p 0.86). There was no significant difference in neonatal outcome in fetuses with and without hydrops in terms of POG and mode of delivery, NICU admissions and requirement of exchange transfusions at birth (Table 2). The hematocrit at birth was 36.96 ± 9.02 % and 36.7 ± 7.95 % in the non-hydropic and the hydropic group, respectively. The hemoglobin at birth was 12.32 ± 3.0 gm/dl in the non-hydropic group and 12.23 ± 2.65 gm/dl in the hydropic group.

Of the total procedures, 61.4 % were transplacental while 38.6 % were transamniotic. The needle was inserted only once in majority of the patients (94.5 %) while in 5.5 % a second insertion was performed. A third insertion as a practice is discouraged and almost never performed. Hydrops resolved following second or third transfusion in all but one patient who went into a spontaneous preterm labor after the second transfusion at 29 weeks before the resolution of hydrops. The baby, however, was discharged and went home after a prolonged stay in the NICU.

There were five unsuccessful procedures. These were the procedures in which either the umbilical vein could not be accessed or the needle was dislodged due to which the total calculated blood volume could not be transfused. There were 15 cases of transient fetal bradycardia not necessitating an urgent fetal delivery.

Procedure-related complications occurred at rate of 2.97 % per procedure and 8.8 % per pregnancy. Procedure-related pregnancy loss rate was 1.65 % per procedure or 4.9 % per pregnancy.

To determine factors associated with procedure-related complications per pregnancy, a logistic regression analysis with backward elimination was carried out. There was no association of hydrops, parity, gestational age at first IUT,

Table 1 Survival of hydropic and non-hydropic fetuses following intrauterine transfusions for anemia in red cell alloimmunization

	Hydrops absent ($n = 80$)	Hydrops present ($n = 22$)	Total ($n = 102$)	p value
Gestational age at first IUT[a]	29.97 ± 3.5 (19.7–33.8)	26.54 ± 2.4 (22.1–30.7)	26.9 ± 3.3	0.57
Hemoglobin at first[a] IUT(gm/dl)	6.11 ± 2.73 (1.9–10)	4.13 ± 1.23 (2–6.1)	5.67 ± 2.6	0.001
Hematocrit (%) at first IUT[a]	18.33 ± 8.2 (5.7–30)	12.41 ± 3.7 (6.1–18.3)	17.0 ± 7.82	0.001
Number of IUTs[a]	2.61 ± 1.32 (1–7)	4.27 ± 1.61 (2–7)	2.97 ± 1.54	0.000
Perinatal death				
Fetal	3 (3.8 %)	1 (4.5 %)	4 (3.9 %)	
Neonatal	2 (2.5 %)	1 (4.5 %)	3 (2.9 %)	
Survival	75 (93.8 %)	20 (90.9 %)	95 (93.1 %)	0.86

IUT intrauterine transfusion; p value < 0.5 significant

[a] Values as mean and standard deviation and range in ()

Table 2 Comparison of hydropic and non-hydropic live-born fetuses with respect to delivery details and neonatal characteristics

	Hydrops absent ($n = 80$)	Hydrops present ($n = 22$)	Total ($n = 102$)	p value
Gestational age at birth[a]	34.67 ± 1.8 (28.3–37.4)	33.97 ± 2.24 (29.4–36.8)	34.52 ± 1.94	0.22
<34 weeks	21 (26.2 %)	8 (36.4 %)	29 (28.4 %)	0.418
Cesarean section	45 (56.2 %)	12 (54.5 %)	57 (55.9 %)	0.0.81
Hematocrit at birth (%)[a]	36.96 ± 9.02	36.7 ± 7.95	36.9 ± 8.77	0.59
Hemoglobin at birth[a]	12.32 ± 3.0	12.23 ± 2.65	12.30 ± 2.93	0.59
Birth weight (gms)[a]	2283 ± 420	2215 ± 510	2268 ± 439	0.079
NICU admission				
Yes	12 (15 %)	5 (22.7 %)	17 (16.6 %)	0.51
Exchange transfusion				0.98
DVET	12 (15 %)	4 (18.2 %)	16 (15.7 %)	
DVET + PET	27 (33.8 %)	7 (31.8 %)	34 (33.3 %)	
PET	8 (10 %)	2 (9.1 %)	10 (9.8 %)	

NICU neonatal intensive care unit, *DVET* double volume exchange transfusion, *PET* partial exchange transfusion

[a] Values in mean with standard deviation and range in ()

hematocrit at first IUT or the number of IUTs to the procedure-related complications.

Complications

Intrauterine deaths (IUD)

There were three cases of IUD occurring within a week of IUT (Table 3). For the first case, IUT was started at 19.7 weeks, with a Hct of 8 %. IUD occurred 1 day after 5th IUT at 30 weeks. The second patient presented with severe fetal anemia without hydrops. IUD occurred after first procedure. The third case was a hydropic fetus, which succumbed in utero after second IUT. There were no intraoperative complications. The fetuses were not over transfused as evidenced by the volume of blood transfused and post-transfusion hematocrit (Table 3). The intrauterine deaths in the last two cases could be unrelated to the transfusion, possibly due to underlying pathological process.

Cesarean section for fetal distress

Four women underwent cesarean section for persistent fetal bradycardia during the procedure. Of these one newborn, delivered at 29.3 weeks after 3rd IUT died of severe birth asphyxia 2 h after birth. The other three babies went home. Three of four neonates delivered by emergency cesarean section suffered birth asphyxia.

Preterm birth

Four women (4 %) went into preterm labor within 7 days of intrauterine transfusion and delivered. Overall 29.3 % of women delivered at less than 34 weeks gestation.

Chorioamnionitis

There was no case of clinical chorioamnionitis in the mother but two newborns delivered because of poor biophysical profile had early onset sepsis, possibly intrauterine infection. Case 5 had cesarean delivery for poor BPP one week after IUT and baby died of sepsis on day 2. Case 9 had cesarean delivery the day after IUT for poor BPP, baby that had early-onset sepsis was treated but has cerebral palsy on follow-up (Table 3).

Majority of newborns required exchange transfusion at birth.

NICU admissions and morbidity

Excluding newborns requiring admission to NICU for purpose of exchange transfusion, there were 17 admissions to NICU. Three of these 17 neonates died, of which two were procedure related as has been discussed before. Seven babies admitted to NICU had moderate to severe birth asphyxia. Sepsis was reported in a total of six neonates and respiratory distress syndrome in four. Two babies underwent ligation of the patent ductus arteriosus and two others developed bronchopulmonary dysplasia. One of the NICU admissions was for meconium aspiration syndrome and seven admissions were because of prematurity. Ten babies were ventilated and one required CPAP.

Discussion

Intrauterine intravascular transfusion is the definitive treatment for fetal anemia due to rhesus isoimmunization, resulting in improved neonatal outcome. However, being

Table 3 List of cases with complications due to IUT

	G	P	GA at 1st IUT	Hct at 1st IUT	GA at index IUT	Hct at index IUT	Hydrops	Number of IUT	Complications
1	5	4	19.7	8	30	Pre 28 % vol 80 ml post 50 %	No	5	IUD one day after last transfusion
2.	6	3	23.8	Pre 6 % Vol 25 ml Post 25 %			No	1	IUD day after IUT
3.	4	2	24.4	7.6	24.8	Pre 12 % Vol 30 ml Post 30 %	Yes	2	IUD after 3 days
4.	5	4	27.4	17.5	29.3	18.9	Yes	3	Fetal bradycardia, LSCS, died after 2 h due to severe birth asphyxia
5.	4	2	32.5	17.5			No	1	LSCS at 33.5 wks for poor biophysical profile expired due to sepsis on day 2
6.	15	2	26.1	17.7	32.8	NA	Yes	5	LSCS for fetal bradycardia, severe birth asphyxia, surfactant for RDS. Discharged
7.	5	3	28.2	17.5	32.4	31	No	2	LSCS for fetal bradycardia Discharged
8.	6	5	22.5	NA	32.4	NA	No	4	LSCS for fetal bradycardia severe birth asphyxia discharged
9	3	2	22.8	13	34	20	No	3	LSCS for poor biophysical profile 24 h after IUT, early-onset sepsis discharged

G gravidity, *P* parity, *Hct* hematocrit, *IUT* intrauterine transfusion, *GA* gestational age in weeks, *NA* not available, Pre-hematocrit pre-transfusion, post-hematocrit post-transfusion, *vol* volume, *LSCS* lower segment cesarean section, *RDS* respiratory distress syndrome, *IUD* intrauterine death

an invasive procedure, it has its own complications resulting in significant morbidity and mortality. We share our experience of intrauterine transfusions done in the last 4 years. This is probably the largest series from a developing country (102 cases).

The incidence of fetal anemia due to red cell alloimmunization is decreasing in developed countries due to widespread use of anti-D injections for Rh prophylaxis as is evident from the recently published studies of a small number managed over a long period of time [6, 7]. However, in our country we continue to see a large number of cases every year because of the lack of awareness, cost of the injection and its non-availability in remote parts of the country. Hence, it is imperative to compare our results with that of other specialized centers of the world.

The overall survival in fetuses undergoing IUT in our series was 93 %, which is comparable to that reported in recent literature. Van Kamp et al. reported an overall survival of 86 %, and Tiblad et al. 91.8 % [4, 6]. The survival between hydropic and non-hydropic group was comparable in our study. Van Kamp et al. reported lower survival rates for hydropic fetuses, 78 % in 80 hydropic fetuses with mean Hct at first transfusion of 10 %. Altunyurt et al. reported survival of 73.7 % in 19 hydropic fetuses with median Hct of 12 % at first transfusion [8]. In our series of 22 hydropic fetuses, survival rate was 91 % and Hct at first transfusion was 12.4 %. The survival has probably improved with availability of better ultrasound machines and improved neonatal care. In a previous publication by the authors, the survival for hydropic fetuses undergoing intrauterine transfusion was 88 % [9].

Procedure-related complications and loss rates in our series are comparable to the reported literature. The published reports have quoted the procedure-related fetal losses ranging from 0.9 to 4.9 % [6, 7, 10–13]. The largest series from Netherlands reported PR complication rate of 3.1 % and fetal loss rate of 1.6 % per procedure [10]. More recent data from Stockholm cite PR perinatal death of 1.4 % [6]. We had a PR complication rate of 2.97 % and a loss rate of 1.65 %. The most serious procedure-related complication is fetal bradycardia requiring immediate delivery or causing fetal death. Vessel spasm, cord hematoma or bleeding from punctured vessel causing fetal exsanguination are the possible causes of fetal distress. To

avoid complications, procedure was performed after fetal paralysis, as fetal movement can cause needle dislodgement and subsequent complications. Similarly, umbilical vein was targeted for puncture as vessel spasm is more likely if artery is punctured and wherever possible vessel was entered near cord insertion. If vessel was not accessible at cord insertion, we used a free loop. We did not use the intrahepatic portion of umbilical vein. In most cases where emergency cesarean section was performed for fetal bradycardia, there were no procedure-related technical difficulties. Unfortunately, the data for the site of needle entry were not available for all transfusions. Sometimes fetal loss may be unrelated to procedure per se but may be due to underlying pathology itself, as in severely anemic fetuses. In the literature, fetal loss related to procedure has been associated with fetal hydrops [11, 12], early gestational age [6, 13], not using fetal paralysis [9, 10], transfusion in a free loop or arterial puncture [7, 10], experience of operator [7, 14] and severity of fetal anemia [15].

Besides cord-related accidents, fetal distress can also occur due to volume overload or chorioamnionitis. There was no case of maternal clinical chorioamnionitis, but two babies had early onset sepsis, possibly due an acquired intrauterine infection. One baby was delivered a day after IUT and other one week after IUT for poor biophysical profile. Chorioamnionitis has been reported as a complication in 0 to 0.3 % of procedures [6, 10, 15]. In the largest series, Van Kamp et al. reported two cases of chorioamnionitis, one with maternal septicemia and other with maternal fever and chills with associated fetal death, both within 48 h of procedure [10]. As the chances of infection after IUT are low, most authors do not routinely prescribe prophylactic antibiotics.

The mean gestational age at delivery in our series was 34.5 weeks which is less than that reported in the other series by Van Kamp et al. and Tiblad E et al. (median of 36 weeks and mean of 36.1, respectively) [4, 6]. This could be attributed to the fact that we were slightly more predisposed to deliver the fetus rather than perform an IUT after 34 completed weeks of gestation to avoid the procedure-related morbidity and mortality.

Recently, in a large long-term observational follow-up study (LOTUS study), 291 children who had received IUT were followed up for a period of 2–16 years. Of these, neurodevelopment impairment was reported in 4.8 % of the children. The second part of study is ongoing to look into subtle abnormalities that include behavioral problems or quality of life issues [16]. In our study, however, we looked only at the immediate survival of the babies. The long-term neurological outcome data are not available especially for those who had severe birth asphyxia.

Some authors have looked into the affect of IUT on other organ systems. They have proposed that transfusions may lead to less myocardial mass in childhood, which might have a long-term cardiovascular impact. This aspect needs to be investigated further. [17]. Neonates undergoing ET after delivery are at higher risk of developing sepsis, leukocytopenia, thrombocytopenia, hypocalcemia and hypernatremia [18].

Though Rh isoimmunization has become uncommon with anti-D prophylaxis, IUT is performed increasingly for many other indications (e.g., IUT for twin anemia polycythemia sequence after laser ablation in FFTS). IUT is the standard of care for the treatment of severe fetal anemia. Our study shows comparable survival rates and low procedure-related complication rates to those reported in the literature.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Author contribution Deka D: Protocol/project development (Patient management protocols). Vatsla D: Protocol/project development, Data management, Manuscript writing. Sharma KA: Protocol/project development, Data collection and management. Shende U: Data collection. Agarwal S: Data Collection. Agarwal R: Protocol/project development (neonatal management). Perumal V: Data analysis.

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