Neonatal outcomes of pregnancies affected by haemolytic disease of the foetus and newborn and managed with intrauterine transfusion: a service evaluation

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Background. This study, conducted in the tertiary Foetal Medicine Unit at St Michael's Hospital, Bristol, was designed to obtain information regarding neonatal outcomes of pregnancies affected by haemolytic disease of the foetus and newborn and managed by intrauterine transfusion, and to determine whether a change in intrauterine transfusion protocol in 2004 had improved safety. The new protocol included attendance of two Foetal Medicine Unit consultants, foetal sedation and use of the intrahepatic vein as an alternative route to placental cord insertion if deemed safer.

Materials and methods. Data for pregnancies affected by haemolytic disease of the foetus and newborn as a result of haemolytic red cell alloimmunisation and managed with intrauterine transfusion at St Michael's Hospital between 1999 and 2009 were retrospectively collected using local databases, and medical note review.

Results. Overall, 256 relevant intrauterine transfusions were performed. The median number of intrauterine transfusions per pregnancy was two. Ninety-three per cent of the live deliveries had 5-minute APGAR scores ≥9 and 98% were admitted to a Neonatal Intensive Care Unit/Special Care Baby Unit, requiring phototherapy (96%), top-up transfusions (44%: 23.2% immediate, 13.4% late, 7.3% both), and exchange transfusion (37%). An association was found between increased intrauterine transfusion number and reduced phototherapy duration and hospital admission: each additional intrauterine transfusion reduced the duration of phototherapy by 16% (95% CI: 0.72-0.98), and Neonatal Intensive Care Unit/Special Care Baby Unit admission by 44% (95% CI: 0.48-0.66). Following the change in intrauterine transfusion protocol, there was a significant reduction in the number of emergency Caesarean sections occurring directly after an intrauterine transfusion (n =5 *vs* 0; P =0.02). The foetal loss rate within 48 hours of an intrauterine transfusion was 1.9% per pregnancy, or 0.8% per intrauterine transfusion: no losses occurred under the new protocol (n =3 *vs* 0; P = NS).

Discussion. Although the majority of neonates required admission to a Neonatal Intensive Care Unit/ Special Care Baby Unit and phototherapy, the medium-term outcomes were positive. Importantly, the safety of the intrauterine transfusion procedure has improved significantly since the change in protocol.

Keywords: neonatal outcomes, haemolytic disease, intrauterine transfusion, haemolytic disease of the foetus and newborn (HDFN), Rhesus.

Introduction

Haemolytic disease of the foetus and newborn (HDFN) affects approximately 500 pregnancies in England and Wales each year[1]. The major red blood cell antigens against which the causative maternal antibodies form are Rhesus C, c, D, and E, Fy and Kell[1]. Maternal antibody formation against foetal Rhesus D is the most common cause of HDFN, although its incidence decreased greatly following the introduction of routine administration of exogenous anti-D immunoglobulin to at-risk pregnant women[2,3]. In the United Kingdom (UK), HDFN causes the death of 25-30 foetuses or neonates annually, and approximately 20 spontaneous miscarriages prior to 28 weeks of gestation[4]. In the United States it is estimated that HDFN causes 200 foetal losses each year[3].

If untreated, HDFN can result in foetal heart failure, hydrops, and intrauterine death[4]. For the neonate, the most significant consequences of HDFN are anaemia and hyperbilirubinaemia. Current management for at-risk pregnancies includes monitoring for foetal anaemia, followed by intrauterine intravascular transfusion (IUT) for those foetuses with evidence of significant anaemia demonstrated by a middle cerebral artery peak blood flow of 1.5 multiple of median or higher[4,5].

IUT was introduced in 1981[6], and involves the injection of donor blood into the foetal circulation under

ultrasound guidance. Complications of this procedure include rupture of membranes, preterm delivery, infection, the need for emergency Caesarean section, and foetal or neonatal death. A pregnancy affected by HDFN may require multiple IUT, and the National Institute for Health and Clinical Excellence (NICE) guidelines state that each IUT carries a 2% risk of foetal loss[1]. It has been shown that the use of foetal paralysis during the IUT procedure improves outcomes[6].

The Foetal Medicine Unit at St Michael's Hospital (SMH) in Bristol, UK, is a tertiary referral unit that manages pregnancies affected by HDFN throughout South West England and South Wales. In 2004, a change in the local IUT administration protocol was introduced to further optimise safety for the mother and foetus. The aims of this study were: (i) to determine whether IUT outcomes have improved since the introduction of the change in local protocol (outlined in the methods section below); and (ii) to provide better information regarding neonatal outcomes for parents of pregnancies affected by HDFN.

Materials and methods

Data for pregnancies affected by HDFN as a result of haemolytic red cell alloimmunisation and treated with IUT at SMH between 1999 and 2009 were retrospectively collected. Our hospital Foetal Medicine Unit Viewpoint database (Viewpoint Bildverarbeitung GmbH, Webling, Germany) was used to identify all relevant pregnancies; additional maternal data were collected from the UK maternity database (STORK). Neonatal data were collected from the medical notes at the hospitals in which the neonates were delivered. The ethical code of the University Hospitals Bristol NHS Foundation Trust was complied with at all times, and data protection and confidentiality protocols were adhered to.

The maternal data collected were: parity, maternal Rhesus status, number of IUT received during pregnancy, gestational age of the foetus at first IUT, mode of delivery, foetal haemoglobin (Hb) level at the time of IUT, and foetal Hb level post-IUT. The neonatal data collected were: gestational age of the baby at delivery, birth weight, 5-minute APGAR score, cord Hb concentration at delivery, cord bilirubin concentration at delivery, amount of time spent in a Neonatal Intensive Care Unit (NICU) or Special Care Baby Unit (SCBU), duration of phototherapy required, number of exchange transfusions required, and number of top-up transfusions required.

The IUT were later categorised into those performed before and those performed after the introduction of the amended IUT protocol in 2004. The amended protocol included: the attendance of two foetal medicine consultants, the use of foetal sedation with pancuronium or vecuronium, consideration of the intrahepatic vein as the target vessel (rather than solely placental cord insertion), and the use of updated ultrasound equipment.

Results

Missing data

Data regarding the IUT procedures, such as indication, total number required and Hb measurements, were complete for all pregnancies as these were obtainable from the local ViewPoint database. However, it was necessary to collect further neonatal and maternal data from the hospitals throughout the region in which the neonates had been delivered. Unfortunately this was not possible for 18.7% (20/107) of the maternal cases and 21.6% (22/102) of the neonatal cases, because records were not obtainable from satellite hospitals or were missing. As the findings presented in this report are intended to give an overview of outcomes, we have calculated results for the women and neonates for which we have data, and have excluded all those for which data are incomplete.

Intrauterine transfusion procedures

In total, 138 pregnancies were treated with IUT at SMH during the period 1999 to 2009. Of these, 78% (107/138) required IUT for haemolytic red cell alloimmunisation, 15% (21/138) for infection (primarily by Parvovirus), 4% (6/138) for anti-Kell antibody-induced anaemia, 2% (3/138) for complications of monochorionic twin pregnancies, and <1% (1/138) for alpha-thalassaemia. Only cases of haemolytic red cell alloimmunisation were included in this study.

Neonates from the 107 pregnancies managed with IUT for haemolytic red cell alloimmunisation were delivered in 13 hospitals throughout the South West of England and South Wales. In total, 256 IUT were performed for these pregnancies, which were distributed between the six Foetal Medicine Consultants.

Maternal and foetal data

Complete maternal and foetal data were obtained for 83% (89/107) of the pregnancies. The median number of IUT performed per pregnancy was 2 (range, 1 to 7), and the median gestation at the time of the first IUT was 30 weeks (range, 16+0 to 35+5 weeks). An increase in the number of IUT required per pregnancy was associated with a 9% decrease in the duration of phototherapy required (95% CI: 0.84-0.99). Not unexpectedly, higher Hb level and greater gestational age at first IUT were associated with lower numbers of IUT (95% CI: 0.91-0.95 and 0.87-0.96, respectively).

With regards to the mode of delivery, 31.5% (28/89) of pregnancies resulted in induced vaginal delivery, 25.8% (23/89) resulted in elective Caesarean section, 22.5% (20/89) in emergency Caesarean section, and 14.6% (13/89) in spontaneous vaginal delivery; 5.6% (5/89) of the pregnancies did not result in a live birth. The median foetal Hb at the time of the first IUT was 8.1 g/dL (range, 1.9-13.4), and the median gestation at delivery was 36 weeks (range, 24+4 to 42+1 weeks).

Of the 107 pregnancies, five (4.7%) concluded with foetal losses. However, four of these pregnancies required an initial IUT between 16 and 18 weeks of gestation (n =7); the foetal loss rate for pregnancies requiring the first IUT in the 19th week of gestation or beyond (100/107) was 1% (1/100). Importantly, only two of the total foetal losses occurred within 48 hours of an IUT, giving a "direct" foetal loss rate of 1.9% per pregnancy (2/107), or 0.8% per IUT procedure (2/256). This latter figure is below the 2% rate suggested in the NICE guidance[1].

Five of the emergency Caesarean sections recorded occurred within 24 hours of an IUT. Procedure-related foetal distress was recorded as the indication for four of these cases; for the final case it was not possible to retrieve the exact indication from the hospital notes. All five of these emergency Caesarean sections performed within 24 hours of an IUT procedure occurred before the introduction of the new protocol, and all had positive outcomes.

Neonatal data

Complete data were obtained for 80% (82/102) of the live deliveries. Ninety-three per cent (76/82) of the live deliveries had 5-minute APGAR scores of 9 or 10 (range, 7 to 10). All but two neonates were admitted to a NICU/SCBU, with a median admission of 8 days (range, 0-43 days, excluding one neonate who died before discharge at 3 months of age). Eighty-three per cent (85/102) of pregnancies were delivered after 35 weeks of gestation, with 5-minute APGAR scores of 9 or 10.

A higher foetal Hb level at first IUT was associated with a shorter stay in hospital; each point increase in Hb at first IUT reduced hospital admission by 9% (95% CI: 0.86-0.96). Higher gestational age at first IUT was also associated with a shorter hospital admission time, with a 5% decrease in days in hospital for each added week of gestational age (95% CI: 0.92-0.98). Two neonates died before discharge (2.4%): one on the day of delivery due to a complication of exchange transfusion following vessel damage by the umbilical vein catheter; and the other due to extreme prematurity. The latter baby required three IUTs and was born spontaneously at 24 weeks of gestation. It later developed necrotising enterocolitis, requiring surgery, and died after three months in the NICU.

Only two of the neonates did not receive phototherapy. The median duration of phototherapy was 4 days (range, 0-12 days). Thirty of the 82 neonates (37%) received an exchange transfusion as well as phototherapy for hyperbilirubinaemia. The cord blood bilirubin level ranged from 34 to 230 µmol/L. Applied multiple regression models were carried out for duration of phototherapy and duration of hospitalisation: both regressions included Hb at first IUT, gestational age at first IUT, and number of IUT. These models revealed an association between increased number of IUT and a reduced requirement for phototherapy and shorter stay in the NICU/SCBU; each additional IUT received reduced the duration of phototherapy by 16% (95% CI: 0.72-0.98) and hospital stay by 44% (95% CI: 0.48-0.66). The duration of hospital admission was also reduced by 15% for each additional week of gestational age at first IUT (95% CI: 0.81-0.90).

Top-up transfusions were required by 43.9% (36/82) of the neonates: 23.2% (19/82) only required an immediate top-up transfusion before discharge, 13.4% (11/82) did not require immediate top-up but were readmitted within the first 4 months of life for a late (after 1 month) top-up transfusion, and 7.3% (6/82) required both an immediate and a late top-up transfusion. The maximum number of top-up transfusions received was five (two neonates). Intravenous immunoglobulin is not routinely given to neonates at SMH, as is supported by evidence in the literature[7].

Introduction of the new protocol

Table I presents a comparison of data regarding the IUT performed before the implementation of safety measures in 2004, and those performed after. The total number of pregnancies with complete data returned was 44 for the first period, and 45 for the second. Overall, the results are similar for the two groups, but importantly there was a significant reduction in the number of emergency Caesarean sections performed within 24 hours of IUT following the protocol change (n =5 *vs* 0; P =0.02). In addition, although not statistically significant, while overall foetal loss rate within 48 hours of an IUT was 1.9% per pregnancy (2/107), or 0.8% per IUT (2/256), none of these losses occurred under the new protocol (n =3 *vs* 0; P = NS).

Discussion

In keeping with previous studies, our overall findings are positive[2,8]. The majority (83%) of pregnancies with HDFN managed with IUT at SMH during the period 1999 to 2009 were delivered after 35 weeks of gestation and most of the neonates had 5-minute APGAR scores of 9 or 10. Despite this, all but two neonates were admitted to a NICU/SCBU and received phototherapy. An increased number of IUT per pregnancy was found to decrease both the duration of phototherapy and the time spent in hospital.

Five of the 107 (4.7%) pregnancies resulted in foetal loss and there were also two neonatal deaths (1.9%; 2/107), giving an overall loss rate of 6.5% (7/107). Importantly, only 1.9% of the foetal losses (2/107) occurred within 48 hours of an IUT and were, therefore, likely to have been directly procedure-related. In addition, among the pregnancies in which the first

Table I - Maternal and neonatal outcomes before and after the protocol change in 2004.

	Pre-protocol change (1999-2004) n =44	Post-protocol change (2004-2009) n =45	p-values
Maternal outcomes			
Median gestational age at first IUT (range)	30+0 (16+0-35+4)	28+3 (16+1-34+6)	0.204
Median number of IUT (range)	2 (1-4)	2 (1-7)	0.308
Post-IUT Hb successfully measured	77% (34/44)	73% (33/45)	0.859
Mode of delivery:			
- El. CS	8 (18%)	12 (27%)	0.27
- EM. CS	8 (18%)	10 (22%)	0.558
- IVD	14 (32%)	9 (20%)	0.251
- SVD	8 (18%)	7 (7%)	0.818
- Unknown	3 (7%)	4 (9%)	0.67
N. of emergency CS within 24 hours of IUT	5	0	0.02
Neonatal outcomes			
Median n. of days admitted to NICU (range)	7 (0-94)	8 (0-43)	0.957
Median time of phototherapy (range)	5 (0-12)	4 (0-12)	0.798
N. of top-up transfusions required:			
- 0	21	25	0.528
- 1	8	11	0.513
- 2	6	3	0.261
- 3	1	1	0.976
- 4+	4	2	0.369

Legend El. CS: elective Caesarean section; EM. CS: emergency Caesarean section; IVD: induced vaginal delivery; SVD: spontaneous vaginal delivery.

IUT was performed at or after 19 weeks of gestation (100/107), the overall loss rate fell to 2% (2/100), with only 1% (1/100) occurring within 48 hours of an IUT. The loss rate per IUT was 0.8% (2/256) which is in concordance with the 2% rate suggested in the NICE guidance[1].

In particular, our results are largely concordant with those of McGlone *et al.* (2011) in Scotland. This group found that the median gestational age at delivery in a similar population was 35 weeks, with all neonates requiring admission to a NICU and an overall survival rate to discharge of 97.4% (compared with 36 weeks and 97.6% in this present study)[8]. The median duration of phototherapy received by neonates in our study was 4 days, in agreement with both the 3.8 days reported by De Boer *et al.* (2008) and the 5 days by McGlone *et al.* (2011). However, our finding of an association between the number of IUT received per pregnancy and a decrease in both the duration of phototherapy and the time spent in hospital was not replicated in these other studies.

The elective delivery rate among the women in our study is lower than that found by McGlone *et al.* (58% and 87%, respectively), which is surprising considering the similar gestational age at delivery (36 and 35 weeks, respectively), and may be secondary to differences in local protocol regarding gestational age for elective delivery. Interestingly, a higher percentage of our neonates received exchange transfusions, with a corresponding lower percentage of top-up transfusions than other groups: exchange transfusions: 37% *vs* 20% and 50% (Rh c)/44% (RhD); top-up transfusions: 44% *vs* 54% and 62% (Rhc) and 78% (Rh D)[8,9]. This may be due to differences between local protocols regarding gestational age for elective delivery, and NICU criteria for exchange transfusions and top-up transfusions. Rath *et al.* (2010) found that the introduction of a restrictive exchange transfusion protocol for neonates with Rhesus haemolytic disease led to a reduction in the rate of such transfusions with a corresponding increase in the number of top-up transfusions[10]. This is an important finding, as exchange transfusion in neonates with HDFN is reported to be associated with an increased risk of sepsis, leucocytopenia, thrombocytopenia, hypocalcaemia and hypernatraemia[11].

In the management of pregnancies affected by haemolytic red cell alloimmunisation at SMH, the last transfusion is usually given at 35-36 weeks, followed by induction of labour at 37 weeks. This is in order to allow maturation of both the pulmonary and hepatic enzyme systems in the hope of avoiding the need for neonatal exchange transfusions and reducing neonatal management. The NICU at SMH uses neonatal bilirubin concentration and age to determine the need for phototherapy and exchange transfusion, according to treatment thresholds suggested by NICE[12]. The Hb thresholds used for top-up transfusion depend upon the ventilation status and age of the neonate.

The comparison of outcomes before and after the implementation of the amended protocol reveals an improvement in the safety of the IUT procedure, with no emergency Caesarean sections occurring within 48 hours of an IUT since its introduction. Although such a change in protocol had not been specifically tested before, McGlone *et al.* also found a reduction over time in the rate of intrauterine death as a complication of IUT (from 2.3% between 1993 and 1998 to only 0.8% for the period 1999-2004). In a study assessing the feasibility of using cumulative sum (CUSUM) analysis for quality control in IUT, the IUT practice of four clinicians at a hospital in The Netherlands was monitored. The clinician who pioneered IUT at the hospital had a longer learning curve than two clinicians who joined once IUT was established. Analysing the results, the authors suggested that the learning experience was more effective for those taught in an experienced setting, enabling a more acceptable performance from the start[13]. Thus, the improvement in safety of IUT in our hospital after the introduction of the new protocol may in part be due to a natural improvement over time. However, the new protocol was introduced in order to standardise, for all clinicians, the best techniques that the Foetal Medicine Consultants at SMH had developed individually, therefore instigating a definite change in practice that can be measured, rather than a gradual improvement.

It is possible that the missing data affected the outcomes calculated in this study, however the missing information was evenly spread between the different hospitals and throughout the time-course, and it is hoped that this has kept any inconsistencies to a minimum.

Conclusion

Neonatal outcomes of pregnancies managed for HDFN with IUT are positive in the short-term, and the results of this study can be viewed as reassuring by parents of affected pregnancies. However, most neonates will spend at least some time in a NICU/SCBU for phototherapy. Importantly, the safety of the IUT procedure has improved since the introduction of the attendance of two foetal medicine consultants and the use of foetal sedation. In addition, the duration of neonatal hospital admissions and phototherapy has been found to be reduced with increased numbers of IUT given. These data could be useful for other units using similar techniques.

The Authors declare no conflicts of interest.

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