RH HAEMOLYTIC DISEASE OF THE NEWBORN, 1960-1961

BY

PETER M. DUNN*

From the Maternity Hospital, Birmingham

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Before 1941, erythroblastosis foetalis was treated at Birmingham Maternity Hospital by repeated intramuscular injections of fresh blood (Braid, 1939). During the next decade infants with Rh haemolytic disease of the newborn were given repeated intravenous transfusions of Rh negative blood. The exchange transfusion was not introduced until 1950. The first three years’ experience (1950-53) with this new technique was reviewed by Davies, Gerrard, Hatchuel and Howarth in 1953. Two years’ experience of Rh haemolytic disease at the same hospital a decade later forms the subject of this paper.

Methods

Haemoglobin (Hb 100% = 14·8 g./100 ml.) was estimated as oxyhaemoglobin by a photoelectric absorptiometer (Unicam) and serum bilirubin by the Lathe and Ruthven (1958) modification of the diazo method.

Exchange transfusions were performed through the umbilical vein using Henderson’s apparatus (1950). Where possible the tip of the catheter was advanced until it was felt to pass through the ductus venosus into the inferior vena cava, usually a distance of approximately 3½ in. (9 cm.). Warm, fresh, citrated, two-thirds packed donor blood was used. Individual 10 ml. volumes were exchanged until a total of 80-100 ml./lb. (175-220 ml./kg.) had been reached; 5 ml. volumes were used when the infant was very small or sick. Clotting in the apparatus was prevented by regular flushing with heparinized saline. The infant was kept comfortable by laying him, with the minimum of restraint, on a pillow warmed by an electric blanket or, occasionally, by performing the transfusion through the port-hole of an incubator. Oxygen was administered to all severely affected infants with the aid of a small ‘perspex’ hood. Digoxin was given by intramuscular injection if there was evidence of heart failure. Signs suggestive of tetany due to citrate intoxication were counteracted with calcium gluconate. The ‘exchange’ usually took one and a half to two hours, but was extended for several hours when necessary.

Simple transfusions were given by slow injection into a scalp vein of 10-15 ml. per lb. (22-36 ml./kg.) body weight of fully packed Rh negative blood.

Clinical Material

During 1960 and 1961, 4,754 babies were born at the Birmingham Maternity Hospital. 3·8% of all babies delivered suffered from Rh haemolytic disease in contrast to the national average of 0·5%. The booking policy probably resulted in a greater proportion of severely affected infants than would be expected.

The fate of the 215 babies born to women with Rh antibodies is summarized in Fig. 1. Of these, 35 infants (16%) were Rh negative and unaffected. The Coombs test on the remaining 180 (84%) was positive. Incompatibility was due to Rh ‘D’ in all cases except three in which either Rh ‘E’ (2) or Rh ‘C’ (1) was implicated. Of the affected infants, 14 (7·7%) were stillborn and a further nine died (5%), bringing the perinatal mortality to 12·7%. One clinical diagnosis of early kernicterus was made.

The cord blood findings of the 166 liveborn babies are shown in Fig. 2 in relation to exchange transfusion therapy, the development of obstructive jaundice and mortality. 86 infants (51-9%) did not require an exchange transfusion. Of the remaining 80 babies (48·1%), 47 received one and 33 two exchange transfusions. Three of the latter required yet a third exchange, bringing the total to 116 exchanges.

‘Early’ exchange transfusion within nine hours of birth (Walker, 1961) was performed 69 times. The remaining 11 first and the 36 repeat exchange transfusions were performed because the indirect reacting bilirubin level rose or threatened to rise over 20 mg./100 ml. 88% of the exchange transfusions were performed during the first 48 hours of life and 98% before the age of 72 hours.

All the nine infants that died did so during the first day of life, two within minutes of birth, two during exchange transfusion, and five later. No baby with a cord-blood haemoglobin over 75% (11·0 g./100 ml.) died. Half the 12 babies with cord blood haemoglobins
below 50% (7.4 g./100 ml.) survived, one of these having a haemoglobin of 25% (3.7 g./100 ml.) at birth.

Simple transfusion for late anaemia, defined as a haemoglobin below 45-50% after the first week of life, was required by 17 infants, or 10-7% of the survivors. Five infants who had not previously received an exchange transfusion, required a simple transfusion during the first month but not thereafter (Fig. 3). Eleven infants who had previously received an exchange transfusion, required simple transfusion between the fourth and seventh weeks. Over half (six) had shown evidence of obstructive jaundice.

From an analysis of the babies’ weight, the haemoglobin before and after transfusion and the volume of blood given in these cases, it was found that for every 1 ml. of packed blood/lb. (2-2 ml./kg.) body weight transfused, the haemoglobin was raised on the average by 3-6% (0.53 g./100 ml.), the range being 2-5-5-0%.

While outside the scope of this paper, it might be of interest to add that during this two-year period eight babies received exchange transfusions for hyperbilirubinaemia due to either ABO incompatibility (four) or associated with prematurity (four). One late transfusion was given for anaemia of prematurity.

Discussion

The changes in the incidence of Rh haemolytic disease, its management and mortality at the Birmingham Maternity Hospital between 1950-53 and 1960-61 are shown in the Table.

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<tr>
<td>Average number of babies with Rh haemolytic disease per year</td>
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<tr>
<td>Babies receiving exchange transfusion therapy (%)</td>
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<td>Babies receiving repeat exchange transfusion (%)</td>
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<td>Babies receiving simple transfusion only (%)</td>
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<td>Babies receiving no transfusion therapy (%)</td>
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<td>Perinatal mortality (%)</td>
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<td>Incidence of kernikterus (%)</td>
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The number of babies with Rh haemolytic disease delivered in this hospital increased nearly threefold in a decade. This was probably in the main due to improved prenatal diagnosis and also to the attempt to deal with this problem in a few large centres (Walker and Mollison, 1957; Walker, 1958). However, it is possible that there has been an actual
increase in incidence. If this is so, it might be due to modern trends in the management of the third stage of labour. If the umbilical cord is clamped before the uterus is well contracted, a considerable quantity of foetal blood may remain in the placenta. Rupture of the foetal placental vessels into the maternal sinuses and sensitization might then more easily follow expulsive uterine contractions, especially if these are enhanced by the use of ergometrine.

The fivefold increase in the annual number of exchange transfusions from 11 (1950-53) to 58 (1960-61) reflects both the increased preference of exchange to simple transfusion and the realization that repeated exchange transfusions are often necessary (Diamond, Allen, Vann and Powers, 1952). Also the decrease in the perinatal mortality indicates that an increased number of severe cases survives to require transfusion.

The perinatal mortality depends largely on the prenatal management. At this hospital it was usual to leave these women to reach term and then to induce labour when necessary. Premature induction or delivery by caesarean section was mainly reserved for those cases with a past history of rhesus stillbirth or very severely affected infant, or where clinical examination, knowledge of the father's genotype, liquor amnii and maternal antibody studies suggested that the baby was at severe risk. The mortality among 13 babies delivered before 36 weeks' gestation (Fig. 4) was 10 times as high as for the whole series, accounting for seven of the nine deaths. The susceptibility of these babies, usually severe cases delivered by caesarean section, to develop the respiratory distress syndrome was undoubtedly a major factor. Because of these results, delivery before 36 weeks was, in the latter half of this series, rarely practised, but it was on occasion followed by success. For example, a mother with a past history of two premature hydropic stillbirths was delivered by caesarean section at 33 weeks of a prehydropic infant. After two exchange transfusions and in spite of respiratory distress syndrome, the infant survived.

Without selective premature delivery, the neonatal mortality might have been reduced, but the stillbirth rate would almost certainly have risen more. Our policy resulted in a survival rate of 87-3, which stands comparison with the 84% reported from Newcastle (Walker, 1959) and the 87·8% from Bristol (Tovey and Valaes, 1959) and appears to have struck a fair balance between the increased hazards of prematurity and the risks of intrauterine death.

Of the 23 perinatal deaths in this series, 14 infants were either stillborn or delivered in a hydrotic state before the 37th week of gestation and a further baby was an anencephalic. It could be argued that only the remaining eight infants (4·8% of the series) had a chance of survival with different management.

The decision to perform an 'early' exchange transfusion used to be made entirely on the cord blood findings. This has been found to result in a number of unnecessary transfusions, for as Walker (1961) has shown, a 'wait and watch' policy for infants with cord haemoglobin above 77%, 11·5 g./100 ml., was not only safe but might be of benefit. In this series, both cord blood findings and clinical judgement was used in deciding whether to transfuse, and the high proportion of babies not receiving exchange transfusion (51·9%) without ill effects vindicates this policy. Walker (1959) states that 40% of affected infants do not require any transfusion therapy at all. In this series, the figure was 48·9%. In retrospect, babies that showed clinical evidence of haemolytic disease such as jaundice, hepatosplenomegaly or pallor due to anaemia during the first nine hours, required an exchange transfusion. Prematurity alone was not an indication but acted as a bias in borderline cases. From Fig. 2 it can be seen that the need for exchange transfusion could have been predicted in 90% of cases by the cord blood findings of a haemoglobin below 90% combined with a serum bilirubin above 3·5 mg./100 ml. The needs of the remaining 10% and the need for repeat exchange transfusion were only recognized by observation, in particular of the rate of rise of the serum bilirubin. As a working hypothesis, it was considered that the serum bilirubin would 'peak' in a full-term baby at 60 hours of age and in a baby of 36 weeks' gestation at 80 hours. By using a graph (Fig. 5) containing these data, it was possible to anticipate the likelihood of hyperbilirubinaemia and, where necessary, transfuse
in advance. This method implies that a rise of serum bilirubin greater than 0.3 mg./hour in a mature baby (0.2 mg./hour at 36 weeks' gestation) was potentially dangerous. Although this is a considerably lower criterion than the rate of 0.5 mg./hour recommended as a guide by Walker (1959) and Adelman, Bell, Giunta, Barrett, Bellin and Appleton (1959), its use in this series was not reflected by a high 'exchange' rate. The value of this hypothesis was supported by the fact that only 3% of the exchange transfusions were performed on babies more than 60 hours old.

No baby was ever considered too ill to transfuse and, with the exception of the two infants that died, the full exchange was always completed. Unexplained deaths during exchange transfusion as described by Forfar, Keay, Elliott and Cumming (1958) and Walker (1959) were not seen, an adequate cause of death being apparent for the two babies that died. One had a cerebral birth injury and the other died from heart failure due to severe anaemia (cord blood Hb, 40%, 5.9 g./100 ml.) and an over-rapid transfusion. Air embolism, umbilical infection and portal vein thrombosis were not encountered.

The baby who showed signs of kernikterus did so at the age of 48 hours after receiving three full exchange transfusions. At the time his indirect reacting serum bilirubin level was 20.9 mg./100 ml. though owing to an error in estimation we believed it to be lower. This infant showed signs of slight muscular incoordination and selective deafness at the age of 1 year.

The follow-up of babies with haemolytic disease may be difficult when there are long distances to travel. The data on simple transfusion for late anaemia in this series (Fig. 3) may help to indicate what supervision is necessary. The high incidence of severe anaemia amongst babies that had exhibited the 'inspissated bile syndrome' is worth re-emphasizing. This condition, in which obstructive jaundice develops, occurred in approximately 8% of the babies with Rh haemolytic disease and was considered to be due to liver damage (Dunn, 1963).

Summary

The management of 180 infants with Rh haemolytic disease of the newborn at a maternity hospital during 1960 and 1961 is described and discussed. The perinatal mortality was 12.7% and there was one case of kernikterus.

The changes in the incidence of this disease, and its management and mortality at this hospital during the past decade are reviewed.

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REFERENCES