THE PLACE OF EXCHANGE TRANSFUSION IN NEONATAL JAUNDICE

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In this era of sharply reduced perinatal mortality, erythroblastosis foetalis is still responsible for many deaths and will continue to be a major problem until full protection of Rh negative mothers can be achieved with anti-D immunoglobulins. Due to increasing knowledge of pathophysiology of erythroblastosis foetalis and the prediction of its severity by amniotic fluid analysis, intrauterine foetal deaths can be avoided by intrauterine foetal transfusion or preterm delivery. Yet, exchange transfusion is the most important part of the treatment to combat anaemia and hyperbilirubinaemia.

During the period of seven years, that is from January 1965 to October 1971, 390 cases of neonatal jaundice were investigated and analysed in the N. A. Purandare Research Centre at K.E.M. Hospital. Table 1 shows the causes of jaundice.

In 137 cases etiological factor was presumed to be ABO incompatibility as no other factor responsible for jaundice could be found. Probably, prematurity might have played some role in the production jaundice. Anti-A and -B antibody titre was detected only in 37 mothers and thus ABO incompatibility was proved.

TABLE I

Etiological Factors

Etiological factor	No. of cases	Percentage
Rh incompatibility	72	18.5
ABO Incompatibility	137	35
G6PD deficiency	12	3.1
Prematurity	140	36
Infection	13	3.3
Haemorrhagic conditions	14	3.6
Syphilis	2	0.5

In Rh incompatibility, the jaundice was severe enough to require exchange transfusion in 75% of babies while in ABO incompatibility few required exchange transfusion as the severity of jaundice was less. Table II shows the number of babies requiring exchange transfusion in each group.

The details of the 40 cases of neonatal jaundice who were treated by exchange transfusion in the Department of Obstetrics of K.E.M. Hospital are presented. Table III shows the causes of jaundice in these 40 cases and number of exchange transfusions given in each group.

The number of exchange transfusions required by Rh immunised babies was more than by those with ABO incompatibility and G6PD deficiency.

Management of Rh immunised patient:

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TABLE II

Number of Babies Requiring Exchange Transfusion

Disease	No. of babies jaundiced	No. of babies requiring exchange transfusion	Percentage
Rh incompatibility	72	54	75
ABO incompatibility	137	37	28
G6PD deficiency	12	9	75
Prematurity	140	7	5
Haemorrhagic conditions	14	3	21.5
Infection	13	1	7.5
Syphilis	2	-	-

TABLE III

Causes of Jaundice in 40 Cases Requiring Exchange Transfusion

	Etiological Factor			Total
	Rh incompatibility	ABO incompatibility	G6PD deficiency	
No. of babies transfused	26	11	3	40
No. of exchange transfusions	52	13	3	68

(a) *Antenatal Care:*

Rh negative immunised mothers were carefully examined for antibody titre. Serial spectrophotometric studies of amniotic fluid were done in those with antibody titre of more than 1:32 or with a history of previous neonatal deaths. Preterm delivery was thus advised in selected cases.

(b) *At and After Birth:*

Every effort was made to prevent anoxia at birth. Cord blood samples were collected and following studies were done:

(a) Direct Coombs test,
(b) ABO and Rh blood grouping,
(c) Estimation of plasma bilirubin,
(d) Measurement of haemoglobin.

Baby was examined for pallor, jaundice, petichiae, oedema and hepatosplenomegaly. Baby was kept in the labour ward until the baby steered past the risk of hyperbilirubinemia.

Indications for Exchange Transfusion

1. A positive direct Coombs test though indicates the sensitization of foetal cells, other parameters such as haemoglobin, bilirubin, past obstetric history, are also necessary to judge the indication of exchange transfusion.

2. A cord blood haemoglobin less than 10.5 g.% or cord blood indirect bilirubin more than 4 mg% was an indication for exchange transfusion as soon after birth as possible. In premature babies, exchange transfusions were given even when bilirubin was less.

3. The presence of clinically severe disease as evidenced by pallor, oedema, petichiae, enlarged liver and spleen was an indication for prompt exchange transfusion.

4. If the cord blood haemoglobin was higher than 10.5 g.% or bilirubin less than 4 mg%, haemoglobin and bilirubin estimations were regularly followed up at intervals of 6-12 hours depending upon the degree of jaundice and general condition of the baby until serum bilirubin started falling. When the rate of rise was 6 mg/6 hours, it definitely showed the need for exchange transfusion. When the rate of rise was 2 mg/6 hours, we waited till further estimations were done.

5. Repeat exchange transfusions were given when serum bilirubin exceeded 20-25 mg% or earlier if the rate of rise of serum bilirubin was considerable. As many as 3-4 exchange transfusions were necessary in severely involved infants.

6. Past obstetric history revealing a history of jaundice and exchange transfusion in previous baby of a homozygous father or a high antibody titre in mother were additional factors to judge the need for exchange transfusion.

The decision for exchange transfusion was taken after assessing the overall picture and not merely by presence of one indication.

The babies who developed jaundice in the ward and whose mothers have had no antenatal investigations done were managed in the following manner:

Baby's blood was investigated for Coombs test, haemoglobin, bilirubin, ABO and Rh grouping. Screening of mother's blood was done for Rh and ABO antibodies. Serological investigations were done for G6PD deficiency and syphilis.

In our study, cord blood haemoglobin and bilirubin estimations were done in 25 babies out of which 24 were known Rh immunised and one was ABO immunised. Table IV shows level of cord blood bilirubin in Rh immunised babies.

TABLE IV

Level of Cord Blood Bilirubin in Rh Immunised Babies

Bilirubin in mg%	No. of babies
2.5 - 4	7
4.1 - 6	10
6.1 - 8	6
More than 8	1

Minimal cord blood bilirubin recorded was 2.5 mg% and maximum was 9 mg% in one baby. This baby was immediately taken for exchange transfusion but could not stand the procedure and died within half an hour of the procedure.

Pre-exchange transfusion bilirubin levels in the remaining 16 babies are shown in Table V.

In ABO group, pre-exchange bilirubin was more than 20 mg% in most of the cases as these babies were followed after jaundice developed. Bilirubin estimations were not done from the first day. In one case, history of jaundice and exchange transfusion in previous baby was available and the cord blood bilirubin was 3 mg%. Mother also showed a high anti-A antibody titre. On the third day, bilirubin level had reached 19 mg% when the first exchange transfusion was given. On the fourth day, second exchange transfusion was given when bilirubin rose to 26 mg%.

TABLE V

Pre-exchange Transfusion Bilirubin Levels in 16 Babies

Bilirubin in mg%	No. of babies		
	Rh	ABO	G6PD
Less than 20	1	1	-
21 - 25	1	6	3
26 - 30	-	2	-
31 - 35	-	1	-
More than 35	-	1	-

TABLE VI

Day of First Exchange Transfusion

Etiological factor	1st day	2nd day	3rd day	4th day
Rh incompatibility	17	5	3	1
ABO incompatibility	-	3	6	2
G6PD deficiency	-	-	3	-

The day of first exchange transfusion is shown in Table VI.

Seventeen babies with Rh incompatibility and cord blood bilirubin of more than 4.0 mg% were transfused on the 1st day. Remaining were observed closely for severity of jaundice. Haemoglobin and bilirubin estimations were done at 6-12 hours interval and accordingly exchange transfusions were carried out on the 2nd, 3rd or 4th day. In ABO incompatibility jaundice was not severe enough to need exchange on 1st day and majority of exchange transfusions were given on 3rd or 4th day.

Selection of Donor

Donor's blood compatible with mother's serum was selected. In Rh incompatibility, fresh Rh negative blood was used preferably of less than 48 hours duration, so as to transfuse red cells with maximum life span and to lessen the toxic effect of potassium. Faced with the poor choice of donors we have at times used donor's blood after removing quite a good amount of plasma. Removal of plasma not only improved haemoglobin level but also reduced the toxic effect of citrate and potassium. In general, we used Rh negative blood of the same major group of the baby. In ABO incompatibility, O positive blood was used. In those cases in which severe disease was anticipated, we obtained group 0 Rh negative blood while the mother was in labour and used without a slightest hesitation, no matter what the ABO group of the baby was. In any case, donor's blood used was always compatible with mother's.

Technique of Exchange Transfusion

The whole procedure including the apparatus is very simple but requires meticulous asepsis and great vigilance to prevent complications. The apparatus consists of 2 three-way connections, a catheter for umbilical vein and polythelin tubings for connecting three-way to donor's and discard bottles.

All exchange transfusions were carried out in the operation theatre under strictest possible asepsis. The catheter was inserted in the umbilical vein. By alternate withdrawing and introducing equal amounts (20 ml) transfusion was carried out. Total amounts withdrawn and put in was accurately balanced. One ml. of calcium gluconate 10% was injected every 100 ml. of blood in order to maintain the blood calcium level in the infant and thus prevent tetany. Duration required for each exchange transfusion varied between 1-2 hours according to the infant's condition. It was carried out very slowly in premature babies and in babies with general poor condition. Total amount of blood given per exchange was calculated according to the weight of infant, 160 ml./kg. and averaged between 400-500 ml. Utmost care was taken to prevent air entry in the system and prevent air embolism. Throughout the procedure, infant was carefully observed for signs of cardiac and respiratory distress.

Pre- and post-exchange samples of baby's blood were collected to determine the haemoglobin and bilirubin levels and to assess the effectiveness of exchange transfusion.

Following exchange transfusion, antibiotics, sedatives and digitalis, if necessary, were given. Bilirubin and haemoglobin levels were measured every 8-12 hours. Repeat exchange transfusions were carried out for the reasons already discussed. Multiple exchanges were required by Rh incompatible babies. Maximum number given to one baby was 4. The number of exchange transfusions given is shown in Table VII.

carefully observed. All preparations for exchange transfusions were made when patients were in labour.

In ABO group, incompatibility was diagnosed after the appearance of jaundice on 2nd or 3rd day. The bilirubin levels had already reached or exceeded critical levels and thus the fall in bilirubin level was more.

The rise in the haemoglobin level was also dependent upon the pre-exchange haemoglobin level. Rise was inversely proportional to pre-exchange value. It was quite significant by 3-4 gms in those with haemoglobin less than 13 g.%. No significant change was observed where haemoglobin level was between 13-16 g.%. A slight fall in level was noticed in those with haemoglobin more than 16 g.%.

TABLE VII

Day of First Exchange Transfusion

Disease	No. of babies transfused	No. of exchange transfusions given			
		1	2	3	4
Rh incompatibility	26	7	13	5	1
ABO incompatibility	11	9	2	-	-
G6PD deficiency	3	3	-	-	-

Average fall in bilirubin per exchange in different groups is shown in Table VIII.

TABLE VIII

Average Fall in Bilirubin After Exchange Transfusion

Rh incompatibilty	8.8 mg.%
ABO incompatibility	12.5 mg.%
G6PD deficiency	11.0 mg.%

The average fall in serum bilirubin was proportional to pre-exchange bilirubin levels. In Rh incompatibility, the fall was less as the initial or pre-exchange levels were low. The reason being most of the exchanges were carried out earlier within 24 hours before the critical levels were reached. Another reason was most of the Rh negative mothers were detected during antenatal period and were

Mortality

The total number of deaths among the 40 babies transfused was 9, out of which 8 belonged to Rh group while one to ABO group. Out of the 8 deaths, 4 were attributable to severe anaemia and associated cardiac failure due to haemolysis. These babies could not stand the procedure and died during it. All the 4 cases had haemoglobin levels of less than 8.5 g.%. Among the rest of the deaths, 3 were due to septicaemia which was of course a complication of exchange transfusion; and one died 15 days after the

exchange. Baby was given a top up transfusion for anaemia and death occurred during transfusion. The one in ABO group died of diarrhoea and thus the death was not related to exchange transfusion.

Total mortality rate after excluding the death due to diarrhoea was 20%. Mortality rate per 100 exchange transfusions was 6%.

Discussion

Commonly, obstetrician is confronted in making a diagnosis in infants with syndrome characterised by jaundice, specially in early neonatal period. The aim of the exchange transfusion is to reduce neonatal mortality and morbidity due to hyperbilirubinaemia and resultant kernicterus or anaemia which may culminate into heart failure. Occasionally, an infant with kernicterus survives and initially appears normal, later however, he will show varying degrees of athetosis, spasticity, deafness and mental retardation, etc. Before the advent of exchange transfusion, kernicterus accounted for 5% of all cases of cerebral palsy and 20% of those with athetoid cerebral palsy.

Exchange transfusion was first advocated and performed by Wallerstein in 1946 by removing blood from sagittal sinus and transfusion through canulated peripheral vein. Exchange transfusion through umbilical vein was given first by Allen and Diamond.

Exchange transfusion is essentially a flushing out process whereby the circulating blood of the baby is gradually replaced or diluted with donor's blood until at the end of the transfusion, most of the circulating blood, 85-90%, is donor's blood. In this way, Rh positive cells of the baby which get haemolysed, are replaced by Rh negative cells, Rh antibodies present in the plasma are removed and lastly the excess of bilirubin is also removed. Thereby, kernicterus is prevented and anaemia is also corrected. Amount of bilirubin removed is only 20-25% of the total body bilirubin. The rest of the bilirubin which has already been diffused in the tissues is not removed. A gradient is formed between tissue and blood levels of bilirubin and thus bilirubin from the tissues goes back to the blood and a further rise in its level takes place. This explains the importance of timely administration of 1st and need of repeat transfusions.

Although the procedure sounds very plain and simple, it is not devoid of hazards which include:

(1) *Cardiac:* Heart failure due to hypervolaemia transfusion over load, cardiac arrest due to hypercalaemia, hypocalaemia and citrate toxicity.

(2) *Emboli and thrombosis*—Air emboli due to faulty transfusion technique, portal thrombosis due to excess of trauma to umbilical vein.

(3) *Bleeding* due to perforation of umbilical vein at the time of catheterisation or thrombocytopenia.

(4) *Sepsis*—Bacterial due to poor technique at exchange transfusion and hepatitis due to donor's blood borne virus.

Majority of the complications are avoidable.

Summary

The possible etiology of 390 cases of neonatal jaundice is presented.

Forty cases of neonatal jaundice who were treated with 68 exchange transfusions are discussed in greater details.

The investigations of sensitised and jaundiced babies are enumerated.

The principles and aims of exchange transfusions and the indications, techni-

que and complications of the procedure are described.

The etiopathology of neonatal jaundice and the place of exchange transfusion in neonatal jaundice is discussed.

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References

1. Allen, F. H. and Diamond, L. K.: Erythroblastosis Foetalis by Allen & Diamond, J. A. Churchill Ltd., London P—51.
2. Bentley, H. A., Ziegler, N. R. and Krivit, W.: Am. J. Dis. Child. 99: 8, 1960.
3. Boggs, T. R. Jr. and Westphal, M. C.: Paediatrics 26: 745, 1960.
4. Brown, A. K., Zuelzer, W. W. and Robinson, A. R.: Am. J. Dis. Child. 93: 274, 1957.
5. Crosse, V. M., Wallis, P. G. and Walsh, A. M.: Arch. Dis. Childh. 33: 403, 1958.
6. Forfar, J. O., Keay, A. J., Elliot, W. D. and Cumming, R. A.: Lancet 2: 1131, 1958.
7. Jablonski, W. J.: New Engl. J. Med. 266: 155, 1962.
8. John, M., Borrman, M. B., Rhinehant, F. and Friesen, M. D.: Current paediatric therapy 4. 1966-67.
9. Marting, L., Wagoner, S. C. and Wilson, V. C.: Am. J. Dis. Child. 89: 289, 1955.
10. Wallestein, H.: Quoted in Erythoblastics is foetalis by Allen & Diamond London. Churchill Ltd., P—52.
11. Wright, T.: Arch. Dis. Childh. 36: 400, 1961.