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"EARLY" EXCHANGE TRANSFUSION

BY

WILLIAM WALKER, M.D.

Department of Child Health, Durham University Medical School, King's College, Newcastle upon Tyne

"Early" exchange transfusion is the accepted treatment in severe haemolytic disease of the newborn, but the definition of early is rarely precise. In the most severely affected infants—those very anaemic and in congestive heart failure at birth—exchange transfusion is urgently required and should be undertaken within a few minutes. In such cases the immediate benefit results from the lowering of venous pressure and the raising of the haemoglobin level. In other cases the chief purpose of exchange transfusion is to remove "sensitized" erythrocytes from the infant, and to replace them with donor cells that will not be affected by the antibody concerned. At the completion of exchange transfusion at least 80% of the circulating red cells should be donor cells having a normal life-span. Thus haemolysis is reduced and the risk that jaundice or anaemia will develop is minimized.

In the majority of infants exchange transfusion is not urgently required and a delay of some hours may be advantageous in enabling the infant to recover from distress associated with delivery. However, during the delay red cells are being destroyed and the resulting bilirubin accumulates because the capacity of the liver to excrete bilirubin is greatly reduced in the newborn infant (Billing *et al.*, 1954).

These factors must be taken into account in choosing the time for exchange transfusion, and during the trial of exchange transfusion *versus* simple transfusion in haemolytic disease of the newborn (Mollison and Walker, 1952) the rules required that exchange transfusion, if selected, should be undertaken within nine hours of birth. After this trial was completed we continued to perform exchange transfusion within this time limit whenever possible, but in recent years we have been prepared to delay transfusion up to about 16 hours provided that the infant's cord haemoglobin value was higher than 11.5 g./100 ml.—that is, the infant was not severely affected.

The purpose of the present study is to review this new policy in the light of experience and to judge whether it is justified.

Material and Method

In the years 1958, 1959, and 1960 80 infants born in hospitals and selected for exchange transfusion on the basis of cord blood values (Walker, 1959) were treated between 9 and 24 hours of life, 67 between 9 and 16 hours. Of these infants, 76 had cord haemoglobin values greater than 11.5 g./100 ml. and four had values between 7.4 and 11.5 g./100 ml. Some infants were born in "outside" hospitals and transferred to

Newcastle for treatment, and this caused delay. However, their inclusion is thought to be justified, for any effect produced would be to disfavour later treatment. In fact, their exclusion does not materially affect the results. During the same period 126 additional infants with cord haemoglobin values greater than 11.5 g./100 ml. were selected for exchange transfusion and treated within one to nine hours of birth.

The usual factor determining the age at which exchange transfusion was performed was the time of day when birth occurred. Thus 80% of infants treated between 9 and 24 hours but only 14% of those treated between one and nine hours were born between 7 p.m. and 3 a.m. Exclusion of the exceptions does not alter the findings significantly.

Although the need for and time of exchange transfusion were decided on the cord-blood results it is appreciated that some "selection" may have occurred. Thus if the cord haemoglobin value was only a little above 11.5 g./100 ml., or if early clinical evidence of disease was present, exchange transfusion was probably performed earlier.

In considering the results we sought to avoid bias due to "selection" by a system of "paired cases." Each infant who had been treated between 9 and 24 hours was "paired" with regard to birth weight, cord haemoglobin, and cord bilirubin level with an infant treated earlier. Four pairs with cord haemoglobin values below 11.5 g./100 ml. were included.

Fifty infants with cord haemoglobin values greater than 11.5 g./100 ml. but who were treated in the first nine hours of life were not paired. That the time of exchange transfusion may have been advanced in some of these cases is suggested by our observation that in 46% of them jaundice occurred within the first eight hours of life, whereas this was true for only 35% of both groups of paired cases. With regard to the cord haemoglobin value, too, there is a difference, as shown in Table I.

TABLE I.—Distribution of Cord Haemoglobin Value for "Paired" and "Unpaired" Cases in Relation to Age at Exchange Transfusion

	Cord Haemoglobin (g./100 ml.)			
	7.4-11.5	11.6-14	14-15	Over 15
Paired cases treated after 9 hours	5%	24%	36%	35%
Paired cases treated before 9 hours	5%	25%	32%	38%
Unpaired cases treated before 9 hours	4%	58%	36%	2%

A large proportion of unpaired cases had relatively low cord haemoglobin values and only one had a value over 15 g./100 ml., a level above which bilirubin estimation would be needed before deciding on the need for exchange transfusion. This suggests that where the cord haemoglobin value was relatively low and exchange transfusion clearly indicated there was a tendency to proceed with this within nine hours of birth.

We consider that the pairing of cases has largely eliminated errors due to selection, for close correspondence between each pair was achieved for birth weight, cord haemoglobin, and cord bilirubin values (Table I and Fig. 1).

The average weight of infants treated after nine hours was 2½ oz. (70 g.) less than that of infants treated earlier. In 58 pairs the difference in weight was 8 oz. (227 g.) or less, and differences greater than this were confined to babies with a birth weight of over 6 lb. (2,720 g.). In fact, all but eight of these weighed over 7 lb. (3,175 g.).

The average cord bilirubin value of infants treated after nine hours was 0.05 mg./100 ml. lower than

FIG. 1.—Birth weight and cord haemoglobin and bilirubin values in 80 pairs of cases receiving exchange transfusion before (white columns) or after (hatched columns) nine hours.

that of infants treated earlier. All but six pairs had cord bilirubin levels within 0.5 mg./100 ml. Greater differences were restricted to patients with relatively mild disease, the biggest difference being 1.8 mg./100 ml., which occurred in a pair of infants each of whom had a cord haemoglobin value of 15.5 g./100 ml.

The average cord haemoglobin value of infants treated after nine hours was 0.05 g./100 ml. higher than of those treated earlier. In all but 10 pairs the cord haemoglobin value of each pair corresponded within 1.5 g./100 ml. Greater differences, the greatest being 3 g./100 ml., were confined to relatively mildly affected infants. In the group treated early there were six infants in whom the cord haemoglobin value had not been determined but who corresponded with regard to both weight and cord bilirubin.

Sex was not taken into account when the selection of pairs was made, but the distribution was similar in the

two groups, being equal in the cases treated before nine hours and 37 males to 43 females in the group treated after this time.

The age at which exchange transfusion was performed is shown in Fig. 2. Otherwise the method and details of exchange transfusion were the same for both groups

FIG. 2.—Age of infants at time of exchange transfusion.

of infants: 76 in each group receiving an exchange transfusion of over 70 ml./lb. (154 ml./kg.), the remainder receiving between 60 and 70 ml./lb. (132 and 154 ml./kg.).

Any differences that can be demonstrated between the two groups can probably be attributed to the effect of age at exchange transfusion, for there is no real difference with regard to the other factors most likely to influence response to treatment—namely, birth weight, cord haemoglobin level, cord bilirubin value, sex, and method of exchange transfusion.

The two groups have been compared with regard to the time of onset and severity of jaundice, the bilirubin level after exchange transfusion, the need for subsequent transfusion, and the final result.

Results

Jaundice After Exchange Transfusion.—The maximal degree of jaundice in relation to the time at which exchange transfusion was performed is shown in Table II. Sixty-seven of the infants treated in the first nine hours of life developed jaundice, but this was so for 75 of those treated later. The frequency of mild and severe jaundice was the same in both groups, but moderate degrees of jaundice were more common in the group treated after nine hours. The development of jaundice within the first eight hours of life was not

TABLE II.—Age at Exchange Transfusion in Relation to Subsequent Maximal Jaundice

Maximal Jaundice after Transfusion	Time of Exchange Transfusion	
	1-9 Hours No. of Cases	9-24 Hours No. of Cases
Nil	13	5
Mild	25	21
Moderate	24	35
Severe	12	14
Very severe	6	5
Total cases ..	80	80

related to the age at which exchange transfusion was performed but was probably determined by factors already present at birth. However, jaundice developed between 9 and 24 hours more frequently in infants where later exchange transfusion was carried out. Thus jaundice was present on the first day in 68 of the infants treated after nine hours but in 55 treated before this time. On the other hand, jaundice developed between one and three days in 12 infants treated before nine hours but in only seven treated later. It would therefore

seem that early exchange transfusion may delay the onset of jaundice in some infants and prevent it altogether in others. On the other hand, exchange transfusion in the period one to nine hours was not more effective than exchange transfusion between 9 and 16 hours in preventing severe jaundice. Bilirubin estimations were performed only in infants who developed moderately severe jaundice. The maximal levels reached in relation to the age at transfusion are shown in Table III. Bilirubin levels of over 15 mg./100 ml. were observed in 16 infants treated between one and nine hours but in 18 infants transfused after this time.

TABLE III.—Age at Exchange Transfusion in Relation to Subsequent Maximum Recorded Bilirubin Level

Maximum Recorded Bilirubin Level	Time of Exchange Transfusion	
	1-9 Hours No. of Cases	9-24 Hours No. of Cases
0-10 mg./100 ml. . .	5	3
10-1-15 " . .	9	5
15-1-20 " . .	9	9
20-1-25 " . .	5	6
>25 " . .	2	3
Total cases . .	30	26

Need for Subsequent Treatment.—During the years concerned repeated exchange transfusion was carried out if the bilirubin level reached approximately 25 mg./100 ml. Five infants in each group required two exchange transfusions, while an additional two in each group required more: three received three exchange transfusions and one four. This latter infant had been treated initially at six hours. Of the 14 cases requiring repeated exchange transfusion, no two constituted a corresponding pair. Seventeen infants received simple transfusion for the relief of anaemia because the haemoglobin level fell to approximately 7.4 g./100 ml. within the first six weeks of life. Twelve of these had been treated initially in the first nine hours of life and five had received later exchange transfusion.

Effect of Treatment.—Deterioration of the infant's clinical condition during exchange transfusion occurred in six infants transfused within one to nine hours but in only three treated after this time. The condition during exchange transfusion was recorded as good in 46 and satisfactory in 24 infants treated early, and as good in 51 and satisfactory in 25 treated later. All the infants treated by exchange transfusion between 9 and 24 hours survived, but two deaths occurred in the cases treated between one and nine hours, although neither was attributed to haemolytic disease of the newborn. Both occurred from congenital heart disease.

Discussion

Antenatal prediction of haemolytic disease of the newborn is sought in order that affected infants may be born in hospitals which provide full facilities for early exchange transfusion. In infants very severely affected the clinical condition at birth provides a clear indication for immediate exchange transfusion, and in such cases delay even to complete tests on cord blood is not justified. In less severely affected infants tests of cord blood are required before the need for exchange transfusion can be decided, but in such cases exchange transfusion is not urgently required. When the cord haemoglobin value is less than 11.5 g./100 ml. exchange transfusion is clearly indicated, and we have found it satisfactory to perform this within the first nine hours of life, a time limit arbitrarily laid down for cases

included in the British trial of exchange transfusion *versus* simple transfusion in this disease. For infants with higher cord haemoglobin values (80% of all Coombs-positive infants) further tests may be required before the need for exchange transfusion can be decided. The present communication is concerned only with such cases, for in recent years we have been prepared to delay treatment of these up to 16 hours if this proved most convenient.

In order to decide whether this policy is justified we have taken all 80 infants treated between 9 and 24 hours during the past three years and have matched each with a case treated between one and nine hours. Each pair was selected to correspond closely with regard to birth weight and cord haemoglobin and cord bilirubin values. These may not provide perfect controls but they were the best available, and in fact selection for early or late exchange transfusion had depended almost entirely on the time of day at which the infant was born. Thus 80% of those treated late were born between 7 p.m. and 3 a.m. while the reverse was the case for the early group. Individual circumstances had been responsible for the choice of time for exchange transfusion for the 20% of cases not born within these time limits, but there is no evidence that an excess of severely affected infants have been included in the early group because of early jaundice or other evidence of severe disease.

Overall, the onset of jaundice was earlier in the infants whose exchange transfusion was delayed until after nine hours of life. The average bilirubin level at the time of exchange transfusion was 6.95 mg./100 ml. in the cases treated early but 10.44 mg./100 ml. in those treated later. Similarly, there was an increase in the frequency of mild or moderate jaundice, and only five of the late group escaped jaundice whereas 13 of the early cases did so. The frequency of severe jaundice and bilirubinaemia of over 15 mg./100 ml., and the need for repeated exchange transfusion, were the same in both groups. It would appear, therefore, that in moderately affected infants exchange transfusion, even though delayed up to about 16 hours, will prevent the development of severe jaundice, and in the small number of cases where exchange transfusion was delayed beyond the first 16 hours this also seemed to apply. Indeed, 15 of the 19 infants in the late group who developed severe jaundice had been treated in the first 15 hours, and all who required repeated exchange transfusion had been transfused initially within the first 13 hours. There was some suggestion that the older the infant at exchange transfusion the better it tolerated the procedure.

No death attributable to haemolytic disease of the newborn occurred in either group.

If exchange transfusion is delayed too long hyperbilirubinaemia with the attendant danger of kernicterus may occur, and, moreover, exchange transfusion performed initially when the bilirubin has already reached a very high level is less effective in preventing subsequent hyperbilirubinaemia than when performed earlier (Walker, 1959). We think that exchange transfusion should be performed within the first nine hours if an infant is severely affected with haemolytic disease of the newborn. On the other hand, if an infant is not severely affected—that is, the cord haemoglobin value is greater than 11.5 g./100 ml.—exchange transfusion in the first 16 hours of life is usually safe and satisfactory. If the cord bilirubin level is over 5 mg./100 ml., or if early severe jaundice develops, the infant is probably more severely affected than the

cord haemoglobin level suggests and early exchange transfusion is indicated.

There were, in addition to the 80 pairs of cases described, 50 infants with cord haemoglobin values over 11.5 g./100 ml. but who were treated within the first nine hours of life. Evidence has already been presented indicating that exchange transfusion was performed in the first nine hours in some of these either because the cord haemoglobin value was relatively low or because early jaundice developed. In many, however, the time of exchange transfusion and whether or not the case was paired was determined by chance. The subsequent course in these cases did not differ from either of the paired groups. The same proportion developed severe jaundice, a similar number required additional transfusion, and only one infant died, not from haemolytic disease but from hyaline membrane disease. Six of the 50 infants were upset by the transfusion itself, a slightly higher proportion than in either of the other two groups.

Even where haemolytic disease of the newborn has not been predicted, relatively severe disease should be diagnosed within 24 hours of birth, and if prompt exchange transfusion is carried out satisfactory results should be achieved.

Summary

During 1958, 1959, and 1960 we performed exchange transfusion between 9 and 24 hours in 80 infants in whom the cord haemoglobin values exceeded 11.5 g./100 ml. From the same period we selected 80 infants treated between one and nine hours but who were otherwise similar with regard to birth weight and cord haemoglobin and cord bilirubin levels.

Although jaundice was more common in the group treated after nine hours, the frequency of severe jaundice or bilirubinaemia exceeding 15 mg./100 ml. was the same in the two groups, as was the need for subsequent exchange transfusion. There was a suggestion that the infants treated later tolerated the procedure better.

No death attributed to haemolytic disease of the newborn occurred in either group.

We conclude that if the cord haemoglobin value exceeds 11.5 g./100 ml. in the absence of clinical or other evidence of severe haemolytic disease exchange transfusion may safely be delayed up to 16 hours of life.

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The London County Council is to resume the recruitment of women ambulance drivers. The service is at present short of 80 drivers—770 are employed but 850 are needed. There is a high rate of wastage and the demands on the service are increasing: 243,342 patients were carried in 1947, 803,134 in 1953, and 1,356,965 in 1960.

CYCLOPHOSPHAMIDE IN TREATMENT OF DISSEMINATED MALIGNANT DISEASE

BY

C. J. ANDERS, F.R.C.S.

Surgical First Assistant, St. George's Hospital, London

AND

N. H. KEMP, M.B., B.S.

Registrar to Haematology Department, St. George's Hospital, London

A clinical trial has been undertaken at St. George's Hospital since November, 1959, using a new alkylating agent known as cyclophosphamide ("endoxan," "endoxana," "cytoxan"). This drug was first synthesized in 1958 with the specific purpose of preparing a form of nitrogen mustard which would be inactive when administered and activated only on reaching the site where its therapeutic effect was required. Toxic side-effects should be reduced and tolerance to the drug thereby improved.

Malignant cells are known to be rich in phosphatases and phosphamidases. With this in mind, Arnold and Bourseaux (1958) and Arnold *et al.* (1958) synthesized a number of nitrogen mustard phosphamides and phosphamide esters in the hope that they would be split by these enzymes to an active form within the tumours.

Cyclophosphamide is one of these "transport-form/active-form" compounds. It is a cyclic nitrogen mustard phosphamide ester, belonging to the group of diamide-mono-esters. Arnold *et al.* (1961) consider it to be inert *in vitro* and highly effective *in vivo*. The chemical formula is as follows:

Choice of Cases.—Ninety-two cases with widespread malignant disease have been treated since November, 1959. All these patients were either beyond the scope of conventional forms of therapy or had suffered recurrences after surgery, irradiation, nitrogen mustard, or hormone therapy. Treatment has been undertaken even in the most advanced stages of disease.

Method of Treatment

The recommendations of the German workers (Gross and Lambers, 1958) have been followed in estimating dosage: the amount given has been regulated by the effect of the drug on the haemopoietic system. As a general rule therapy has been started by the intravenous route—with an initial test dose of 100 mg. and subsequent daily doses of 200 mg. intravenously. On occasion this has been increased to 300 mg. and sometimes even 400 mg. daily if there has been no reduction of the circulating white-cell count within five days. This dose has never been exceeded on any one day—except on one occasion, to which reference will be made later.

A deliberate attempt has been made to bring the total white-cell count down to 2,000/c.mm. in order to obtain a maximal anti-tumour effect. It is felt that anything