Controlled trial of fresh frozen plasma in asphyxiated low birthweight infants

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Hambleton, G., and Appleyard, W. J. (1973). *Archives of Disease in Childhood*, 48, 31. **Controlled trial of fresh frozen plasma in asphyxiated low birthweight infants.** A controlled trial of fresh frozen plasma in asphyxiated newborn infants weighing less than 2.5 kg is reported, together with coagulation and other data obtained from the infants. The findings based on 66 infants were as follows. (1) There was no evidence that infusion of fresh frozen plasma prevented intraventricular haemorrhage. (2) Thrombotest did not appear to be a useful discriminant test for 'at risk' infants. (3) Asphyxiated low birthweight infants do not respond to vitamin K₁ in respect of thrombotest or prothrombin time. (4) The initial coagulation status of small-for-dates infants could not be distinguished from normal premature infants.

The importance of hypoxia in the pathogenesis of intracranial haemorrhage in low birthweight infants is well recognized (Frederick and Butler, 1970; Towbin, 1968). The exact mechanism is still not fully understood, but it has been suggested that hypoxia may cause defects in coagulation (Chadd *et al.* 1971) and that it is those infants with prolonged clotting tests who are particularly at risk from cerebral haemorrhage (Gray, Ackerman, and Fraser, 1968).

On this basis, Gray *et al.* have advocated the infusion of fresh frozen plasma to correct the deficiencies of clotting factors. In an uncontrolled trial of this therapy, given to low birthweight infants who had thrombotest levels under 10%, they claimed a reduction of mortality in the treated infants from a previously expected 19% to 4%. In the study, 46% of those infants who had suffered from an episode of birth asphyxia were found to have thrombotest values under 10%, indicating a particular risk from intracranial haemorrhage as identified in a previous study (Gray and Smith, 1966). In a smaller series, Appleyard and Cottom (1970) did not find any significant difference in the thrombotest values at birth between normal and asphyxiated low birthweight infants. However, the thrombotest values of the 'normal' infants rose significantly over the first 24 hours after the adminis-

tration of vitamin K₁, whereas the low birthweight infant who had suffered from birth asphyxia failed to show any improvement. From these results it was apparent that an episode of hypoxia was a better indication of those low birthweight infants at risk from intracranial haemorrhage than the initial coagulation status as measured by the thrombotest. In view of the apparent protective effect of the fresh frozen plasma, a controlled trial of the use of fresh frozen plasma in infants of low birthweight who had suffered from significant birth asphyxia has been instituted to evaluate the effect on the coagulation status, and to seek any difference in mortality or morbidity between the treated and untreated groups. Our initial results are presented in this paper.

Subjects and methods

Neonates weighing less than 2500 g who required resuscitation at birth (Apgar 4 at 5 minutes, Aberdeen Class C or D) were randomly allocated to control or treatment groups. Venous samples of blood were withdrawn into citrate and sequestrene tubes at 0 to 6, 24, and 48 hours. Thrombotest (Owren, 1959), prothrombin time (Quick, 1942), and partial thromboplastin time (Langdell, Wagner, and Brinkhous, 1953) were performed and the haemoglobin concentration estimated. Treatment consisted of two infusions of fresh frozen plasma (10 ml/kg), the first at 0 to 6 hours after the first sample was collected, the second at 24 hours after birth.

Sixty-six babies entered the trial: 35 were normal

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TABLE I
Weights and gestations of infants admitted to trial

	No.	Birthweight (kg)		Gestational age (wk)	
		Mean	Range	Mean	Range
All babies	66	1.81	0.88-2.45	35	27-42
Control	33	1.88	0.97-2.41	35	28-42
Treated	33	1.85	0.88-2.45	35	27-40
Premature	35	1.85	0.88-2.45	33	27-38
SFD	31	1.9	0.98-2.38	37	32-42

SFD, small-for-dates.

weight for gestation, 31 were small-for-dates (Tanner and Thomson, 1970). There were 33 controls (16 premature, 17 SFD) and 33 received treatment (19 premature, 14 SFD). The means and ranges of gestational ages and birthweights of the babies are shown in Table I. For technical reasons it was not possible to perform coagulation studies on all the babies on every occasion. The number of babies who were investigated is indicated in the tables.

TABLE II
Mean thrombotest values (%) in asphyxiated low birthweight infants aet. 0 to 6 hours (n = 39)

	Thrombotest %	SD	SE	No. <10%
Uncorrected	21.8	11.7	1.7	5
Corrected for Hb	24.8	15.0	2.1	5

Results

Initial thrombotest values. Table II shows the mean thrombotest values of all babies aet. 0 to 6 hours. All the results were corrected for Hb concentration. 5 infants had values less than 10%; 42 out of the 49 infants in whom the test was performed had values less than 35%. The Fig. shows the range and distribution of initial thrombotest values. There was no difference between

those infants of normal weight and those small-for-dates (Table III).

Response to treatment.

Thrombotest. Table III shows thrombotest values of the control and treated groups over the

FIG.—Distribution of thrombotest values in asphyxiated low birthweight infants.

first 48 hours of life, and a comparison of normal and small-for-dates infants. None of the changes is statistically significant (Student 't' test).

TABLE III
Thrombotest values % $\pm$ SD during the first 48 hours of life (n values in brackets)

	Control			Treated		
	0-6 hr	24 hr	48 hr	0-6 hr	24 hr	48 hr
Premature	24.3 $\pm$ 13.6 (12)	31.2 $\pm$ 22.2 (11)	28.4 $\pm$ 15.2 (8)	24.0 $\pm$ 12.5 (15)	30.7 $\pm$ 13.9 (12)	28.6 $\pm$ 12.5 (11)
SFD	27.9 $\pm$ 19.6 (12)	33.4 $\pm$ 21.5 (10)	37.4 $\pm$ 10.8 (7)	23.2 $\pm$ 15.7 (10)	25.1 $\pm$ 15.3 (13)	34.8 $\pm$ 21.9 (10)
Totals	26.1 $\pm$ 16.6 (24)	32.3 $\pm$ 21.3 (21)	32.6 $\pm$ 13.7 (15)	23.7 $\pm$ 13.5 (25)	27.8 $\pm$ 14.6 (25)	31.5 $\pm$ 17.4 (21)

SFD, small-for-dates.

TABLE IV
Prothrombin ratios in the first 48 hours of life (*n* values in brackets)

	Control			Treated		
	0-6 hr	24 hr	48 hr	0-6 hr	24 hr	48 hr
Premature	1.56 ± 0.58 (12)	1.45 ± 0.44 (10)	1.64 ± 1.23 (7)	1.47 ± 0.33 (14)	1.45 ± 0.27 (11)	1.40 ± 0.27 (10)
SFD	1.91 ± 1.06 (14)	1.47 ± 0.45 (14)	1.55 ± 0.57 (7)	1.49 ± 0.39 (13)	1.55 ± 0.47 (13)	1.27 ± 0.19 (10)
Totals	1.75 ± 0.88 (26)	1.46 ± 0.44 (24)	1.60 ± 0.92 (14)	1.48 ± 0.35 (27)	1.51 ± 0.39 (24)	1.33 ± 0.23 (20)

SFD, small-for-dates.

Prothrombin times. Table IV gives values over the first 48 hours. Treatment appears to reverse the expected deterioration seen in the control group, but none of the changes was statistically significant. The premature and small-for-dates infants also show no significant differences; further analysis also showed no difference in initial prothrombin ratios when the premature and small-for-dates infants were compared (Table VI).

Partial thromboplastin times. Initial PTTs are the same in all four groups.

Table V shows that there is a tendency for PTT to improve in the first 24 hours in the control

group as well as in the treated group. A similar pattern is seen when normal and SFD infants are compared. The SFD infants appear to respond to treatment by 48 hours better than normal premature infants.

Small-for-dates infants aet. 0 to 6 hours. Table VI shows data comparing SFD and premature infants during the first 6 hours of life. The mean gestational age of the premature group was 4 weeks less than the small-for-dates infants. There was no significant difference between them in the coagulation status as measured by the

TABLE V

Geometric means of prolongation of partial thromboplastin time over control (seconds) (*n* values in brackets)

	Control			Treated		
	0-6 hr	24 hr	48 hr	0-6 hr	24 hr	48 hr
Premature	30.8 (12)	9.1 (9) P < 0.05	12.7 (7)	20.0 (13)	21.4 (13)	19.2 (11)
SFD	17.9 (13)	9.1 (11)	9.0 (7)	31.14 (13)	21.1 (13)	6.9 (10) P < 0.001
Totals	23.2 (25)	9.1 (20) P < 0.02	10.7 (14)	25.0 (26)	21.2 (26)	11.8 (21) P < 0.02

TABLE VI

Coagulation studies in asphyxiated low birthweight infants aet. 0 to 6 hours (*n* values in brackets)

	Mean gestational age (wk)	Mean birthweight (kg)	Thrombotest (%)	Prothrombin ratios	Mean prolongation PTT (sec)
Premature	33	1.85	24.1 ± 12.7 (27)	1.51 ± 0.45 (26)	24.6 (25)
SFD	37	1.90	25.8 ± 17.7 (22)	1.71 ± 0.83 (27)	23.6 (26)

PTT, partial thromboplastin times; SFD, small-for-dates.

thrombotests, prothrombin ratios, and partial thromboplastin times.

Effect of fresh frozen plasma (FFP) in preventing intracranial haemorrhage. Table VII

TABLE VII

Comparison of deaths and incidence of cerebral haemorrhage in asphyxiated low birthweight infants

	No. of patients	No. of deaths	No. of necropsies	IVH	Other ICH
Control	33	10	7	0	2
Treated	33	9	7	3	0

IVH, intraventricular haemorrhage; ICH, intracranial haemorrhage.

shows that 3 babies in the treated group died with intraventricular haemorrhage, proven at necropsy. In the control group there was 1 infant who showed a tentorial tear at necropsy, and another who had subarachnoid haemorrhage alone. A further infant in the control group survived the neonatal period after several days on a ventilator, but by the age of 6 months had obvious microcephaly. None of the babies who died with intracranial haemorrhage was small-for-dates. The 3 babies who died from intraventricular haemorrhage were all of 27 or 28 weeks' gestation.

Table VIII summarizes the coagulation data on these infants. Only one of their initial thrombotests was under 10% and all were less than 20%, though the Fig. shows that 23 out of 49 initial thrombotests on the other low birthweight infants were also below this level.

Discussion

The results fail to confirm that thrombotest is of any value as a screening test for low birthweight infants at risk from intracranial haemorrhage. From the data in Tables II, III, and VIII, and the

Fig., it would be exceedingly difficult to choose a value below which a particular risk applies, and the thrombotest values of the infants who died with intracranial haemorrhage do not show a consistent pattern.

The initial values of PT ratios and PTT are similar to those cited for term babies by Aballi and Lamerens (1962) and by Hathaway (1970). This suggests that being premature, small-for-dates, or hypoxic at birth does not affect the initial levels of these clotting functions. The fresh frozen plasma does not result in any real improvement in either the thrombotest or prothrombin times, though there was a significant change in the partial thromboplastin times in small-for-dates infants so treated.

The failure of vitamin K₁ to affect the thrombotest values or prothrombin ratios in asphyxiated low birthweight infants over the first 24 hours is confirmed in Tables III and IV. The fact that there is no subsequent deterioration shown in the results suggests that this is due to interference in liver function rather than to disseminated intravascular coagulation.

Small-for-dates babies cannot be distinguished from normal premature infants as judged by the coagulation data obtained in this trial. The results do not confirm a recent suggestion that such infants are initially deficient in vitamin K₁-dependent liver factors (Chessells and Wigglesworth, 1971).

We have found no evidence that fresh frozen plasma prevents intraventricular haemorrhage. The infants in the trial are being followed up with periodic developmental assessments. So far there are no apparent differences between the two groups. It is established that heparinized, fresh plasma should be given to those infants who have the clinical appearance of secondary haemorrhagic disease proved by laboratory investigation (Leissring and Vorlicky, 1968; Skyberg and Jacobsen, 1969). However, the use of fresh frozen plasma

TABLE VIII

Some data relating to infants dying with intracranial haemorrhage

Case no.	Birthweight (kg)	Gestation (wk)	T or C*	Thrombotest (%)			Prothrombin ratio			Prolongation PTT		
				0-6 hr	24 hr	48 hr	0-6 hr	24 hr	48 hr	0-6 hr	24 hr	48 hr
1	1.58	31	C	—	—	—	1.95	2.46	—	21.3	66.5	—
2	2.3	33	C	9.2	9.0	—	2.3	—	—	22.7	—	—
3	1.2	27	T	18.2	—	—	1.52	—	—	48	—	—
4	1.15	27	T	12.2	14.0	13.1	2.45	1.76	1.62	137.0	81.4	74.4
5	1.22	28	T	18.0	17.0	—	1.60	1.47	1.37	21.4	21.7	14.4

*T, treated; C, control. PTT, partial thromboplastin times.

as a prophylactic measure cannot be recommended on the results of this trial.

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