Prevention of intraventricular haemorrhage by fresh frozen plasma

D W BEVERLEY, T J PITTS-TUCKER, P J CONGDON, R J ARTHUR, AND G TATE

Departments of Paediatrics, Radiology, and Haematology, General Infirmary at Leeds

SUMMARY Seventy three preterm infants weighing less than 1500 g or less than 32 weeks' gestation, or both, were allocated randomly to treatment (fresh frozen plasma 10 ml/kg on admission and at 24 hours of age) or control groups. Fifteen (41%) out of 37 control patients sustained intraventricular haemorrhage compared with five (14%) of 36 patients receiving treatment ($\chi^2=5\cdot24$, $P=0\cdot022$). No difference was found in coagulation factors measured at birth or at 48 hours of age in both groups. Fresh frozen plasma appears to have a beneficial effect in the prevention of intraventricular haemorrhage.

Intraventricular haemorrhage is the most common neurological disorder in preterm infants, occurring in 30–40% of babies weighing less than 1500 g.[1-3] Defects in haemostasis have been associated with the occurrence of intraventricular haemorrhage,[4-6] and intervention studies have produced equivocal results.[7-9] These studies, however, were performed before the advent of cranial ultrasound when diagnosis was based on clinical grounds and necropsies. As infants with major intraventricular haemorrhage are at high risk of neurological handicap we conducted a randomised prospective controlled trial using fresh frozen plasma to investigate its effectiveness in preventing intraventricular haemorrhage.

Patients and methods

Each year the Regional Neonatal Unit at Leeds General Infirmary admits about 120 infants of low birthweight (less than 1500 g), of whom half are inborn. All infants weighing less than 1500 g or less than 32 weeks' gestation, or both, were considered to be eligible for the study.

On admission each child was given vitamin K 1 mg intramuscularly, and a cranial ultrasound was performed to exclude an early intraventricular haemorrhage. Each infant was allocated to a treatment or control group by the opening of a presealed envelope that randomised allocation to study groups. Blood was taken for coagulation studies, and the infants assigned to the treatment group were given fresh frozen plasma 10 ml/kg on admission and again at 24 hours of age. In both groups coagulation studies were repeated at 48 hours of age. It was not possible to perform coagulation studies on all infants because of sampling and technical difficulties.

Ultrasound scans were repeated in all infants at age 48 hours, age 7–10 days, and before discharge home. Additional scans were performed when clinically warranted; thus in all children who died scans were performed shortly before death. The scans at 7–10 days and subsequent scans were performed by a radiologist (RJA) who had no knowledge of the clinical state of the infants. When haemorrhages were identified serial scans were performed at regular intervals to grade the maximum extension of the haemorrhage according to Papile's classification.[10]

All infants were given vitamin E from birth as prophylaxis against retrolental fibroplasia,[11] and any infant with an unstable intra-arterial blood pressure trace, as described by Perlman,[12] was paralysed with pancuronium.

Collection of blood and coagulation studies. Blood samples (2 ml) were collected from most infants on admission at the time of insertion of an indwelling umbilical arterial catheter or if this was not possible, by radial artery puncture. Half of the blood sample was anticoagulated with trisodium citrate and used to determine the prothrombin time (Manchester Comparative Reagent), activated partial thromboplastin time (General Diagnostics Automated APTT Reagent), and fibrinogen concentration (clot opacity method). A further 0·5 ml was added to thrombin and aprotinin before the detection of fibrin and fibrinogen degradation products. The remaining 0·5 ml was anticoagulated with edetic acid and used to determine the platelet count and mean

platelet volume with a Coulter counter model S+IV. A further 2 ml blood sample was taken at age 48 hours and treated similarly.

Ultrasound studies. The occurrence of intraventricular haemorrhage was detected with a portable real time ATL ultrasound sector scanner with a 5 MHz probe by methods described previously.[13]

Results

During December 1983 to August 1984, 85 babies weighing less than 1500 g or less than 32 weeks' gestation, or both, were admitted to the neonatal intensive care unit. For administrative reasons five babies were not included in the study and seven were withdrawn from the analysis of the results (two treatment and five control patients; Table 1). The remaining 73 patients form the basis of our report.

No significant difference was found between the treatment group and control group in birthweight, gestational age, and other clinical factors that have been associated with the development of intraventricular haemorrhage (Table 2). Five of 36 infants in the treatment group, however, developed intraventricular haemorrhage compared with 15 of 37 control patients ($\chi^2 = 5\cdot24$, P=0·022, Yates's correction, 1 df) (Table 3). Furthermore, if the seven patients who were excluded from the study are included in the analysis the degree of significance is increased. We were unable to show any difference in the coagulation studies undertaken on admission and at 48 hours of age in both groups (Table 4). We noticed a consistent trend for infants with intraventricular haemorrhage to have a longer prothrombin time, longer partial thromboplastin time, and increased fibrin/fibrinogen degradation products at birth and at 48 hours than children without haemorrhage, though this trend was not significant.

Table 2 *Clinical data on treatment and control groups**

	Control group (n=37)	Treatment group (n=36)
Mean (SD) gestation (weeks)	28·75 (2·05)	29·36 (2·36)
Mean (SD) weight (g)	1·216 (0·32)	1·246 (0·40)
Mean (SD) Apgar score at 1 min	6·1 (2·3)	4·9 (2·9)
Mean (SD) Apgar score at 5 min	8·2 (2·0)	7·5 (2·0)
Vertex delivery (%)	11 (30)	11 (31)
Inborn (%)	19 (51)	23 (64)
Respiratory distress syndrome (%)	28 (76)	24 (67)
Ventilation (%)	31 (84)	29 (81)
Arterial carbon dioxide tension >8KPa (%)†	10 (27)	9 (25)
pH<7·15 (%)†	9 (24)	7 (19)
Mean (SD) maximum peak airway pressure (mm H$_2$O)	26·7 (7·9)	26·7 (7·2)
Mean (SD) maximum F$_1$O$_2$	0·65 (0·25)	0·69 (0·25)
Pneumothorax (%)	9 (24)	7 (19)
Patent ductus arteriosus (%)	9 (24)	10 (28)
Paralysed (%)	21 (57)	20 (56)

*All differences between groups not significant.
†Occurrence on one or more occasion of these values on arterial gas sampling.

Table 3 *Occurence and severity of intraventricular haemorrhage*

Grade of intraventricular haemorrhage	Control group (n=37)	Treatment group (n=36)
I	4	2
II	3	0
III	6	3
IV	2	0
		$\chi^2 = 5\cdot24$*
Total	15	5 P=0·022*

*Yates's correction 1 df.

The mean (SD) volume of crystalloid that the treatment and control groups received on the first day of life (72·8 (19·1) ml/kg/day and 68·7 (16·2) ml/kg/day) and second day of life (84·5 (16·3) ml/kg/day and 82·1 (16·6) ml/kg/day) were similar. The treatment group received 10·4 (0·68) ml/kg/day

Table 1 *Clinical details of patients withdrawn from study*

Study group	Gestation (weeks)	Weight (g)	Reason for withdrawal	Outcome
Treatment	26	750	Died at 6 hours, before fresh frozen plasma given	Died age 6 hours Grade IV intraventricular haemorrhage
Treatment	29	1050	Intraventricular haemorrhage on admission	Died age 4 days Grade III intraventricular haemorrhage
Control	26	950	Severe disseminated intravascular coagulation secondary to intraventricular haemorrhage at 24 hours treated with fresh frozen plasma	Grade III intraventricular haemorrhage. Discharged home
Control	31	1100	Severe hypotension treated with fresh frozen plasma to maintain blood pressure	Grade III intraventricular haemorrhage. Discharged home
Control	25	800	Severe hypotension treated with fresh frozen plasma to maintain blood pressure	No intraventricular haemorrhage Discharged home. Retrolental fibrohyperplasia
Control	32	1400	Severe hypotension treated with fresh frozen plasma to maintain blood pressure	No intraventricular haemorrhage Discharged home
Control	29	970	Severe disseminated intravascular haemorrhage at 36 hours treated with fresh frozen plasma	No intraventricular haemorrhage Discharged home

Table 4 Coagulation studies on admission and at age 48 hours (mean (SD))

	Prothrombin time (secs)	Activated partial thromboplastin time (secs)	Fibrinogen (g/l)	No of patients with fibrinogen degradation products > 10 mg/l	Platelet count (10^9/l)	Mean platelet volume fl
			Control group (n=37)			
Admission	22·4 (5·6) (n=33)	61·5 (28·8) (n=33)	1·36 (0·99) (n=22)	2 (n=27)	223 (156) (n=30)	8·1 (0·7) (n=24)
48 hours	18·8 (4·3) (n=25)	48·6 (16·1) (n=25)	1·28 (0·65) (n=22)	2 (n=26)	194 (84·3) (n=27)	8·8 (1·8) (n=21)
Mean change from admission to 48 hours	−3·96 (5·2) (n=25)	−10·23 (34·1) (n=25)	−0·08 (0·77) (n=20)	−0·42 (3·0) (n=24)	−23·8 (147·8) (n=26)	0·36 (0·47) (n=20)
			Treatment group (n=36)			
Admission	20·5 (5·2) (n=28)	58·6 (25·3) (n=28)	0·95 (0·61) (n=20)	4 (n=26)	206 (96·5) (n=28)	8·6 (2·3) (n=17)
48 hours	19·1 (5·2) (n=22)	48·0 (12·5) (n=22)	1·42 (0·80) (n=18)	1 (n=20)	183 (78·4) (n=21)	9·0 (2.3) (n=14)
Mean charge from admission to 48 hours	−0·95 (5·9) (n=21)	−7·05 (17·7) (n=21)	+0·39 (0·50) (n=17)	−0·21 (8·16) (n=19)	−13·9 (96·4) (n=21)	−0·23 (0·49) (n=14)

fresh frozen plasma during the first 24 hours of life and 10·6 (0·69) ml/kg/day on the second day. None of the control patients received fresh frozen plasma during the study period, though three were given small volumes of purified protein fraction during the first 24 hours of life to help maintain their blood pressures. The treatment patients who were inborn received their fresh frozen plasma at a mean (SD) age of 2·9 (1·3) hours whereas those who were not inborn received their fresh frozen plasma at 8·9 (4·8) hours. No difference was found between the mean age of recruitment into the trial of the treatment and control patients.

Thirteen infants died during our study; five were from the treatment group, two of whom sustained intraventricular haemorrhage. Four of the deaths from the treatment group occurred before 48 hours of age, and one of these infants had developed an intraventricular haemorrhage. In the control group eight infants died: five died before 48 hours of age, three of whom had developed intraventricular haemorrhages. Three infants from the control group died after 48 hours of age; two had developed intraventricular haemorrhages. Necropsies were undertaken in seven infants who died, and in these the diagnosis by ultrasound was confirmed.

We were unable to detect any adverse effects of our treatment; the incidence of patent ductus arteriosus, congestive cardiac failure, and necrotising enterocolitis was similar in the two groups. Two infants developed asymptomatic hypoglycaemia during infusion of fresh frozen plasma, but each responded with an intravenous infusion of 10% dextrose. Subsequently, we gave fresh frozen plasma in addition to maintenance fluids to prevent hypoglycaemia.

Discussion

Recent reports have described the potential beneficial effects of phenobarbitone,[14] sodium ethamsylate,[15] and vitamin E[16] as prophylaxis for the prevention of intraventricular haemorrhage. Reports of the use of fresh frozen plasma have provided equivocal results,[7–8] although Turner's report showed that specific coagulation deficits could be corrected but had no effect on mortality.[9]

Our results showed that infusions of fresh frozen plasma have a beneficial effect in the prevention of intraventricular haemorrhage without any noticeable effect on mortality. In accord with Johnson et al,[17] we were unable to show any lasting improvement in the coagulation variables measured due to infusions of fresh frozen plasma. The beneficial effects of fresh frozen plasma may, therefore, be exerted by a mechanism other than the improvement of coagulation factor concentrations.

The association among unstable blood pressure traces, variable cerebral blood flow, and intraventricular haemorrhage has been well documented,[12] and profound changes in blood pressure are used as a model in beagle puppies to produce intraventricular haemorrhage.[18] Fresh frozen plasma may exert its effect by stabilising the circulation and thus preventing rapid changes in blood pressure. Although this is a feasible explanation, the number of babies who were paralysed because of unstable blood pressures was the same in both groups.

Follow up studies have shown that infants who survive the more severe grades of intraventricular haemorrhage have only a 20% chance of being normal on follow up.[19-21] Although we showed that the incidence of intraventricular haemorrhage was reduced by treatment with fresh frozen plasma, we do not know if it alters the neurological outcome for these infants. Treatment with fresh frozen plasma and other agents described previously[14-16] may only remove the marker of a neurological insult instead of preventing the insult itself. Long term follow up of our population and those of other studies will answer this question.

Our results, and those of others[4-6] showed that coagulation abnormalities are common in preterm infants. Fresh frozen plasma infusions reduced the incidence of intraventricular haemorrhage from 41% to 14% in infants less than 32 weeks' gestation, and we therefore recommend its routine use as a prophylaxis for this disorder. A trial of treatment with fresh frozen plasma and another plasma expanding agent will determine whether the beneficial effect described here occurs by the coagulation system or by action on the stability of the circulation.

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Correspondence to Dr D Beverley, Regional Neonatal Medical and Surgical Unit, General Infirmary at Leeds, Leeds LS2 9NS.