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Early albumin infusion to infants at risk for respiratory distress

R. D. BLAND, T. L. CLARKE, L. B. HARDEN, JUDITH L. MEYER, J. P. RIES, W. A. MADDEN, F. W. CRAST, W. F. COYER, and J. W. BASS

From the Department of Pediatrics, Tripler Army Medical Center, Honolulu, Hawaii

Bland, R. D., Clarke, T. L., Harden, L. B., Meyer, J. L., Ries, J. P., Madden, W. A., Crast, F. W., Coyer, W. F., and Bass, J. W. (1973). *Archives of Disease in Childhood*, **48**, 800. **Early albumin infusion to infants at risk for respiratory distress.** In a randomized prospective study, 100 high-risk infants (selected on the basis of a cord serum protein level of 4·6 g/100 ml or less, gestational age under 37 weeks, birthweight 2500 g or less, and/or arterial *p*H below 7·25) received 8 ml/kg of either 25% salt-poor albumin or 5% dextrose in water before the age of 2 hours. All infants were then managed supportively with warmth, appropriate oxygen supplementation, isotonic fluid infusion, and close monitoring, without further administration of colloid or hypertonic alkali solutions over the first 4 hours of life.

No statistically significant difference was shown between early colloid and early dextrose-water administration for either the incidence of idiopathic respiratory distress syndrome (RDS) or the mortality of high-risk infants, suggesting no apparent advantage of albumin over simple glucose-water infusion to hypoproteinaemic newborns shortly after birth. However, among the infants of 28 weeks' gestation or less admitted to the study, 3 of 4 albumin-treated patients survived, while 5 comparable infants in the dextrose-water group died within 12 hours of birth.

For the 100 infants taken together there was a significant improvement in morbidity and mortality from previous experience in the same nursery, indicating that prompt supportive care, including early fluid administration, may be instrumental in reducing the incidence and severity of RDS.

The association of systemic hypotension (Rudolph *et al.*, 1961; Neligan and Smith, 1960) and pulmonary ischaemia (Chu *et al.*, 1967) with the development of the idiopathic respiratory distress syndrome (RDS) suggests that immediate measures to combat shock shortly after birth may be a critical step in the management of the 'high-risk' infant. It has been proposed that the administration of a placental transfusion or delayed clamping of the cord results in a diminished incidence of hyaline membrane disease (Moss, Duffie, and Fagan, 1963; Oh *et al.*, 1967; Bound, Harvey and Bagshaw, 1962; Emmanouilides and Moss, 1971) and that mortality from the disease is reduced by the early infusion of colloid to low birthweight, hypoproteinaemic infants (Cooke, 1960). A communication by Fraillon and Kitchen (1962) failed to substantiate the efficacy of albumin administration, though the experimental design differed significantly from that of the previous study.

In a recent report it was shown that over 95% of newborn infants who develop RDS may be detected within minutes of birth by a simple refractometric measurement of the total serum protein content of umbilical cord venous blood (Bland, 1972). In the same study it was shown that RDS occurs in over one-third of newborn infants with a cord protein level of 4·6 g/100 ml or less and in one-half of all low birthweight (<2500 g) or preterm (<37 weeks' gestation) infants with low cord serum proteins, thereby establishing the 'high-risk' nature of this group of infants.

In an effort to resolve the conflicting results of previous clinical trials, a prospective evaluation of early fluid and colloid infusions to randomized, preterm, low birthweight hypoproteinaemic infants was undertaken. We report on the morbidity and mortality of 100 infants admitted to the study.

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Material and methods

A stoppered glass tube of umbilical cord venous blood, from each neonate admitted to the Tripler General Hospital newborn nursery during the course of this study, was used for investigation. A small amount of serum was extracted from the cord blood sample after centrifugation for rapid determination of serum total protein level by a modified refractometric technique requiring only one drop of undiluted serum transferred by pipette onto a hand refractometer* (Wolf *et al.*, 1962). Previous experience with this method has shown that these simplified protein measurements are not only rapid, reproducible, and inexpensive to perform, but they correlate well with levels obtained by the biuret method ($r = 0{\cdot}958$) (Bland, 1972).

Infants were weighed on admission and gestational age was assessed on the basis of maternal menstrual history and obstetric milestones, adjusted according to various physical (Usher, McLean, and Scott, 1966) and neurological (Koenigsberger, 1966) criteria for maturity.

Criteria for admission to the study were as follows. Cord serum protein level $\leqslant 4{\cdot}6$ g/100 ml *and* at least one of the following. (a) Birthweight $\leqslant 2500$ g. (b) Gestational age <37 weeks. (c) Arterial (or 'arterialized capillary') *p*H $<7{\cdot}25$.† The investigation included only infants with spontaneous respirations at the time of their arrival in the nursery.

When the above standards were met, peripheral blood haematocrit and total serum protein determinations were carried out, and a clinical assessment of respiratory distress was recorded using the 0–10 scale of Silverman and Andersen (1956). Therapy cards were randomized in pairs matched for weight. A card was then selected instructing the nurse to draw up 8 ml/kg of either 5% dextrose in water or 25% salt-poor albumin‡ in a sterile 30 ml syringe.

Informed consent of one or both parents was obtained for all infants admitted to the study. Within 2 hours of birth, most often in the first 20 minutes, a polyethylene catheter was inserted into the umbilical vein through the ductus venosus to the inferior vena cava where venous pressure was taken, followed by the infusion of the albumin or glucose-water over a 5- to 10-minute period. The catheter was removed promptly and if there was any evidence of sustained distress, a peripheral venous line or an indwelling umbilical arterial catheter was inserted. A chest *x*-ray was obtained in all cases, and arterial blood gas determinations were made as indicated to assess the degree of acidosis and right-to-left shunting. After the initial infusion of fluid or colloid, all infants were managed supportively with warmth, appropriate oxygen supplementation, isotonic fluid administration, and close monitoring without further infusion of colloid or hypertonic alkali solutions over the first 4 hours of life.

A diagnosis of RDS was established on the basis of a sustained respiratory rate greater than 60 per minute, repeated observations of xiphoid retraction, an expiratory grunt, and cyanosis out of oxygen, with symptoms of at least 72 hours' duration or until death, thereby excluding all cases of transient neonatal tachypnoea. *X*-ray evidence of a granular pulmonary pattern with 'air bronchograms' was shown for all infants in whom a diagnosis of RDS was made.

Therapeutic failures were defined as all infants who died within the first 28 days after birth, in addition to those infants who required continuous assisted ventilation for more than 2 hours to maintain life. The criteria for initiation of assisted ventilation included (1) sustained apnoea, or (2) persistent arterial oxygen tension <40 mmHg in 100% oxygen, accompanied by a falling *p*H $<7{\cdot}20$.

Daily determinations of peripheral blood haematocrit, total serum protein level, and total and direct-reacting bilirubin were made over the first 5 days of life, as well as clinical assessment of distress, blood gas determinations, and chest *x*-ray, as indicated. Antibiotics were not administered routinely. At the conclusion of 50 paired clinical trials, results were assessed for significance by χ^2 analysis.

Results

As noted in Table I, the group that received salt-poor albumin was strikingly similar to the group that received dextrose in water, except for the

*TS meter, model number 10400: American Optical Corporation, Scientific Instrument Division, Buffalo, N.Y., U.S.A.

†Determined on the Instrumentation Laboratory Inc. (Boston, Mass., U.S.A.) blood gas analyzer, model number 127.

‡Albumin, Normal Human Serum, U.S.P., Salt Poor. Metrix, Clinical and Diagnostics Division, Armour Pharmaceutical Company, Chicago, Illinois, U.S.A.

TABLE I

Summary of comparative data for infants in the two therapy groups

	Infants given 8 ml/kg 5% dextrose in water	Infants given 8 ml/kg salt-poor albumin
(1) No.	50	50
(2) Males	25	29
(3) Females	25	21
(4) Gestational age (wk)*	33·7 (0·4)	33·6 (0·4)
(5) Birthweight (g)	1925 (79)	2003 (85)
(6) Initial *p*H	7·28 (0·015)	7·28 (0·015)
(7) Cord total serum protein level (g/100 ml)	4·0 (0·07)	4·1 (0·05)

*Figures for categories 4–7 represent mean value and SEM.

TABLE II

Comparison of morbidity and mortality results between dextrose-water and albumin-treated groups, and a group of similar high-risk infants previously managed without early infusions

	Dextrose-water group	Albumin group	Infants with low cord proteins (≤4·6), immaturity (<37 wk)
No. of infants	50	50	58
Incidence of RDS (%)	16 (32%)	14 (28%)	30 (51·7%)
Total mortality (%) (from RDS and non-RDS)	12 (24%)	9 (18%)	20 (34·5%)
Therapeutic failures (%) (includes infants who died and those who survived by assisted ventilation)	15 (30%)	11 (22%)	21 (36·2%)

slight difference in sex distribution, with more males among the albumin-treated infants. There was no significant difference between the two groups for gestational age, birthweight, initial *p*H, or cord serum protein level.

From Table II it can be seen that the control (dextrose-water) group had an RDS incidence of 32% compared to the 28% in the albumin-treated group. The mortality rate was 24% in the control group and 18% in the colloid-infusion group. Neither of these differences is statistically significant ($P > 0{\cdot}1$).

Among the nonsurvivors treated with albumin, 8 of 9 had severe hyaline membrane disease at necropsy examination, while 1 infant died of sepsis and necrotizing enterocolitis 8 days after birth. The median duration of life for this group was 21 hours, with a range of 6 hours to 8 days (only 1 infant expired after 72 hours).

Likewise, hyaline membranes were shown in 8 of the 12 deaths in the dextrose-water group, including 1 infant who died at 28 days of age with pulmonary oxygen toxicity. 2 patients in this group succumbed to pneumonia and sepsis; 1 infant had immature lungs without hyaline membranes; and in another, sudden death at 2½ hours of age was preceded by unexplained shock. The median duration of life in this group was 17 hours, with a range of 2½ hours to 28 days.

In order to eliminate as a variable the progressive improvement in the management of assisted ventilation during the course of the study, those who survived only by respirator therapy were included among the 'therapeutic failures'. As in the comparisons between the two treatment groups for incidence of RDS and mortality, there was not a statistically significant difference for therapeutic failures, suggesting that there is no apparent advantage of early colloid *vs* glucose-water administration for high-risk infants. Yet when the incidence of RDS among *all* infants in the study was compared to the incidence in a similar group of infants previously managed with a less aggressive approach (Bland, 1972), there was a statistically significant difference ($P < 0{\cdot}01$).

In Tables III and IV figures for incidence of RDS, mortality, and therapeutic failures are listed according to gestational age and birthweight groups respectively, revealing a comparable distribution of outcomes except in the very immature group where the numbers are insufficient for a meaningful comparison. Among the smallest, most premature infants, 3 of 4 albumin-treated patients survived, while all 5 comparable infants in the dextrose-water group died within 12 hours of birth, suggesting that further studies of very small, premature infants may be warranted.

Table V analyses the incidence of RDS and

TABLE III

Incidence of RDS, mortality, and therapeutic failures for the two therapy groups according to gestational age

Gestational age (wk)	Infants given 8 ml/kg 5% dextrose in water				Infants given 8 ml/kg salt-poor albumin			
	No. of infants	RDS	Death	Treatment failure	No. of infants	RDS	Death	Treatment failure
≤28	5	4	5	5	4	1	1	1
29–32	10	3	3	3	9	5	4	5
33–36	27	6	3	6	35	8	4	5
≥37	8	3	1	1	2	0	0	0

TABLE IV

Incidence of RDS, mortality, and therapeutic failures for the two therapy groups according to birthweight

Birthweight (g)	Infants given 8 ml/kg 5% dextrose in water				Infants given 8 ml/kg salt-poor albumin			
	No. of infants	RDS	Death	Treatment failure	No. of infants	RDS	Death	Treatment failure
⩽1000	3	3	3	3	3	0	0	0
1001–1500	8	2	4	4	8	4	3	4
1501–2000	14	4	3	3	12	5	4	4
2001–2500	20	4	1	4	18	4	1	1
>2500	5	3	1	1	9	1	1	2

TABLE V

Outcome of albumin infusion study according to sex distribution

	Dextrose-water group (25 males, 25 females)			Albumin group (29 males, 21 females)		
	Male	Female	Total	Male	Female	Total
RDS	6	10	16	6	8	14
Death (RDS/non-RDS)	3	9	12	4	5	9
Failures	3	12	15	4	7	11

mortality according to sex distribution for the two groups. It is apparent that females were more commonly and more severely affected with both treatment regimens, making it unlikely that the difference in sex distribution had a significant effect on the outcome of the study.

As shown in the Fig., peak total bilirubin levels were almost identical for both groups ($11 \cdot 4 \pm 0 \cdot 65$ in the infants treated with dextrose-water *vs* $11 \cdot 7 \pm 0 \cdot 60$ in the albumin-treated infants), as were peripheral haematocrit and total serum protein levels from 24 hours to 5 days after infusion. During the first day of life, haematocrit levels were lower ($P < 0 \cdot 05$, by Student's 't' test analysis) and serum protein measurements were higher ($P < 0 \cdot 05$) in the albumin-treated infants, consistent with a transitory colloid osmotic effect.

Discussion

The histological finding that pulmonary hyaline membranes are made up of fibrin derived from an antecedent state of effusion (Gitlin and Craig, 1956) led Cooke (1960) to propose that the serum albumin level may be an important variable in the development of 'the pulmonary hyaline membrane syndrome'. He reported that the administration of salt-poor albumin in a dose of 4 ml/454 g body weight to premature newborns with serum protein levels of less than 5 g/100 ml resulted in a significant diminution in the incidence of, and mortality from,

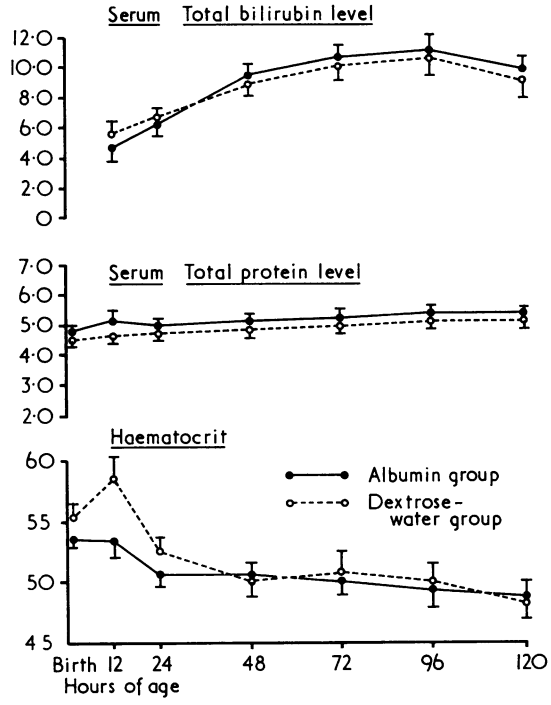

FIG.—*Serial determinations (mean and SEM) of serum total bilirubin levels in mg/100 ml, total serum protein levels in g/100 ml, and peripheral blood haematocrits, taken from capillary samples of infants admitted to the study.*

hyaline membrane disease. In that work, however, the control group did not undergo umbilical catheterization nor was a placebo solution administered.

A subsequent study, reported by Fraillon and Kitchen (1962), refuted the beneficial effect of early albumin infusions, though that investigation was performed on consecutive rather than randomly-selected simultaneous populations, 10 ml samples of blood were withdrawn before administration of colloid, and the treated group was selected strictly on the basis of weight (<2500 g), not protein levels; consequently, only 26 of the 54 patients receiving albumin had protein levels of <5 g/100 ml. Of those 26, only 1 died with hyaline membrane disease, compared with 9 of 119 in the control group. Several others died of 'other pulmonary disease', perhaps related to the design of the study—without any measurement of cardiovascular status or knowledge of serum protein levels, administration of salt-poor albumin to some of these babies may have resulted in the development of hypervolaemia and pulmonary oedema. Their conclusions that 'the use of concentrated salt-poor human albumin in the first hour of life does not affect neonatal mortality or the incidence of hyaline membrane disease', though founded on a tenuous experimental design and statistical analysis, brought a halt to further investigation of this therapeutic regimen.

Based on the apparent inconsistencies of these previous reports and the fact that such a high percentage of infants with RDS are hypoproteinaemic and hypotensive with inadequate peripheral perfusion, this study was undertaken in an attempt to resolve the efficacy of early colloid administration to 'high-risk' infants. The discovery of, at best, a marginal advantage of such infusions over glucose-water alone in the management of RDS is not surprising in light of the transitory effect of albumin infusions on neonatal blood volume (Smith, Phillips, and Roth, 1950) and the limited data which are available on the osmotic effect of stored albumin. The studies of Hinkley and Blechner (1969) and Delivoria-Papadopoulos, Battaglia, and Meschia (1969) showed that the colloid osmotic pressure (COP) of fetal and newborn plasma proteins is low by adult standards. In addition, the more recent report of Baum *et al.* (1971) showed that not only is COP directly related to gestational age, but it was also noted that the commercially available albumin preparations may be even less osmotically active than the native newborn plasma colloids, presumably because of molecular aggregation during storage or administration.

The possible implications of the quantitative and qualitative deficits in plasma proteins of preterm infants towards the pathogenesis of hyaline membrane disease are notable. In accord with the Starling hypothesis (1896), the presence of hypoproteinaemia with reduced colloid osmotic pressure, in conjunction with raised pressures in the pulmonary circulation of preterm newborns (many of whom are stressed by hypoxaemia and acidaemia), may be expected to yield extravasation of fluid and protein into the lungs. The resultant pulmonary oedema may have an adverse influence on surfactant activity with associated atelectasis, as has been shown by previous investigators (Said *et al.*, 1965; Tierney and Johnson, 1965; Taylor and Abrams, 1966).

The speculation that pulmonary oedema may be a critical component of RDS is supported by histological findings at necropsy (Gandy, Jacobson, and Gairdner, 1970), by the demonstration of dilated, engorged pulmonary lymphatic channels in newborn infants with the disease (Lauweryns, Claessens, and Boussauw, 1968), and by biochemical data from experimentally induced disease in fetal lambs (Adams, Fujiwara, and Latta, 1971). Moreover, it is consistent with the discovery that lungs from infants who die with hyaline membranes are heavier than those of newborns who succumb from other causes (Naeye, Harcke, and Blanc, 1971). It may afford some insight into the clinical observation that recovery from the disease is associated with diuresis.

Speculation aside, the overall improvement in morbidity and mortality for the 100 patients included in this study in comparison with those of a comparable group, managed with less vigor at an earlier date, suggests that intensive supportive care of high-risk newborn infants by careful thermoregulation, oxygenation, fluid administration, and constant monitoring in conjunction with prudent utilization of continuous positive airway pressure is of significant benefit.

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Correspondence to Dr. R. D. Bland, Cardiovascular Research Institute, University of California, San Francisco, California 94143, U.S.A.