

Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants

King W So, Tai F Fok, Pak C Ng, William W Wong, Kam L Cheung

Abstract

Aim—To compare the efficacy of a colloid (5% albumin) and a crystalloid (isotonic saline) solution for treating hypotension in mechanically ventilated preterm infants.

Methods—Sixty three preterm infants weighing 540 to 1950 g at birth and with gestational ages of 23 to 34 weeks, who developed hypotension (mean arterial pressure < 25, 30, and 35 mm Hg for infants with birthweight <1, 1-1.49, and 1.5-1.99 kg, respectively) within the first 2 hours of life, were randomly allocated to receive intravenous infusions at 10 ml/kg of either 5% albumin (group 1, n=32) or isotonic (0.9%) saline (group 2, n=31). Inotropic support with dopamine infusion was given if the infants remained hypotensive after a total of three infusions (30 ml/kg). Subsequent extra doses of volume expander in the form of 5% albumin was given, depending on the infant's blood pressure.

Results—There was no difference in the volume of the test solutions required between the two groups. Outcome, as assessed by the number of infants requiring inotropic support and death or chronic lung disease, did not differ between the groups. After inotropic support, however, group 1 required significantly more volume expander to maintain normal blood pressure (median: 27.5 ml/kg vs 10 ml/kg; P=0.0187) and had a higher mean (SEM) percentage weight gain within the first 48 hours of life (at 24 hours: 6.3(1.3)% vs 3.3(0.8)%; P=0.049; at 48 hours: 5.9(1.9)% vs 0.9(1.7)%; P=0.045). The difference in weight gain was significant at 48 hours even when only those infants not requiring inotropic support or extra 5% albumin were compared (group 1: 1.5(1.5)%, group 2: -4.2(1.1)%; P = 0.027).

Conclusions—Isotonic saline is as effective as 5% albumin for treating hypotension in preterm infants, and it has the additional advantage of causing less fluid retention in the first 48 hours.

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Keywords: blood pressure; hypotension; colloid; crystalloid, inotropic support

Both colloids and crystalloids are volume expanders frequently used in neonatal intensive care nurseries for the treatment of hypotension in preterm infants. There is no uniform practice regarding choice of the two

types of solutions.^{1,2} The therapeutic efficacy of colloids and crystalloids in treating hypotension has been compared in adult surgical patients but the results were inconclusive.^{3,4} Although the choice of volume expanders in infants and children has been debated,² studies comparing the two types of fluid in preterm infants are not available. We therefore undertook a randomised controlled study to investigate the efficacy of using a colloid (5% albumin) and a crystalloid (isotonic saline) for the treatment of hypotension in mechanically ventilated preterm infants during the period immediately after birth.

Methods

Inborn preterm infants admitted consecutively to the neonatal unit at this hospital, from September 1994 to March 1996, were recruited into the study when all the following criteria had been fulfilled: (1) gestational age < 34 weeks; (2) birthweight < 2 kg; (3) mechanically ventilated for respiratory distress syndrome; (4) presence of hypotension, defined as mean arterial pressure < 25, 30, and 35 mm Hg for infants with a birthweight of <1 kg, 1-1.49 kg, and 1.5-1.99 kg, respectively,³ within the first 2 hours of life; and (5) absence of fluid replacement or inotropic support during resuscitation at birth. Infants whose mothers had received antihypertensive medication within 24 hours of delivery were not enrolled. Also excluded were infants with severe congenital anomalies, cyanotic congenital heart disease, or with lesions involving the left ventricular outflow tract.

All infants were given daily maintenance intravenous fluid at a rate of 80-150 ml/kg depending on birthweight (<750 g:150 ml/kg; 750-999 g:120 ml/kg; 1000-1249 g/kg:100 ml/kg; 1250-1999 g: 80 ml/kg). Arterial blood pressure was monitored from birth continuously through an indwelling arterial catheter or, when this was not available, at 15 minute intervals using a non-invasive oscillometric blood pressure monitor (Dinamap Neonatal Vital Sign Monitor, Critikon Inc., Tampa, Florida, USA). Hypotensive infants were randomly allocated into two groups and stratified according to birthweight and gestational age. These infants were given volume expander in the form of either 5% albumin (Plasmatein, Alpha Therapeutic Corporation, California, USA) (group 1), or isotonic saline (0.9% NaCl solution) (group 2) at a dose of 10 ml/kg by slow intravenous infusion over 30 minutes. Up to a maximum of three doses could be given if the infant remained hypotensive 30 minutes

Department of Paediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong
KW So
TF Fok
PC Ng
WW Wong
KL Cheung

Correspondence to:
Dr TF Fok.

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after completion of the previous infusion, or if hypotension recurred within the first 24 hours of life.

Those infants who remained hypotensive after receiving three doses of the test solutions were given continuous dopamine infusion at an initial rate of 5 µg/kg/min. If hypotension persisted, the rate of dopamine infusion was increased in increments of 5 µg/kg/min until a maximum rate of 20 µg/kg/min was reached. Subsequently, infants with persistent hypotension were given further volume expander in the form of 5% albumin, as decided by the attending neonatologist.

The efficacy of 5% albumin and isotonic saline was compared by the proportion of infants who failed the treatment. Treatment failure was defined as the requirement of inotropic support after three doses of the test solutions within the first 24 hours of life. For infants with treatment failure, the extra volume of 5% albumin required within the first 48 hours of life after institution of inotropic support was recorded. The blood pressure and oxygenation status of the infants at 2, 4, 8, 12, 24, 36 and 48 hours of age were also compared. Oxygenation status was assessed by the product of mean airway pressure (Paw) and the fraction of inspired oxygen (FIO₂) required to maintain a transcutaneous oxygen saturation of 90-95%. The more conventional oxygenation index (Paw × FIO₂/PaO₂) was not used because not all the infants had arterial assessment throughout the study period. The time intervals between each infusion and, for infants with treatment failure, between the third infusion and institution of inotropic support, were documented. These values represented the duration for which normal blood pressure could be sustained by each dose of the test solutions.

Other variables, including urine output, body weight, and serum sodium concentration were closely monitored in the first 48 hours. The occurrence of major neonatal complications, including clinically important patent ductus arteriosus, intraventricular haemorrhage, and necrotising enterocolitis, were also documented. Patent ductus arteriosus was

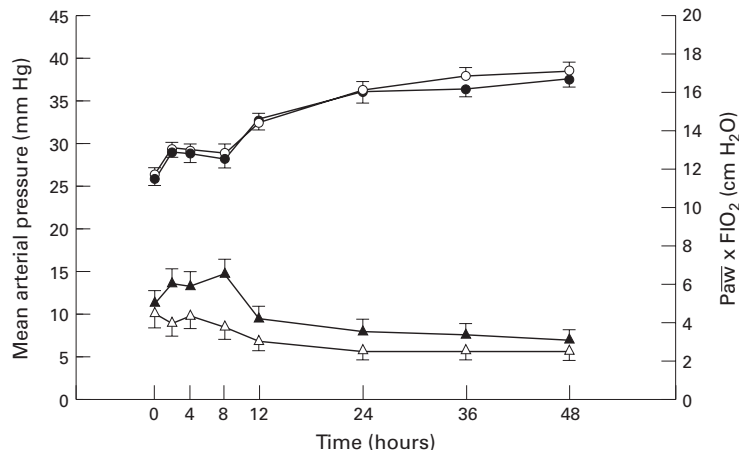


Figure 1 mean (SEM) arterial pressure (▲ group 1, ○ group 2) and ventilation requirement (Paw × FIO₂) of the infants (▲ group 1, △ group 2) immediately before the first dose of the test solutions (zero time), and at 2, 4, 8, 12, 24, 36, and 48 hours of life.

Table 1 Characteristics of study infants (values are mean (SEM) * or absolute number (%))[†]

	Group 1	Group 2
Male:female [†]	18:14	15:16
Gestation (weeks) *:	28.1 (0.7)	28.5 (0.5)
Range	23.1-34.6	23.3-33.6
Median	28.6	28.6
Birth weight (g) *:	1123 (81)	1163 (66)
Range	540-1950	555-1900
Median	1145	1150
Apgar score at 5 minutes [†] :		
≤ 3	2 (6.3)	1 (3.2)
4-6	5 (15.6)	4 (12.9)
≥ 7	25 (78.1)	26 (83.9)
Pre-treatment mean arterial pressure (mm Hg) * Paw	26.0 (0.8)	26.5 (0.7)
Pre-treatment Paw × FIO ₂ (cm H ₂ O) *	5.07 (0.7)	4.55 (0.7)
Diagnosis [†] :		
Respiratory distress syndrome	32 (100)	31 (100)
Clinical sepsis	3 (9.4)	4 (12.9)

considered clinically important when it was confirmed by echocardiography and required treatment with either indomethacin or surgical ligation. Intraventricular haemorrhage was routinely screened for by cranial ultrasound scan on days 2 and 6, and at 3 weeks of age, or more frequently if clinically indicated. The diagnosis of necrotising enterocolitis required confirmation at laparotomy, or by radiological evidence of pneumatosis intestinalis or peritoneal free gas. The number of infants who died or developed bronchopulmonary dysplasia was also recorded. The latter was defined as oxygen dependency at 28 days of life or at 36 weeks of postconceptional age.

Informed consent was obtained from the parents of all infants enrolled, and the study was approved by the Ethics Committee, the Chinese University of Hong Kong.

The sample size was calculated from the estimated proportion of infants with treatment failure. In our unit 5% albumin was routinely used for the treatment of hypotensive preterm infants. Our experience showed that about 50% of these infants required inotropic support after receiving three doses of the volume expander. A total sample size of 60 should demonstrate a 50% difference in failure rate between the two groups with a power of 0.8 and an alpha error of not more than 0.05. For data analysis, continuous variables were compared using the two sample two tailed *t* test or Wilcoxon rank sum test, where appropriate. Proportions were compared using the χ^2 test.

Results

A total of 63 infants was randomly allocated to receive either 5% albumin (group 1, n = 32) or isotonic saline (group 2, n = 31). There were no significant differences between the two groups in gestational age, birthweight, Apgar scores, and pretreatment blood pressure or oxygenation status (table 1). All infants were ventilated for respiratory distress syndrome and were given surfactant (Exosurf, Burroughs Wellcome Laboratories, UK) at 1 and 12 hours of life. Infection was suspected in three infants in group 1 and four in group 2, although blood culture for bacteria was negative in all cases. In all infants in both groups the first infusion of

Table 2 Therapeutic measures required for the treatment of hypotension (values are mean (SEM) *, absolute number (%))†, or median‡)

	Group 1	Group 2
Volume of test solutions received (ml)*	25.6 (1.3)	23.9 (1.4)
Number of infants requiring inotrope†	19 (59)	18 (58)
Time intervals (min)‡ between:		
First and second infusion of test solution	60	60
Second and third infusion	37.5	60
Third infusion and inotrope	60	60
Extra volume of 5% albumin required by infants with treatment failure (ml)‡	27.5**	10.0**

** P = 0.0187; other values showed no significant differences.

Table 3 Clinical parameters assessed (values are mean (SEM) * or absolute number (%))†

	Group 1	Group 2
<i>Weight gain as percentage of birth weight (%)</i> *:		
Entire group:		
First 24 hours of life	6.3 (1.3)§	3.3 (0.8)§
First 48 hours of life	5.9 (1.9)**	0.9 (1.7)**
Infants with treatment success:		
First 24 hours of life	3.5 (1.5)	0.8 (0.7)
First 48 hours of life	1.5 (1.5)‡	-4.2 (1.1)‡
<i>Urine output (ml/kg/h)</i> *:		
First 24 hours of life	2.48 (0.3)	2.81 (0.3)
24-48 hours of life	4.17 (0.3)	4.61 (0.4)
<i>Serum sodium concentration (mmol/l)</i> *:		
At 24 hours of life	134.9 (1.1)	133.7 (0.9)
At 48 hours of life	138.2 (1.4)	137.2 (1.1)
Patent ductus arteriosus†	20 (63)	18 (58)
<i>Intraventricular haemorrhage</i> †:		
All		
Grade 3 or 4	5 (15.6)	3 (12.9)
Necrotising enterocolitis†	4 (13)	2 (7)
<i>Chronic lung disease</i> †		
Oxygen dependency at 28 days of age	7 (22)	5 (16)
Oxygen dependency at 36 weeks postconception	4 (13)	2 (6)
Death†	7 (22)	5 (16)

§ P = 0.049, * P = 0.045, ‡ P = 0.027; other values showed no significant differences.

the test solution was given within the first 2 hours of life.

Table 2 shows the therapeutic measures instituted for the correction of hypotension. There were no significant differences between the two groups in the volume of the test solutions received, the proportion of infants requiring inotropic support, or the median interval between each of the above interventions. However, the extra volume of 5% albumin required to maintain a satisfactory blood pressure in the first 48 hours after starting dopamine infusion was significantly greater in group 1. The clinical course and outcome of the infants are shown in fig 1 and table 3. The two groups did not differ significantly in their blood pressure and oxygenation status at 2, 4, 8, 12, 24, 36 and 48 hours after birth (fig 1).

All infants had an umbilical or radial arterial catheter at enrolment, but intra-arterial blood pressure was measured throughout the 48 hour study period in only 29 infants in group 1 and 27 in group 2. In the remaining infants the arterial catheter was removed or failed to function after 24 to 36 hours and subsequent blood pressure was measured using the Dinamap. There was significantly greater weight gain in the albumin group both at 24 and 48 hours of life. A similar observation was made at 48 hours when the weight changes of only infants in whom treatment was successful in the two groups were compared. Urine output and serum sodium concentration were, however, similar in the first 48 hours between the two groups. Mortality and complication rates,

including chronic lung disease, intraventricular haemorrhage, patent ductus arteriosus and necrotising enterocolitis, did not differ between the two groups (table 3). Infants with patent ductus arteriosus were all treated with indomethacin started after 48 hours of life.

Discussion

The choice of volume expander for the treatment of neonatal hypotension varies from centre to centre. Our findings show that 5% albumin and isotonic saline have similar short term effects on the blood pressure of hypotensive preterm infants. No significant differences were observed between the two groups in their need for inotropes, the volume of the test solutions received before institution of inotropic support, or the duration for which normal blood pressure could be sustained following each dose of the test solutions. These observations are consistent with those of Emery *et al*, who reported that the effectiveness of volume expanders in treating hypotension in preterm infants was related to the volume of fluid infused rather than to the protein load.⁶ Our findings also concur with those of Pockaj *et al*, who showed that colloid and crystalloid volume expanders were equally effective for the treatment of hypotension in adults with capillary leak syndrome.⁷

Advocates for the use of colloids believe that because of the higher oncotic pressure, colloids stay within the intravascular space for longer and have a more sustained effect on stabilising the blood pressure. This would be true if fluid movement across the capillary wall were solely related to the net difference in the hydrostatic and oncotic pressure across the capillary endothelium. In reality, however, the rate of fluid movement in and out of the capillary vessels is also dependent on the permeability of the capillary wall to solute particles in the solution. The relation can be summarised in the following equation:

$$V = K_f [(P_c - P_{if}) - \sigma_c (\pi_c - \pi_{if})],$$

where V is the rate of fluid movement into/out of capillary; K_f is the capillary filtration coefficient which represents the permeability of capillary wall to small soluble particles; P_c is the capillary hydrostatic pressure; P_{if} is the interstitial fluid hydrostatic pressure; σ_c is the reflection coefficient which represents the ability of the capillary wall to stop large soluble particles from crossing; π_c is the capillary colloid oncotic pressure; and π_{if} is the interstitial fluid oncotic pressure.⁸

In sick preterm infants and also in older patients with capillary leak syndrome, the reflection coefficient may be so low that the net flow of fluid across the capillary wall is independent of the oncotic pressure gradient between the intravascular and extravascular compartments.⁹ In these patients plasma protein infused intravenously may leak into the interstitial space, resulting in interstitial oedema. This was evidenced by the greater weight gain in the group 1 infants within the first 48 hours of life, which could not be explained by their greater fluid intake alone, as a similar difference in weight change was also

observed among infants with treatment success who did not receive any extra volume expander in addition to the test solutions. In infants with respiratory distress syndrome, presence of oedematous fluid and extravasation of plasma protein into the alveolar space may cause inactivation of surfactant,^{10,11} deterioration in lung mechanics,¹² and inflammatory reactions that may lead to the development of chronic lung disease.¹³ Meta-analysis of studies on fluid resuscitation in adult patients has shown an association between the use of colloids and a higher mortality in patients with capillary leak syndrome and adult respiratory distress syndrome.¹⁴ In our study, however, there was no significant difference in the oxygenation status between the albumin and saline groups of infants, possibly as a result of the relatively small sample size.

In accordance with our nursery policy, 5% albumin was given to both groups of infants with treatment failure who required extra doses of volume expander after institution of inotropic support. The use of colloid in the saline group resulted in treatment "contamination" which might reduce the difference in the infants' outcomes, such as weight gain and chronic lung disease, between the two groups.¹⁵

The unblinded nature of the study might also be a source of bias. We were not able to mask the identity of the treatment solutions because of the yellow discolouration and frothy appearance of 5% albumin. We did, however, try to minimise observer bias by following strict guidelines on the use of volume expanders and inotropes. In addition, data were collected by an investigator who was not involved in the daily clinical management of the patients. Despite its limitations, our study shows that at least on a short term basis, isotonic saline is as effective as 5% albumin in the treatment of hypotensive preterm infants. The crystalloid solution might also have the additional advantage of causing less fluid retention in the first 48 hours of life. Further randomised studies are required to evaluate its effect on long term outcomes.

Unlike colloids, crystalloids are non-biological products and their use is not associated with any potential infection hazard. Moreover, crystalloid solutions are less expensive than colloid solutions, and the cost of isotonic saline is only a fiftieth of that of 5% albumin. In light of our findings, we suggest that neonatal units should consider replacing colloids with crystalloid solutions such as isotonic saline as volume expander for the treatment of hypotension in preterm neonates.

- 1 Shoemaker WC. Haemodynamic and oxygen transport effects of crystalloids and colloids in critically ill patients. *Curr Stud Hematol Blood Transfus* 1986;**53**:155-76.
- 2 Huskisson L. Intravenous volume replacement: which fluid and why? *Arch Dis Child* 1992;**67**:649-53.
- 3 Poole GV, Meredith JW, Pennell T, Mills SA. Comparison of colloids and crystalloids in resuscitation from haemorrhagic shock. *Surg Gynecol Obstet* 1982;**154**:577-86.
- 4 Laks H, O'Connor NE, Anderson W, Pilon RN. Crystalloid versus colloid hemodilution in man. *Surg Gynecol Obstet* 1976;**142**:506-12.
- 5 Versmold HT, Kitterman JA, Phibbs RH, Gregory GA, Tolley WH. Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4220 grams. *Pediatrics* 1981;**67**:607-13.
- 6 Emery EF, Greenough A, Gamsu HR. Randomized controlled trial of colloid infusions in hypotensive preterm infants. *Arch Dis Child* 1992;**67**:1185-8.
- 7 Pockaj BA, Yang JC, Lotze MT, Lang JR, Spencer WF, Steinberg SM, et al. A prospective randomized trial evaluating colloid versus crystalloid resuscitation in the treatment of vascular leak syndrome associated with interleukin-2 therapy. *J Immunother* 1994;**15**:22-8.
- 8 Bevan DR. Colloid osmotic pressure. *Anaesthesia* 1980;**35**:263-70.
- 9 White P Jr, Sylvester JT, Humphrey RL, Permutt T, Permutt S, Brower R. Effect of hypoxia on lung fluid balance in ferrets. *Am J Respir Crit Care Med* 1994;**149**:1112-7.
- 10 Ueda T, Ikegami M, Jobe A. Surfactant subtypes. In vitro conversion, in vivo function, and effects of serum protein. *Am J Respir Crit Care Med* 1994;**149**:1254-9.
- 11 Seeger W, Gunther A, Walrath HD, Grimminger F, Lasch HG. Alveolar surfactant and adult respiratory distress syndrome. Pathogenetic role and therapeutic prospects. *Clin Invest* 1993;**71**:177-90.
- 12 Nitta K, Kobayashi T. Impairment of surfactant activity and ventilation by proteins in lung edema fluid. *Respir Physiol* 1994;**95**:43-51.
- 13 Robertson B. The evolution of neonatal respiratory distress syndrome into chronic lung disease. *Eur Respir J* 1989;**3**(suppl):33s-7s.
- 14 Velanovich V. Crystalloid versus colloid fluid resuscitation: A meta-analysis of mortality. *Surgery* 1989;**105**:65-71.
- 15 Bennett K, Tugwell P, Sackett D, Haynes B. Relative risks, benefits, and cost of intervention. In: Sackett P, Haynes B, Tugwell P, eds. *Clinical epidemiology: a basic science for clinical medicine*. Boston: Little Brown, 1985: 205-28.



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