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ORIGINAL PAPER

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# Colloid infusion in the perinatal period and abnormal neurodevelopmental outcome in very low birth weight infants

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**Abstract** In very low birth weight (VLBW) infants, colloid infusion is associated with impaired perinatal lung function and increased oxygen dependency duration. The aim of this study was to determine whether perinatal colloid infusion was associated with abnormal neurodevelopmental outcome. All perinatal fluid input (crystalloid and colloid) given to VLBW infants entered into a randomised trial was recorded. At 1 and/or 2 years, the neurodevelopmental status of VLBW infants was routinely assessed. Of 131 survivors, median gestational age 27 weeks (range 23–33 weeks), 95 were seen at follow-up. Nineteen had abnormal neurodevelopmental outcome and differed significantly from the rest of the cohort with regard to their birth weight, magnitude of colloid infusion received and the proportions who had received postnatal steroids, suffered prolonged oxygen dependency or having had intracerebral haemorrhage/periventricular leucomalacia development. Regression analysis demonstrated that only colloid infusion related significantly to abnormal neurodevelopmental outcome independent of other variables. *Conclusion:* These data suggest that colloid infusion should be used with caution in the perinatal period.

**Keywords** Colloid · Neurodevelopmental delay · Prematurity

**Abbreviations** *DQ* developmental quotient · *ICH* intracerebral haemorrhage · *IVH* intraventricular haemorrhage · *PVL* periventricular leucomalacia · *VLBW* very low birth weight

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## Introduction

Colloid administration may increase the mortality rate of sick adults and children [18]. A systematic review of randomised trials of fluid resuscitation with colloid or crystalloid solutions in critically ill patients revealed that those who had received colloid compared to those who did not were more likely to die [18]. Colloid administration also adversely influences the outcome of very low birth weight (VLBW) infants. The magnitude of colloid infused was directly related to perinatal lung function impairment [11] and oxygen dependency duration [12]. We, therefore, postulated that perinatal colloid infusion might also impact unfavourably on the neurological outcome of VLBW infants. To test this hypothesis, we related the neurodevelopmental outcome of VLBW infants, entered into a randomised comparison of two levels of fluid input, to the amount of colloid they had received in the perinatal period.

## Subjects and methods

VLBW prematurely born infants, without major congenital anomalies and requiring ventilation from within the first 6 h after birth, were eligible for entry into the randomised trial [12]. The trial was approved by the King's College Hospital Research Ethics Committee. When informed written parental consent was obtained, infants were randomised to receive one of two fluid regimes by opening in sequence sealed envelopes containing details of the fluid regime to be administered. One of the regimes was similar to that advocated as standard in a number of neonatal texts [2,16]. Infants randomised to the second regime were to receive approximately 20% less maintenance fluid. Fluid input on either regime was only increased on the next day if the infant had lost weight and there were no signs of fluid overload, such as hyponatraemia (serum sodium <135 mmol/l) [19]. Infants who were small for gestational age were started on "day 2" of the respective fluid regime and progressed accordingly. The clinicians were allowed to deviate from the recommended fluid regime if renal impairment, jaundice or hypotension occurred [12]. Infants who were hypotensive were initially treated by colloid (15 ml/kg of 4.5% albumin) infusion, if they remained hypotensive after

two colloid infusions, inotropes were commenced. Hypotensive infants who had evidence of myocardial ischaemia were given inotropes immediately. Colloid, as fresh frozen plasma, was also given to infants who had abnormal coagulation. No sodium supplements were given in the first 24 h after birth, although the patency of indwelling arterial lines was maintained by infusion of heparinised 0.45% saline. Subsequently, the amount of sodium supplementation was altered to maintain the serum sodium level between 135 and 145 mmol/l [19]. All the infants were nursed, except in the first few hours when arterial and central lines were inserted, in double walled closed incubators with 75%–80% humidification. All fluid input (crystalloid and colloid) was recorded hourly by the nursing staff on observation charts, the crystalloid and colloid were then totalled for each 24 h period. Crystalloid included such fluids as 10% dextrose or total parenteral nutrition. To this was added the volume of all medication the infant received. Urine was collected on open nappies or, for extremely low birth weight babies, on cotton wool balls placed on the nappy. As soon as the infant voided, the nappy or cotton wool ball was weighed to determine the amount of urine passed. If an infant was oliguric and the bladder palpable this was manually expressed. The urine output was totalled for each 24 h period.

Infants were initially nursed in sufficient supplementary oxygen to maintain their arterial oxygen tension between 45 and 80 mmHg. Once continuous intra-arterial oxygen monitoring was no longer possible, oxygen saturation and transcutaneous monitoring was used in conjunction with intermittent arterial sampling. Supplementary oxygen was only discontinued if the infant was able to keep his/her saturation levels above 95% throughout the majority of a 24 h period; this was based on bedside nursing assessments. It was recorded whether infants remained oxygen dependent at 28 days and/or 36 weeks post-conceptional age (PCA). Infants underwent regular cranial ultrasound examination. Note was made if they had suffered a large intracerebral haemorrhage (ICH) (that is the haemorrhage distended the ventricle or extended into the parenchyma, previously described as Grade 3 or 4 haemorrhage [15]) or periventricular leucomalacia (PVL). Infants were given corticosteroids (0.5 mg/kg per day for 3 days, 0.3 mg/kg per day for 3 days and 0.1 mg/kg per day for 3 days of dexamethasone) if they were considered to be at high risk of developing chronic oxygen dependency, that is they remained fully ventilator-dependent beyond 7 days or required at least 40% supplementary oxygen after 3 weeks, without signs of improvement over the subsequent 48 h.

At 1 and/or 2 years of age, neurodevelopmental status was assessed by a paediatrician unaware of their perinatal status with regard to colloid/crystalloid infusion. Infants were routinely seen for neurodevelopmental follow-up if they were born extremely prematurely (<32 weeks of gestational age) and/or VLBW. Each child was seen by a neurodevelopmental paediatrician (MM) who assessed their development using the Griffiths Developmental Scales [8]. The scales assess development of locomotor skills, speech and language, manipulative and informative skills. The developmental quotient (DQ) is the mean of the scores for these scales. A physical examination was also performed and the findings were quantified using the Amiel-Tison neuromotor assessment [1]. Abnormal neurodevelopmental outcome was diagnosed if at year 2 (or at year 1 if the child was not seen at year 2) the child had a DQ less than two standard deviations from the mean (i.e. a DQ <74) and/or an Amiel-Tison neuromotor assessment which demonstrated neurodisability with impairment.

### Statistical analysis

Differences were assessed for statistical significance using the Wilcoxon rank sum, Fisher's exact or the Chi Square test as appropriate. Comparisons were made between infants with an abnormal and a non-abnormal outcome. Infants with an abnormal outcome were then matched with infants with a non-abnormal outcome for as many factors as possible that might have influenced outcome and comparisons made between the two groups. Multiple regression analysis in the whole study group was performed to assess whether the magnitude of colloid or crystalloid infusion, gestational age, birth weight, ICH/PVL, oxygen dependency at 28 days or 36 weeks PCA or post-natal steroid administration related to abnormal neurodevelopmental outcome.

## Results

A total of 168 infants, median gestational age 27 weeks (range 23–33 weeks), were entered into the randomized trial, of whom 131 survived until discharge. Of the survivors, 95 attended for follow-up and these infants did not differ significantly from those who were not seen at follow-up with regard to their gestational age or birth weight. The infants lost to follow-up had received a median colloid intake of 31 ml/kg (range 0–134 ml/kg), which did not differ significantly from the 76 infants with a non-abnormal outcome (Table 1).

A group of 19 infants had abnormal neurodevelopmental outcome. Four of the 19 infants were not seen at year 2 for formal neurodevelopmental assessment, but two of the infants were seen in the general clinic at 2 years of age and examination revealed them to have profound disability. The 19 patients differed significantly from the rest of the cohort with regard to being of lower birth weight ($P = 0.043$), having a significantly greater colloid intake in the perinatal period ($P = 0.00038$), more had had an ICH/PVL ($P = 0.0073$), were oxygen dependent at 28 days ($P = 0.027$) and 36 weeks PCA ($P = 0.021$) and received post-natal steroids ($P = 0.011$) (Table 1). There was no statistically significant difference between those with abnormal and those with non-abnormal developmental outcome with regard to the amount of crystalloid received (Table 1), nor did the neurodevelopmental outcome of the two groups randomised to different levels of maintenance fluid differ significantly (data not shown). Infants with an abnormal outcome in comparison to matched infants with a non-abnormal outcome were more likely to have an intraventricular haemorrhage (IVH)/PVL (non significant) and receive more colloid (non-significant) (Table 2). Regression analysis in the whole study group demonstrated only colloid infusion was significantly related to abnormal neurodevelopmental outcome ($P < 0.01$) independent of other variables.

## Discussion

We have demonstrated that VLBW infants with adverse neurodevelopmental outcome received significantly greater volumes of colloid in the perinatal period. Approximately 20% of the infants seen at follow-up had an

**Table 1** Comparison of infants with and without abnormal outcome at follow-up. Data are given as number or median (range)

| | Abnormal ($n=19$) | Non abnormal ($n=76$) | $P$ |
|---|---|---|---|
| Gestational age (weeks) | 27 (24–30) | 28 (24–33) | 0.058 |
| Birth weight (g) | 854 (618–1286) | 1012 (590–1500) | 0.043 |
| Restricted regime | 8 | 38 | 0.61 |
| Total crystalloid in the perinatal period (ml/kg) | 915 (405–1370) | 736 (423–1653) | 0.137 |
| Total colloid in the perinatal period (ml/kg) | 87 (23–136) | 40 (0–26) | 0.00038 |
| Post-natal steroids | 12 | 24 | 0.011 |
| Oxygen dependency | | | |
| At 28 days | 17 | 47 | 0.027 |
| At 36 weeks | 10 | 19 | 0.021 |
| ICH/PVL | 5 | 6 | 0.007 |

adverse neurodevelopmental outcome. This compares unfavourably to the 5%–8% reported in other series of VLBW infants [22]. All the patients included in our study, however, had required intubation and ventilation within 6 h of birth and thus were a particularly high risk population [22].

We did not report germinal matrix haemorrhage or an uncomplicated IVH as there is general agreement that such lesions are usually associated with a good chance of normal outcome [7,23]. During the study period it was routine policy for all ventilated VLBW infants to undergo serial cranial ultrasound examinations. The examinations, however, were not performed specifically for this study, thus we cannot be absolutely confident all cranial lesions were detected. Nevertheless, the 12% incidence of severe ICH/PVL experienced in the study population is in keeping with previous reports [3]. Not all the infants who had an abnormal outcome had either an ICH or PVL. Meta-analysis of the results of a follow-up of 992 preterm infants with consistently normal cranial ultrasound scans revealed that only 88% had a normal outcome [13].

Corticosteroids have been reported to increase the incidence of cerebral palsy and abnormal neurodevelopmental outcome at follow-up. Those adverse outcomes have usually been reported in infants given dexamethasone within 96 h of birth [14, 20, 26]; when treated after 3 weeks, an increase in cerebral palsy in survivors of only borderline significance was noted [9]. In the present study, a significantly greater proportion of those with adverse neurodevelopmental outcome had received corticosteroids. The corticosteroids were, however, given after 96 h and regression analysis demonstrated that colloid infusion, but not corticosteroid administration, related independently to adverse neurodevelopmental outcome. Previous analyses [9, 14, 20, 26] have not taken into account whether or not the infants received colloid infusions.

Not all of the survivors were seen at follow-up. It has been suggested [17] that 80% of cases should have reported data to withstand a worse case validity of the data. The 73% of infants seen at follow-up in this study is close to that recommended [17]. In addition, there were no significant differences between those who were and were not followed up regarding their gestational age and birth weight. Children should be seen at a minimum of 2 years to yield reliable data regarding prognosis [22]. In this study, the majority had formal neurodevelopmental examinations at 2 years and two of the four of the remainder, who all had severe disability at 1 year, when seen in general clinics at 2 years were found to have persisting profound disability.

The infants were not randomly assigned to received colloid infusion, they were usually given colloid to treat hypotension. Thus, the infants who received the colloid infusions were "sicker" and it might be argued that that is the explanation for their worse neurodevelopmental outcome [22]. Yet, although the incidence of ICH/PVL differed significantly between those who did and did not have abnormal neurodevelopmental outcome, not all infants with poor outcome had ICH/PVL. In addition, regression analysis demonstrated that only colloid infusion was significantly associated with abnormal outcome, independent of other variables. Follow-up of infants entered into a randomised trial assessing the efficacy of colloid versus crystalloid

**Table 2** Comparison of infants with an abnormal outcome to "matched" infants with a non-abnormal outcome. Data are given as number or median (range)

| | Abnormal | Non abnormal | $P$ |
|---|---|---|---|
| Gestational age (weeks) | 27 (24–30) | 27 (24–30) | 0.859 |
| Birth weight (g) | 854 (618–1286) | 884 (678–1450) | 0.6299 |
| Oxygen dependency | | | |
| At 28 days | 17 | 15 | 0.679 |
| IVH/PVL | 6 | 2 | 0.232 |
| Total colloid intake in the perinatal period (ml/kg) | 87 (23–136) | 62 (0–177) | 0.232 |

administration to treat hypotensive infants might help to elucidate whether it was the colloid administration per se or the hypotension which was associated with abnormal neurodevelopmental outcome. It would be inappropriate, however, to undertake such a trial, given that colloid infusion has been associated with an deterioration in respiratory status [11, 12, 24]. In this study, although colloid was usually given to treat hypotension, it was also given to treat coagulation abnormalities. The magnitude of the total amount of colloid given correlated significantly with poor outcome. An alternative explanation for the association of colloid infusion and abnormal neurodevelopmental outcome is that colloid infusion per se made the infants "sicker". In support of that hypothesis is the increased mortality rate in adults given colloid for resuscitation [18] and the finding that when albumin infusion was given for resuscitation in hypovolaemic shock it caused a deterioration in respiratory status, as indicated by an increase in the inspired oxygen requirement, a lower arterial oxygen tension and larger duration of ventilatory support [24]. The prematurely born infants who received colloid in this study lost significantly less weight in the perinatal period, required significantly higher ventilatory support and more developed chronic lung disease [4]. The likely mechanism is extravasation of colloid into the interstitial spaces of the lung, as occurs in septic shock [10]. We, therefore, speculate colloid infusion worsened respiratory status and, as a consequence, the infants were sicker and had a worse outcome.

Colloid infusions have been frequently given to VLBW infants not only to treat hypotension, but also to infants with polycythaemia or a metabolic acidosis. Randomised trials [5, 21, 25] have demonstrated that there are equally effective alternatives. In view of our data, we would suggest that those alternatives (normal saline in hypotensive or polycythaemic infants and sodium bicarbonate in those with a metabolic acidosis) should be used in preference to colloid infusion. It should be noted that it has already been recommended that albumin should preferably not be used for neonatal resuscitation [6].

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