Randomised trial of fluid restriction in ventilated very low birthweight infants

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Abstract

Background—Fluid restriction has been reported to improve survival of infants without chronic lung disease (CLD), but it remains unknown whether it reduces CLD in a population at high risk of CLD routinely exposed to antenatal steroids and postnatal surfactant without increasing other adverse outcomes.

Aim—To investigate the impact of fluid restriction on the outcome of ventilated, very low birthweight infants.

Study design—A randomised trial of two fluid input levels in the perinatal period was performed. A total of 168 ventilated infants (median gestational age 27 weeks (range 23–33)) were randomly assigned to receive standard volumes of fluid (60 ml/kg on day 1 progressing to 150 ml/kg on day 7) or be restricted to about 80% of standard input.

Results—Similar proportions of infants on the two regimens had CLD beyond 28 days (56% *v* 51%) and 36 weeks post conceptional age (26% *v* 25%), survived without oxygen dependency at 28 days (31% *v* 27%) and 36 weeks post conceptional age (58% *v* 52%), and developed acute renal failure. There were no statistically significant differences between other outcomes, except that fewer of the restricted group (19% *v* 43%) required postnatal steroids ($p < 0.01$). In the trial population overall, duration of oxygen dependency related significantly to the colloid ($p < 0.01$), but not crystalloid, input level; after adjustment for specified covariates, the hazard ratio was 1.07 (95% confidence interval 1.02 to 1.13).

Conclusions—In ventilated, very low birthweight infants, fluid restriction in the perinatal period neither reduces CLD nor increases other adverse outcomes. Colloid infusion, however, is associated with increased duration of oxygen dependency.

(Arch Dis Child Fetal Neonatal Ed 2000;83:F91–F96)

Keywords: chronic lung disease; prematurity; very low birthweight; fluid restriction; lungs; survival

High volumes of fluid input increase the likelihood of a patent ductus arteriosus (PDA),¹ a known risk factor for the development of chronic lung disease (CLD).² It is therefore surprising that fluid restriction in only one³ of four^{1–5} randomised trials was associated with improved outcome. Interestingly, the positive effect was a lower mortality rather than a lower CLD rate.³ The population investigated were

relatively mature and it is not clear how many were exposed to antenatal steroids or postnatal surfactant.³ Fluid restriction has a number of important possible side effects, including hypovolaemia which could result in renal impairment. We therefore felt it important to determine, in a high risk population, whether fluid restriction compared with a more liberal regimen was associated with a lower incidence of CLD but no increase in other adverse outcomes.

Methods

A randomised trial of two levels of fluid input was undertaken. Infants born prematurely with a birth weight of ≤ 1500 g, without major congenital anomalies and requiring ventilation from within the first six hours of birth were eligible for entry into the study. If informed written consent was given by the parents, the infant was randomised to receive one of two fluid regimens by opening the next numbered and sealed envelope which contained details of the regimen the infant was to receive. Regimen A was similar to that advocated in a number of neonatal texts.^{6–7} Infants on regimen B (restricted) were to be prescribed at least 20% less fluid than those on regimen A (table 1); regimen B was similar to that previously used on our unit. Infants who were small for gestational age were started on the first day after birth on “day 2” of the respective fluid regimen and progressed accordingly. Fluid input on either regimen 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).⁸ The clinicians were allowed to deviate from the recommended fluid regimen if renal impairment, hypotension, or jaundice occurred. Infants who developed acute renal failure—that is, for any 24 hour period, creatinine levels > 132 $\mu\text{mol/l}$ ^{9–10} and urine output < 1.0 ml/kg/hour, except on day 1 when the urine output had to be < 0.5 ml/kg/hour¹¹—without evidence of dehydration were restricted to a fluid input equal to their urine output plus insensible losses. Infants who were hypotensive (mean blood pressure less than the 10th centile for their gestational age and birth weight¹²) were prescribed up to two boluses of colloid or crystalloid and then an inotrope infusion. Inotropes were used as first choice for blood pressure support if the infant was small for gestational age and had evidence of myocardial ischaemia. Infants who were jaundiced and required phototherapy were prescribed an extra 30 ml fluid/kg/24 hours. Infants who were hypoglycaemic (blood

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Accepted 11 May 2000

Table 1 Comparison of the recommended total fluid input on the two regimens

Day	Regimen A	Regimen B (restricted)
1	70	40
2	90	40–60
3	110	70
4	120	90
5	140	110
6	150	130
7	150	150

Data are given as median or range (ml/kg).

glucose < 2.5 mmol/l) were preferentially given an increased concentration of dextrose rather than an elevated volume of fluid. All fluid input (crystalloid and colloid) was recorded hourly and then totalled for each 24 hour period. To this was added the volume of all medication received by the infant. Urine was collected on open nappies or, for extremely low birthweight 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 hour period.

All infants were routinely monitored; this included at least daily assessment of electrolytes, creatinine, and bilirubin. No sodium supplements were given in the first 24 hours after birth, although the patency of indwelling arterial lines was maintained by infusion of heparinised 0.45% saline. Subsequently, sodium supplementation was altered to keep the serum sodium level between 135 and 145 mmol/l.⁸ Blood pressure was measured once an hour, usually from intra-arterial monitoring. All infants were nursed in double walled closed incubators with 75–80% humidification, except in the first few hours when arterial and central lines were inserted. They were ventilated through shouldered oral endotracheal tubes using humidified gases. Enteral feeding (0.5 ml/h) was begun as soon as the clinical condition of the infant permitted. If enteral feeds were not tolerated, parenteral feeding (initially containing 0.5 g protein/kg/day regardless of the volume of fluid infused) was started on day 4.

The following were documented: duration of ventilation and oxygen dependency and whether the infants remained oxygen dependent at 28 days and/or 36 weeks post conceptional age, died, or developed other complications. An airleak was recorded as occurring if the infant had developed a pneumothorax or pulmonary interstitial emphysema. Regular cranial ultrasound examinations were performed to detect intracranial haemorrhage. A diagnosis of PDA was recorded if the clinical diagnosis was confirmed by an echocardiographic examination and either medical and/or surgical treatment was required. Infants with a proven PDA were fluid restricted and treated with indomethacin unless there was a contra-indication (low platelets or renal failure). Surgical ligation was performed only if at least two courses of indomethacin had failed to close the PDA and the infant remained sympto-

matic. Necrotising enterocolitis was diagnosed if the infant had abdominal distension and occult or gross blood in the stool with or without linear pneumatosis intestinalis on the abdominal x ray picture.

Postnatal steroids (dexamethasone 0.5 mg/kg/day for three days, 0.3 mg/kg/day for three days, and 0.1 mg/kg/day for three days) were prescribed if infants were considered to be at high risk of developing CLD—that is, they remained fully ventilator dependent beyond seven days or required at least 40% supplementary oxygen after three weeks, without signs of improvement over the subsequent 48 hours. Steroids were only administered once infection and a PDA had been excluded. Regular diuretic treatment (chlorothiazide and spironolactone) was prescribed after the first week of life for oxygen dependent infants in incipient right heart failure—that is, they showed rapid weight gain and evidence of oedema on the chest radiograph.

Infants were initially nursed in sufficient supplementary oxygen to keep their arterial oxygen tension between 45 and 80 mm Hg. 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 when infants were able to keep their saturation levels above 95% throughout most of a 24 hour period; this was based on bedside nursing assessments.

ANALYSIS

The primary outcomes of the trial were survival without CLD and acute renal failure. The secondary outcomes were requirement for additional management strategies to improve respiratory status—that is, use of pancuronium, diuretics, steroids, inhaled nitric oxide, or high frequency oscillation—death before discharge, and the development of PDA, necrotising enterocolitis, airleak, or intracranial haemorrhage. Analysis was by intention to treat. Differences between the two groups were assessed for statistical significance using the χ^2 or Fisher's exact test as appropriate. Duration of ventilation and oxygen dependency were compared between the two groups using log rank tests. Data from infants who died were censored. A secondary analysis using a Cox proportional hazards regression analysis was performed on both groups combined to assess the effects of total crystalloid and colloid input in the perinatal period on the duration of oxygen dependency. This led to results expressed in terms of hazard ratios, which show by how much the likelihood of an infant being oxygen dependent increased as a result of a given increase in total input.

SAMPLE SIZE

A retrospective notes audit disclosed that 22% of VLBW infants on our unit developed acute renal failure in the first 48 hours after birth and 62% survived without CLD. The infants had received a fluid input similar to regimen B (restricted). We postulated that infants who

Table 2 Comparison of the characteristics of the two groups

	Regimen A	Regimen B (restricted)
Gestational age (weeks)	27.5 (23–33)	27 (23–33)
Birth weight (g)	914 (486–1500)	980 (522–1499)
Small for dates	17 (20)	15 (18)
Caesarean section	38 (45)	44 (52)
Male	38 (45)	42 (50)
Antenatal steroids	56 (67)	60 (71)
Surfactant	57 (68)	60 (71)
In the first 48 hours		
Max PIP (cm H ₂ O)	19 (12–40)	20 (14–42)
Max Fio ₂	0.63 (0.21–1.00)	0.65 (0.21–1.00)

Data are given as median (range) or n (%). The total number of infants in each group was 84.

Fio₂, fraction of inspired oxygen concentration; PIP, peak inspired pressure.

received a more liberal regimen (regimen A) may have a higher rate of CLD and hence lower survival without CLD but would experience less renal impairment. Randomisation of 168 infants gave 80% power at the 5% level to detect a change in the likelihood of renal impairment from 22% to the 7% reported by others,¹³ and in survival without CLD from 62% to 42%.

Results

The trial ran from April 1995 to October 1998, during which period there were 171 eligible babies. Two sets of parents did not give informed written consent and one unsupported mother was considered to be too psychiatrically unwell to be approached, consequently their three infants were not entered into the trial. The remaining 168 infants, median gestational age 27 weeks (range 23–33), were randomised to receive one or other of the two fluid regimens. Patients in the two groups had similar characteristics (table 2). In particular, the distributions of gestational ages and birth weights were similar between the two groups.

Although on each study day, a wide range of fluid inputs was actually received by infants on both regimens, infants on regimen B (restricted) received significantly ($p < 0.01$) less crystalloid than those on regimen A, up until day 7, but similar levels of colloid (table 3). The usual colloid prescribed was albumin. In the first four days, infants on regimen B (restricted) received 19% less fluid than those on regimen A; overall the difference was 11%. Infants on regimen B had significantly lower urine outputs on days 2–6 inclusive (table 4). The proportions developing CLD or surviving without CLD did not differ significantly between the two groups (table 5). There were

Table 3 Comparison of the amount of fluid actually received on the two regimens

Day	Regimen A		Regimen B (restricted)	
	Crystalloid	Colloid	Crystalloid	Colloid
1	66 [90.6] (26–150)	20 (0–67)	55 [76.0] (26–129)	11 (0–102)
2	82 [92.4] (24–128)	11 (0–50)	70 [82.1] (30–147)	9 (0–63)
3	104 [111.7] (38–184)	10 (0–80)	84 [98.6] (43–233)	0 (0–65)
4	124 [128.3] (48–200)	0 (0–50)	103 [112.9] (30–171)	0 (0–47)
5	142 [143.8] (44–208)	0 (0–39)	121 [125.8] (53–182)	0 (0–57)
6	148 [151.7] (53–205)	0 (0–40)	136 [140.4] (49–204)	0 (0–40)
7	159 [157.2] (36–226)	0 (0–59)	146 [149.0] (54–198)	0 (0–51)

Data are given as median [mean] (range) (ml/kg).

Table 4 Comparison of the urine output (ml/kg/day) of the two groups

Day	Regimen A	Regimen B (restricted)	p Value
1	35 (0–188)	31 (0–139)	NS
2	96 (0–185)	78 (0–204)	<0.05
3	101 (6–204)	73 (4–220)	<0.001
4	109 (31–178)	82 (14–174)	<0.001
5	104 (33–204)	96 (6–207)	<0.01
6	108 (48–193)	93 (16–192)	<0.02
7	113 (53–192)	102 (16–176)	NS

Data are given as median (range).

Table 5 Comparison of primary outcomes for the infants on the two regimens

	Regimen A	Regimen B (restricted)
O ₂ dependency at 28 days	47 (56)	43 (51)
O ₂ dependency at 36 weeks	22 (26)	21 (25)
Survivors without O ₂ dependency		
At 28 days	26 (31)	23 (27)
At 36 weeks	49 (58)	44 (52)
Renal failure on days:		
1	0 [4,1]	0 [7,2]
2	0 [2,2]	1 [7,5]
3	2 [5,3]	1 [8,8]
4	0 [5,3]	1 [9,8]
5	0 [6,5]	1 [11,9]
6	0 [5,5]	1 [14,10]
7	0 [6,5]	0 [18,11]

Data are given as the number of affected individuals (%). The total number in each group was 84. Complete urine output or creatinine levels were not available on all the infants on all the study days. The initial number in the square brackets indicates the number of infants who had died and the second one the number for whom data were missing.

Table 6 Comparison of secondary outcomes for the infants on the two regimens

	Regimen A	Regimen B (restricted)
Required treatment with		
Pancuronium*	11%	13%
Nitric oxide	15 (18)	16 (19)
HFO	13 (15)	18 (21)
Diuretics	16 (19)	9 (11)
Steroids	36 (43)	16 (19)
PDA	22 (26) [15]†	18 (21) [16]†
Airleak	6 (7)	6 (7)
ICH	12 (14)	12 (14)
NEC	3 (4)	4 (5)
Died	16 (19)	21 (25)

Data are expressed as the number (%) of affected individuals. The total number in each group was 84.

*The number of ventilated days for which infants were paralysed is expressed as a percentage of the total number of ventilated days; data are given for day 1 only.

†The numbers in square brackets indicate the number of infants in each group who received indomethacin. HFO, high frequency oscillation; PDA, patent ductus arteriosus; ICH, intracranial haemorrhage; NEC, necrotising enterocolitis.

also no significant differences in the proportion of infants in each group who developed renal failure. On each day there were a few missing data and infant deaths. Repeating the analysis using dummy variables for missing data and deaths also did not highlight a significant difference between the groups with regard to the incidence of renal failure on any of the study days (table 5). There were also no statistically significant differences between the two regimens with regard to occurrence of the secondary outcomes (table 6), except that more infants on regimen A required postnatal corticosteroids ($p < 0.01$). Steroids were prescribed for 52 infants; in 51 cases this treatment was started after the first week. The duration of ventilation (median 7 days (range

Figure 1 Kaplan-Meier curves of the proportion of infants remaining oxygen dependent during the first year of life.

0.5–165) in group A and 7 days (range 0.5–58) in group B) and oxygen dependency (fig 1; median 38 days (range 0.5–350) in group A and 40 days (range 0.5–472) in group B) were similar in the two groups. In the combined sample, the amount of colloid (unadjusted hazard ratio 1.17 for an increase of 10 ml/kg in total colloid input, 95% confidence interval 1.11 to 1.23) but not crystalloid significantly ($p < 0.001$) affected the duration of oxygen dependency. The effect of colloid input on duration of oxygen dependency remained significant (hazard ratio 1.07 for an increase of 10 ml/kg in total colloid input, 95% confidence interval 1.02 to 1.13; $p < 0.01$) after adjustment for the effects of antenatal steroids, delivery mode, gestational age, sex, small for gestational age, postnatal surfactant, steroids, diuretics, and PDA.

Discussion

Fluid restriction was not associated with a significant reduction in CLD. Two definitions of CLD have been commonly used: oxygen dependency beyond 28 days or 36 weeks post conceptional age. Recently,^{14 15} oxygen dependency at 28–30 days has been shown to perform better than beyond 36 weeks post conceptional age as a predictor of chronic respiratory morbidity. This finding was regardless of whether, in one of the studies,¹⁵ morbidity was diagnosed by positive symptom status in years 1 and 2 or in all five preschool years. Using either definition of CLD, we found no significant differences in the proportions of affected infants between the two groups. We did not find any statistically significant difference in the incidence of renal failure between our groups. We defined renal failure as a low urine output¹¹ and a serum creatinine concentration greater than 132 $\mu\text{mol/l}$.^{8 9} Recently it has been suggested that the plasma creatinine rises to a peak in the first 48 hours after birth in preterm infants.¹⁶ We, however, used the same cut off level throughout the perinatal period, but applied the same criteria to both groups, thus our comparison is meaningful. To assess renal failure appropriately it is essential that

urine output is measured accurately. Neonates do not empty their bladders completely on voiding, and 7% fail to void during the first 24 hours of life, thus external urine collection of short duration is inaccurate.¹¹ We measured the infants' urine output over each 24 hour period. The nurses observed the infants' open nappies for the passage of urine at least hourly. Once urine was voided, the nappy and/or cotton wool ball was weighed immediately, as delay could introduce inaccuracy because of evaporative loss. Data were missing from a minority of our patients, but treating those data and the data of infants who had died as dummy variables also did not show any statistically significant difference in the incidence of renal failure between the groups.

There are possible criticisms of our study. Firstly, it may be suggested that our fluid regimens were too similar. We would argue against that, as those on regimen B (restricted) were to receive at least 20% less fluid than those on regimen A and the latter regimen was similar to that recommended in standard texts.^{6 7} More stringent fluid restriction would probably increase the complication rate.⁴ Secondly, the trial regimens were only maintained during the first week. We felt that this was an appropriate duration, as it is in the first week that enhanced capillary permeability is present, and excess fluid is likely to leak into the pulmonary interstitium worsening lung function and predisposing the infant to CLD. Outside the perinatal period, fluid restriction could adversely impact on nutrition. Thirdly, we allowed the clinicians to alter the fluid input if this was dictated by a change in clinical condition—for example, the development of hypotension. As a consequence, the infants in both groups actually received a wide range of fluids on each study day. Nevertheless, those on regimen B (restricted) received significantly less fluid than those on regimen A, as we had intended, and, during the first four days, 19% less fluid. There was, however, considerable overlap in the levels of fluid received by infants on the two regimens, but we do consider that our conclusion that fluid restriction does not reduce CLD is robust, as regression analysis of the data from the total study population confirmed that there was no significant relation between CLD and the level of crystalloid input. This result confirms earlier reports^{1 3–5} and, importantly, is generated from a population who were at high risk of CLD and routinely exposed to both antenatal steroids and postnatal surfactant.

We did not see any statistically significant differences in the mortality rate or occurrence of other adverse outcomes between our two groups. In earlier studies, an excess of PDA,¹ necrotising enterocolitis,¹⁷ and mortality³ was reported to be associated with high, compared with low, fluid input levels. These studies, however, did not control for sodium intake. It has been previously shown¹⁸ that, if sodium intake is controlled, preterm infants are able to tolerate 200 ml/kg from the third day after birth, achieving a urine output of 7 ml/kg.¹⁸ Our unit's routine policy was to avoid sodium supplementation in the first 24 hours and to tailor

it subsequently, using the results of at least daily monitoring, to keep the levels within a predefined range. The infants on regimen A had an intake recommended as standard^{6,7} rather than a "high" fluid intake, and it is the latter that has been linked with adverse outcome.¹ Hence it is perhaps not surprising that we did not see an excess of adverse outcomes among infants on fluid regimen A. In addition, the significantly lower urine output of infants in the restricted group suggests that, within the range of fluids prescribed in this trial, they could compensate for the different intakes by altering their urine output. This may explain the lack of statistically significant differences in outcome relating to the magnitude of crystalloid intake.

Although the level of crystalloid input did not significantly affect CLD, the amount of colloid infused did. Colloid was prescribed to hypotensive infants, and thus an explanation for our findings could be that CLD develops in sicker infants. Interestingly, however, the occurrence of hypotension in the perinatal period did not differ significantly between the two groups,¹⁹ and the association remained significant, although relatively small, after adjustment for factors known to influence the occurrence of CLD. It has been suggested that colloids do not increase the severity of pulmonary oedema in permeability states if equivalent filling pressures are used.²⁰ We have, however, previously shown that colloid administration adversely affects lung function in the perinatal period.²¹ A possible explanation is that colloid given in the perinatal period to infants with increased vascular permeability leaks into the lungs worsening respiratory function,²¹ necessitating higher levels of respiratory support and hence predisposing the infant to CLD. These results²¹ and the present ones further argue^{22,23} that clinicians should be extremely cautious about prescribing colloid infusions for critically ill patients.

A recent meta-analysis showed that, if steroids were started before 14 days of age, CLD was significantly reduced and, if they were started between 7 and 14 days, mortality was also lowered.²⁴ The higher use of steroids for infants on regimen A is therefore likely to have influenced outcome and may explain why fluid restriction apparently did not reduce the occurrence of CLD. The clinicians who prescribed the steroids were not blinded to the infant's fluid regimen, but for most cases began treatment outside the perinatal period. Before the start of the trial, the routine policy of the unit was to use the more restricted fluid regimen. We do not feel, however, that this biased the clinicians with regard to prescription of steroids, as we have a clear protocol for this. Thus the greater use of steroids for the group on regimen A suggests that the clinicians assessed them to have more severe lung disease and hence to be at greater risk of developing CLD. Corticosteroids have many acute side effects and there is increasing concern that they may also have long term adverse consequences,²⁵ including neuromotor dysfunction²⁶ and abnormal lung growth and

Key messages

- High fluid volumes increase the likelihood of a PDA, a risk factor for CLD development
- One of four previous randomised trials showed that fluid restriction improved outcome—that is, a lower mortality in a relatively mature population
- We now show in ventilated VLBW infants that fluid restriction in the perinatal period does not reduce CLD; colloid infusion, however, increases duration of oxygen dependency

development.²⁷⁻²⁹ As it was associated with a lower requirement for postnatal steroids, fluid restriction may therefore be advantageous for the VLBW infant.

We conclude that fluid restriction to less than 90% of usual maintenance values^{6,7} neither reduces CLD nor increases other adverse outcomes. Colloid infusion in the perinatal period, however, may impair long term lung function.

V K was supported by the South Thames Regional Health Authority Research and Development Directorate and G D by the Children 'Nationwide/Nestle' Research Fellowship. We thank Ms Sue Williams for secretarial support.

Appendix

Infants received surfactant (Survanta) if they were ventilated in at least 30% oxygen. The surfactant was administered within two hours of birth; a second dose was given 12 hours later if the infant remained ventilator dependent and still required supplementary oxygen. Infants were initially supported on conventional ventilation at rates of 60–120 breaths/min and inspiratory to expiratory ratios of 1:1.2. Pancuronium was only administered if, after rate and inspiratory time manipulation, the infant continued to actively expire and therefore to be at high risk of developing a pneumothorax. Infants who, after the second dose of surfactant, required a mean airway pressure of at least 12 cm H₂O and an inspired oxygen concentration of 50% were transferred to high frequency oscillation; a high volume strategy was used. Infants with pulmonary hypertension were given inhaled nitric oxide, provided that they had no bleeding tendency, a platelet count > 100 000/μl, and no greater than a grade II intracranial haemorrhage.

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