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The relationship of fluid restriction during the 1st month of life to the occurrence and severity of bronchopulmonary dysplasia in low birth weight infants: a 1-year radiological follow up

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Abstract. One hundred consecutive low birth weight (LBW) infants (< 1751 g) were randomized into a study group having a restricted fluid intake until 4 weeks of age and a control group following the fluid regimen conventionally used in the hospital. Chest X-ray films were examined on admission, at the ages of 3 days, 7 days, 2 weeks and 4 weeks and at 2-monthly visits to the outpatient clinic up to 1 year of age or until the chest examinations were normal. The severity of hyaline membrane disease (HMD) and typical radiological abnormalities of bronchopulmonary dysplasia (BPD) were assessed. Twelve patients succumbed, one in the study group and 11 in the control group. The study group seemed experience less severe HMD than the controls. Fifty-four percent of the former and 32% of the latter were alive and had no radiological signs of BPD at 4 weeks of age ($P < 0.05$). The difference between the groups in the cumulative number of normal chest X-ray examinations during the follow up was even more significant. The percentage of normal X-ray films at 1 year of age was 92% in the study group and 72% in the control group. These results suggest that fluid restriction for the first 4 weeks of life can lower the incidence of radiological abnormalities typical of BPD obtained during the 1st year of life in LBW infants. Pulmonary oedema seems to be a significant aetiological factor causing HMD to develop into chronic lung disease.

Key words: Low birth weight infant – Hyaline membrane disease – Bronchopulmonary dysplasia – Fluid therapy

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease of infants manifested by tachypnoea, dyspnoea, hypoxaemia, and hypercapnia with characteristic roentgenographic features [14]. The disorder commonly occurs after the treatment of hyaline membrane disease (HMD) with mechanical ventilation [18]. The most important other contributing factors described in the pathogenesis of BPD are low birth weight (LBW) and exposure to high concentrations of oxygen [1, 16]. Parenchymal fluid retention is seen in chest films of patients with severe HMD [13], but the significance of a fluid load for the pathogenesis of BPD is obscure [4, 11, 17, 21].

Radiological features of BPD have been well documented since the initial description and naming of the disease by Northway et al. [14], but significant changes have occurred in recent years in its clinical and radiographic presentation [5, 8, 9] and also in the assessment of its severity [6, 18]. Clinical and roentgenographic scoring systems have now been described for assessing BPD [6, 18].

The aim here was to evaluate the possible effect of different fluid regimens used in the therapy provided for LBW infants on the radiographic severity of HMD, along with the later development and resolution of abnormal chest patterns typical of BPD.

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Abbreviations: BPD = bronchopulmonary dysplasia; BW = birth weight; LBW = low birth weight; HMD = hyaline membrane disease; PDA = persistent ductus arteriosus

Patients and methods

Patients

The series consisted of 100 consecutive LBW infants (birth weight < 1751 g) without fatal congenital anomalies born between May 1987 and April 1989 who were admitted to the neonatal intensive care unit at Oulu University Hospital during their first 24 h of life. The subjects were randomized into two groups, 50 in each, a study group with restricted fluid intake and a control group. The randomization was done in advance using numbers taken from randomization tables. The clinical characteristics of the infants are shown in Table 1.

Fluid therapy

Fluid administration in the study group (enteral + parenteral) followed the regimen 50–60–70–80–90–100–120–150 ml/kg per day during the 1st week and 150 ml/kg per day thereafter up to 4 weeks of age (energy intake 145 kcal/kg per day), while that for the control group followed the protocol conventionally used in the

Table 1. Characteristics of the infants and need for assisted ventilation and oxygen supplementation in the study and control groups

	Study group ($n = 50$)	Control group ($n = 50$)	P
Birth weight (g), mean (SD)	1330 (270)	1280 (320)	NS
range	770–1750	600–1750	NS
Gestational age (weeks), mean (SD)	31.0 (3.2)	30.8 (3.0)	NS
range	24–37	24–36	
Male/female ratio	16/34	15/35	NS
Apgar score 1 min, mean (SD)	5.8 (2.9)	5.8 (2.4)	NS
Pulmonary air leak	3	10	0.037
Maximum weight loss %, mean (SD)	8.8 (5.2)	6.2 (6.3)	0.003
range	0–21	0–27	
Intubated/ventilated (n)	45/39	46/39	
Duration of IPPV (days), median and range	1.5 (0.1–91)	2.5 (0.4–83)	NS
Period of oxygen dependence (days), median and range	7.0 (0–122)	9.0 (0–119)	NS
Period of $FiO_2 > 40\%$ (days), median and range	0.4 (0–75)	0.6 (0–60)	NS
Maximum % inspired oxygen, mean and SD	57.9 (22.9)	63.6 (27.4)	NS

Table 2. Radiological classification of the severity of HMD, according to Tudor et al. [20]

Grade 1 (mild)
(a) Fine miliary shadowing throughout the lung fields without a definite air bronchogram
(b) Air-filled alveoli (black spaces) greater in area than collapsed alveoli (miliary shadows)
(c) Distinct outlines of the heart shadow and diaphragm
(d) Lungs well expanded, but not over-inflated

Grade 2 (moderate)
(a) Some coalescence of miliary shadows
(b) Air-filled alveoli equal collapsed alveoli
(c) Distinct outlines of heart shadow and diaphragm
(d) Air bronchogram at the lung bases
(e) Good lung expansion

Grade 3 (moderate to severe)
(a) Further coalescence of miliary shadows producing a coarse granular pattern
(b) Air-filled alveoli less than collapsed alveoli
(c) Indistinct heart shadow and diaphragm
(d) Widespread air bronchogram

Grade 4 (severe)
(a) Almost total alveolar collapse (white lungs)
(b) Indiscernible heart shadow and diaphragm
(c) Distinct or absent air bronchogram

hospital: 80–100–120–150 ml/kg per day during the 1st week and 200 ml/kg per day afterwards (energy intake 155 kcal/kg per day). The mean amounts of fluids (the sum of liquid medications, enteral fluids, and parenteral crystalloids and colloids administered) that the infants in the study group actually received were 65–76–85–94–108–116–126 ml/kg per day during the 1st week and 151 ml/kg per day during weeks 2–4. The mean actual amounts that the infants in the control gorup received were 85–106–124–137–163–178–180 ml/kg per day during the 1st week and 190 ml/kg per day during weeks 2–4, respectively. The difference between the groups was statistically highly significant ($P = 0.0001$).

Pulmonary care and assessment

Infants who required respiratory assistance were supported with a pressure-controlled Baby Bird (Bird Corporation, Palm Springs, Ca., USA) ventilator via a nasotracheal tube. The need for assisted ventilation, its duration and the exposure to different concentrations of oxygen are seen in Table 1. The ventilation regimens were similar in both groups.

Two infants in the control group were treated with human surfactant because of severe IRDS and both died during the 1st week of life. One infant in the study group and two in the control group needed dexamethasone during weaning from assisted ventilation.

Radiological examinations and assessment

Chest X-ray films were obtained upon admission, at the age of 3 (range 2–4) days, 7 days (range 6–9), 2 weeks and 4 weeks and later at follow up visits to the outpatient clinic every 2nd month until the chest X-ray films were normal, or up to 1 year of age. The chest X-ray films were interpreted and scored by a paediatric radiologist (F.P.L.), who was unaware of the fluid administration regimen of the patient. The radiological severity of HMD was assessed using the criteria of Tudor et al. [20] (Table 2). The roentgenographic scoring of BPD involved numerical assessment according to Toce et al. [18] (Table 3).

Statistical analysis

Single measurements among the continuous data were compared by means of the Student's t-test if normally distributed or the Wilcoxon signed ranks test if not. Discrete data were analysed using the chi-square test and Fisher's exact test. The study was approved by the Ethical Committee of the hospital and informed consent was obtained from the parents or guardians of the infants.

Results

Mortality

Twelve of the patients died, 1 in the study group at the age of 7 days due to severe perinatal asphyxia and intra-

Table 3. A system for scoring the roentgenographical severity of BPD, according to Toce et al. [18]

Variable	Score
Cardiovascular abnormalities	
None	0
Cardiomegaly	1
Gross cardiomegaly, right ventricular hypertrophy, or enlarged main pulmonary artery	2
Hyperexpansion	
Anterior plus posterior rib count[a] of 14 or less	0
Anterior plus posterior rib count of 14.5 to 16	1
Anterior plus posterior rib count of 16.5 or more, or hemidiaphragms flat or concave on lateral view	2
Emphysema	
No focal areas seen	0
Scattered small abnormal lucencies	1
One or more large blebs or bullae	2
Fibrosis/interstitial abnormalities	
None seen	0
A few streaks of abnormal density; interstitial prominence	1
Many abnormal strands; dense fibrotic bands	2
Subjective	
Appears mildly diseased	0
Appears moderately diseased	1
Appears severely diseased	2

[a] Counts of anterior and posterior ribs intersecting the level of the dome of the right hemidiaphragm. If the level of the right hemidiaphragm were at the sixth anterior rib and the eighth posterior intercostal space, the total rib count would be 14.5

cerebral haemorrhage, and 11 in the control group. Five of these latter died during the first 24 h of life, but in 6 of the remaining cases who succumbed between the age of 3 days and 3 months, the excessive fluid intake may have been partly responsible for the clinical deterioration. The causes of death were severe HMD (3 cases), intracerebral haemorrhage and HMD (1 case), BPD and necrotizing enterocolitis (2 cases).

Course of HMD

According to the scoring, patients in the study gorup tended to have less severe HMD during the 1st week of life than those in the control group (Table 4). A similar trend was also found in the incidence of a haemodynamically significant open ductus arteriosus (5 cases in the study group and 9 in the control group, $P = 0.125$).

Severity of BPD

There were no significant differences between the groups in the severity of BPD as scored during the worst stage of the disease. Most cases had their maximum score at the age of 4 weeks, after which the radiological abnormalities became less severe. One patient in the study group and two in the control group had a maximum score of 8, while the others developed less severe radiological abnormalities (Table 5).

Table 4. Severity of HMD according to the radiological scoring in the study and control groups

Number of patients	Score category[a]					*P*
Time of examination	0	1	2	3	4	
Day 1						
Study group	16	14	9	6	5	0.365
Control group	9	13	14	5	9	
Day 3						
Study group	16	18	10	5	1	0.134
Control group	9	9	11	10	3	
Day 7						
Study group	28	11	5	5	0	0.137
Control group	16	9	12	4	1	

[a] According to Tudor et al. [18]

Table 5. Incidence and radiologically classified maximum severity of BPD in the study and control groups according to the criteria of Toce et al. [16]

Score category	Number of infants	
	Study group	Control group
8	1	2
7	1	1
6	1	1
5	0	1
4	3	0
3	5	6
2	7	7
1	4	7
0	27	16

Occurrence and course of BPD

The number of infants having normal chest X-ray films at the age of 14 days was the same in both groups (13 versus 13), but at the age of 4 weeks there was a significant difference between them in the number of patients without radiological and also clinical signs of BPD (27 in the study group versus 16 in the control group, $P < 0.05$). The difference then became even more significant during the follow up: the cumulative numbers of infants with normal chest X-ray films being 33/23 ($P < 0.05$) at the age of 2–3 months, 38/27 ($P < 0.025$) at the age of 4–5 months, 43/32 ($P < 0.025$) at the age of 6–7 months and 46/36 ($P < 0.01$) at the age of 12 months (Fig. 1). Poor outcome, including the abnormal chest patterns of BPD or death, seems to be less frequent in the study group than in the control group.

Besides the classification of Toce et al. [18], only three infants developed complete pulmonary opacification: one in the study group at the age of 3 weeks and two in the control group at the ages of 1 and 2 weeks. Two subjects developed opacification at the ages of 2 and 3 weeks during the convalescnece period shortly after extubation and one subject possibly due to pulmonary oedema at the age of 1 week. The patient in the

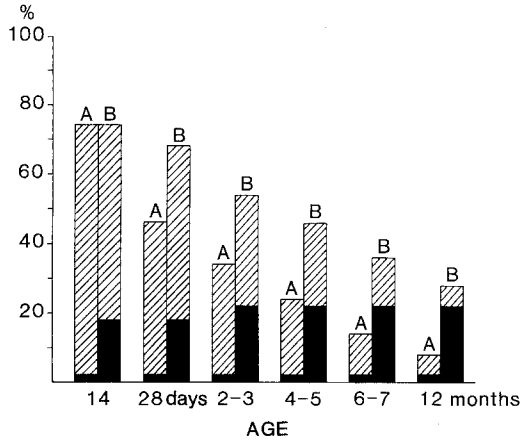

Fig. 1. Percentage of succumbed infants and infants with signs of BPD in the study group *(A)* and in the controls *(B)* ▨ = BPD; ■ = succumbed)

study group had normal chest X-ray films at the age of 4 weeks and the two cases in the control group at the age of 2 and 6 months, respectively.

Discussion

The present results suggest that LBW infants with a fluid load during the first weeks of life tend to suffer from more severe HMD than those with restricted fluid intake. The most important finding is that the group of infants with low fluid regimen contained significantly more cases without signs of BPD at the age of 4 weeks and during the 1-year follow up than that with a higher fluid intake.

Although the birth weights and gestational ages of the infants and the numbers of patients who needed assisted ventilation were similar in the two groups, there were more cases who did not develop HMD according to the radiological classification in the study group than in the control group. There was also a difference in the number who succumbed during the first 24 h of life (0 in the study group and 5 in the control group). Because fluid therapy was started at admission, the randomization had to be made in advance, and therefore these differences must be a matter of chance.

Fluid therapy during the first days and weeks of life for LBW infants and for infants with HMD has been evaluated mostly in retrospective [4, 7, 19, 21] and in only very few prospective studies [2, 11]. According to Tooley [19] a decreased incidence of persistent ductus arteriosus (PDA) and BPD was observed among HMD patients after dramatic changes in fluid therapy. Earlier 100 ml/kg per day was administrated on day 1 and the amount was increased to 150 ml/kg per day by day 5. Later the fluid intake of these subjects was restricted to 50 ml/kg on day 1 and this was increased at the rate 10 ml/kg per day until the neonatal diuresis was complete. In the survey by Brown et al. [4] the mean (SD) fluid intake of infants with HMD (ml/kg per day 1–5) was 118 [8] in subjects who did not develop BPD and 150 [11] in subjects who developed BPD. In the prospective trial of Bell et al. [2] concerning premature infants, the low volume group received 120–125 ml fluids kg per day from days 3 to 30 of life and the lower limit of the high-volume group was set at 20 ml/kg per day above the upper limit for the low-volume group. More cases of necrotizing enterocolitis and an increased risk of haemodynamically significant PDA was observed in the high volume group. Lorenz et al. [11] in their prospective series concerning fluid therapy during the first 1–5 days of life for LBW (BW 750–1500 g) infants administrated intravenous fluids at 60 ml/kg per day until > 13% BW was lost during the first 5 days of life in the fluid restriction group. According to their protocol the high volume group received fluids at 70–80 ml/kg per day on day 1 and the amount of fluids infused was increased to 100–140 ml/kg per day when the urine output exceeded intake during an 8-hour shift. The amounts of fluids administered in the present study group are similar to that in the low fluid regimen reported by Tooley [19]. The control group in the present study received fluids similar amounts as the high volume group described by Lorenz et al. [11].

Both animal experiments and some retrospective surveys of newborn infants show a relationship between pulmonary oedema and many neonatal lung diseases, including HMD and BPD [3, 21]. Premature birth and excessive fluid intake reduce intravascular protein osmotic pressure and thereby facilitate oedema formation in the neonatal lung [3]. It has been stated that overhydration in the presence of mechanical ventilation is more likely to lead to residual lung damage [19], and excessive hydration in sick preterm infants also carries with it an increased incidence of PDA with congestive heart failure [1, 15], which may also lead to more severe HMD, an increased need for oxygen and difficulty in weaning from mechanical ventilation. The present study group on a low fluid regimen contained less cases of haemodynamically significant PDA, although the difference was not statistically significant. Prominent fluid retention can be seen in chest films of severe HMD cases [12]. Fluid restriction in the present study seemed to reduce the severity of HMD, possibly by reducing oedema formation in the lung.

Heneghan et al. [8] found no correlation between fluid balance at 3 and 10 days of age, as inferred from the percentage change in body weight from birth, and the development and severity of BPD. The present data show a significantly greater maximum weight loss relative to birth weight in the study group, and at the same time more cases without radiological signs of BPD at the age of 4 weeks, when compared with the control group. There seems to be a correlation between extracellular fluid balance and the development of BPD, and fluid therapy should be prescribed in such manner as to allow a negative water balance during the first few days of life to reach optimal weight loss.

The number of infants with normal chest X-ray films at the age of 2 weeks was the same in both groups, but there were significantly more cases without radiological and clinical signs of BPD in the study group at the age of

4 weeks. It is possible that fluid restriction maintained for the first 4 weeks of life in the manner of the low fluid regimen used here may partly prevent the development of those radiological features typical of BPD.

There were significantly more cases alive with normal chest X-ray films during the folow up in the study group than in the control group, but the evaluation of the difference is difficult because of the numerous patients succumbing in the latter group. In the six cases who survived the first 24 h but succumbed later the excessive hydration may be partly responsible for clinical deterioration and death. Those subjects were in the poorest condition and developed the most severe HMD on both radiological and clinical criteria. The two infants who succumbed after the age of 4 weeks both had very severe BPD (score 8) together with sequelae of necrotizing enterocolitis, which were also causes of death in both cases. If the six patients had survived they would probably have had the most severe picture of BPD during the follow up.

In a follow-up study of 48 ventilator treated LBW infants (BW < 2.5 kg) by Lindroth et al. [10], 13 patients still had signs of pulmonary fibrosis and hyperinflation in chest roentgenographs at 4 to 6 years of age, while a radiographical follow up of 41 BPD patients described by Mortensson and Lindroth [12] showed residual changes in chest X-ray examinations in 34% of cases at the age of 4–6 years. Griscom et al. [7] mentioned linear shadows representing strands of fibrosis or deep pleural fissuring to be seen in the chest roentgenographs of 15 out of 23 BPD patients in chest roentgenographs at 8–9 years of age. In the present cohort of 100 LBW infants 12 succumbed and 43 patients had normal chest X-ray films at the age of 4 weeks. In the remaining 45 cases the most abnormal chest patterns alluding BPD were resolved during the 1st year, and the six patients with persistent abnormalities at 1 year of age had only mild interstitial fibrosis and signs of hyperinflation (score 2–3). Resolution of the radiological abnormalities typical of BPD seemed to occur more rapidly in the present group of LBW infants than in the series described earlier [7, 10, 12]. Differences in the radiological classification of BPD make comparison of these results difficult, but it is nevertheless possible that the therapy given for HMD has become more effective and less traumatic in recent years, so that convalescence takes place more rapidly.

In conclusion, fluid restriction during the first 4 weeks of life according to the regimen used here seems to have an effect on the severity of HMD in terms of the radiological classification, possibly by preventing pulmonary oedema. It also seems to be of significance in preventing the development of the typical radiological picture of BPD. Mild BPD seems to have a favourable prognosis, being apt to heal during the 1st year.

References

1. Bancalari E, Gerhardt T (1986) Bronchopulmonary dysplasia. Pediatr Clin North Am 33:1–23
2. Bell EF, Warburton D, Stonestreet BS, Oh W (1980) Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. N Engl J Med 302:598–604
3. Bland RD (1983) Edema formation in the lungs and its relationship to neonatal respiratory distress. Acta Paediatr Scand [Suppl] 305:92–99
4. Brown ER, Stark A, Sosenko I, Lawson EE, Avery ME (1978) Bronchopulmonary dysplasia: possible relationship to pulmonary edema. J Pediatr 92:982–984
5. Cleveland RH, Todres ID (1981) Patterns of evolution of X-ray changes in respiratory distress syndrome. Helv Paediatr Acta 36:33–53
6. Farrell PM (1982) Lung development: biological and clinical perspectives. Academic Press Inc, New York, 2:47–57
7. Griscom NT, Wheeler WB, Sweezey NB, Kim YC, Lindsey JC, Wohl MEB (1989) Bronchopulmonary dysplasia: radiographic appearance in middle childhood. Radiology 171:811–814
8. Heneghan MA, Sosulski R, Baquero JM (1986) Persistent pulmonary abnormalities in newborn: the changing picture of bronchopulmonary dysplasia. Pediatr Radiol 16:180–184
9. Hyde I, English RE, Williams JD (1989) The changing pattern of chronic lung disease of prematurity. Arch Dis Child 64: 448–451
10. Lindroth M, Mortensson W (1986) Long-term follow-up of ventilator treated low birthweight infants. Chest X-ray, pulmonary mechanics, clinical lung disease and growth. Acta Paediatr Scand 75:819–826
11. Lorenz JM, Kleinman LI, Kotagal UR, Reller MD (1982) Water balance in very low-birth weight infants: relationship to water and sodium intake and effect on outcome. J Pediatr 101: 423–432
12. Mortensson W, Lindroth M (1986) The course of bronchopulmonary dysplasia. A radiologic follow-up. Acta Radiol (Diagn) 27:19–22
13. Mortensson W, Noack G, Curstedt T, Herin P, Robertson B (1987) Radiologic observations in severe neonatal respiratory distress syndrome treated with the isolated pospholipid fraction of natural surfactant. Acta Radiologica 28:389–394
14. Northway WH, Rosan RC, Porter DY (1967) Pulmonary disease following respirator therapy of hyaline membrane disease. N Engl J Med 276:357–368
15. Shaffer SG, Bradt SK, Hall RT (1986) Postnatal changes in total body water and extracellular volume in the preterm infants with respiratory distress syndrome. J Pediatr 109:509–514
16. Sinkin RA, Phelps DL (1987) New strategies for the prevention of bronchopulmonary dysplasia. Clin Perinatol 14:599–620
17. Spahr RC, Klein AM, Brown DR, Holzman IR, MacDonald HM (1980) Fluid administration and bronchopulmonary Dysplasia. The lack of an association. Am J Dis Child 134:958–960
18. Toce SS, Farrell PM, Leavitt LA, Samuels DP, Edwards DK (1984) Clinical and roentgenographic scoring systems for assessing bronchopulmonary dysplasia. Am J Dis Child 138: 581–585
19. Tooley WH (1979) Epidemiology of bronchopulmonary dysplasia. J Pediatr 95:851–855
20. Tudor J, Young L, Wigglesworth JS, Steiner RE (1976) The value of radiology in the idiopathic respiratory distress syndrome: a radiological and pathological correlation study. Clin Radiol 27:65–75
21. Van Marter LJ, Leviton A, Allred EN, Pagano M, Kuban KC (1990) Hydration during the first days of life and the risk of bronchopulmonary dysplasia in low birth weight infants. J Pediatr 116:942–949