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Full Length Research Paper

Fluid intake in the first week of life: effect on morbidity and mortality in extremely low birth weight infants (less than 900 grams)

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This study was carried out to determine whether lower fluid intake in extremely low birth weight preterm infants < 900 grams birth weight is associated with reduced incidence of PDA and BPD without affecting mortality. Retrospective chart review of two cohorts treated in the same NICU over a 5-year period. The high fluid intake cohort was managed with liberal fluid intakes starting at 155 mL/kg/day. The low fluid cohort was managed starting with 125 mL/kg/day. We compared the rates of mortality and the morbidities of PDA and BPD in these cohorts using ANOVA, chi-square, or the Student t test. One hundred and sixty one infants were admitted during two periods. After exclusion 113 infants were studied; 75 infants in high fluid intake group and 38 in low fluid intake group. The two groups were statistically different in their cumulative weekly fluid intake and the peak daily intake. We found no difference in mortality, PDA, BPD (by either of two definitions), ventilator days, or hospital stay. We were not able to demonstrate any association between fluid intake and mortality or morbidity in this retrospective analysis. The concept of fluid balance may be a more appropriate way to think about fluid intake in ELBW infants rather than absolute fluid intake.

Key words: Patent ductus arteriosus, bronchopulmonary dysplasia, premature infants, fluid balance

INTRODUCTION

Extremely low birth weight (ELBW) premature infants are at high risk of significant early morbidity and mortality (Fanaroff et al., 2007; Eichenwald and Stark, 2008). These infants often experience fluid and electrolyte disturbances in the first week of life that may contribute toward adverse outcomes.

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Abbreviations

PDA: patent ductus arteriosus
BPD: bronchopulmonary dysplasia
CLD: chronic lung disease
PMA: postmenstrual age
LOS: length of stay
ELBW: extremely low birth weight

The volume of fluid prescribed during the first few days of life for ELBW infants is partly driven by their transcutaneous water loss through evaporation from a thin and poorly keratinized epidermal barrier. The tiniest babies may require more than 200 mL/kg/day to prevent dehydration, hypernatremia and hyperkalemia. However, such high rates of fluid intake bear the risk of problems related to a patent ductus arteriosus (PDA), which is present in the majority of these tiny patients.

Several studies have evaluated the impact of high *versus* low volume fluid administration strategies on morbidity and mortality in very low birth weight premature infants (Lorenz, 2004; Bell and Acarregui, 2008). A recent Cochrane Review (Bell and Acarregui, 2008) analyzed five randomized clinical trials comparing restricted with liberal fluid intake for preterm infants. In these trials, the prescribed fluid intake ranged from as low as 50 mL/kg/day to as high as 200 mL/kg/day. Few studies demonstrated significantly higher risk of PDA, necrotizing enterocolitis (NEC), and/or death in the high fluid intake groups (Bell et al., 1979; Bell et al., 1980;

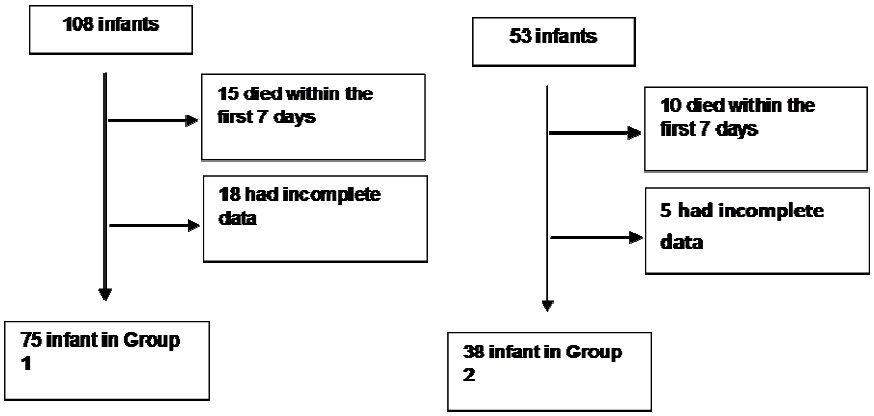

Figure 1.Number of infants admitted during the two periods of cohort analysis.

Tammela and Koivisto, 1992; Tammela et al., 1992). Based on these studies, management in our neonatal intensive care unit (NICU) has shifted in recent years toward more restrictive fluid management in ELBW infants during the first week of life.

We hypothesized that morbidity and mortality for ELBW infants of <900 gram birth weight treated in our nursery would be lower in those born during the period when more restrictive fluid administration was used when compared to a group born earlier, who received higher volumes of fluid.

METHODS

The study populations were consecutive infants weighing <900 grams at birth, who were admitted to the NICU of the Stony Brook University in New York during two periods: from January 1996 to December 1998, when initial fluid intake was 155 mL/kg/day, and from January 2000 to June 2001, when initial fluid intake was 125 mL/kg/day. Infants were excluded from analysis who died within the first 7 days of life, had major congenital malformations, or had incomplete data sets. The infants transferred back to referring hospitals were excluded from analysis when comparing length of hospital stay (LOS) of survivors in the two groups.

Data were collected by chart review onto standardized forms, and set guidelines and item definitions were followed. The following categories were assessed: gestational age, sex, birth weight, dates of birth, admission and discharge, LOS, daily total fluid intake for the first 7 days, daily weight for the first 7 days, cumulative fluid volume intake over first 5 days, number of mechanical ventilation days, oxygen requirement at 28 days of life and at 36 weeks postmenstrual age (more recent definition of CLD or BPD by Jobe and Bancalari, 2001), chest radiographic appearance at those ages, the occurrence of a pulmonary hemorrhage, occurrence and day of development of a clinically significant PDA (*ie,* treated with indomethacin or with surgical ligation), and death in the first week and before discharge. Gestational age was based on maternal dating, prenatal ultrasound, physical examination, and recorded as the age assigned by the attending neonatologist. Diagnosis of a clinically significant PDA was noted by echocardiographic findings, the attending neonatologist's notes, and by documentation of treatment. Echocardiograms were done on babies suspected to have PDA clinically based on the presence of a systolic heart murmur, hyperactive precordium, bounding pulses and wide pulse pressure. Symptomatic PDAs once diagnosed, were initially managed by fluid restriction, diuretics and indomethacin; if not closed by fluid restriction and medications were ligated. The study infants admitted from January 1996 to December 1998 were started on 140 to 150 mL/kg/day of intravenous fluid. Infants admitted from January 2000 to June 2001 were initially given 110 to 130 mL/kg/day of intravenous fluid. Fluid volumes were adjusted according to weight, blood pressure, acid-base status, serum electrolytes and urine output. Infants in both cohorts initially received intravenous fluids without electrolytes on the day of birth. Electrolytes, proteins and lipids were added in fluids on subsequent days. All study infants were nursed in double-walled, heated and humidified incubators except for the first few hours of life, when procedures were being performed under a radiant warmer. Environmental factors, such as use of radiant warmers, incubators and ambient humidity in the NICU, were same during the management of both cohorts. There were no significant changes in nursery practice guidelines between the two time periods.

The sample size was eligible infants weighing <900 grams at birth, who were admitted to the NICU of the Stony Brook University in New York during two periods: from January 1996 to December 1998, and from January 2000 to June 2001.

Repeated measures analysis of variance (ANOVA), unpaired Student t-tests, and chi square analysis were used to evaluate data from each of the above categories. Continuous variable results were summarized as mean $\pm$ standard error of mean (SEM) unless otherwise indicated.

RESULTS

A total of 161 infants below 900 grams admitted during the two periods were included in this cohort analysis. Of these, 108 infants were admitted during the first period (January 1996 to December 1998), and 53 were admitted during the second period (January 2000 to June 2001) (figure 1). Of the 108 infants admitted during the first period, 33 were excluded from further analysis; 15 died within the first 7 days, and 18 had incomplete data. The remaining 75 infants from the first period comprise Group 1(high volume fluid intake)

Of the 53 infants admitted during the second period, 15 infants were excluded from further analysis; 10 infants

Table 1. Demographics of high and low fluid intake groups

Characteristics	Group 1 N=75	Group 2 N=38	P Value
Sex			
Male	33	18	>0.05
Female	42	20	>0.05
Gestational age (wk)	25.42±0.19	25.97±0.35	> 0.05
Range	23-31	23-31	> 0.05
Birth weight (g)	731±13	728±21	> 0.05
Range	505-890	476-885	> 0.05

Numbers represent Mean ± SEM. The groups were compared by c^2 or Student t_{ind} test

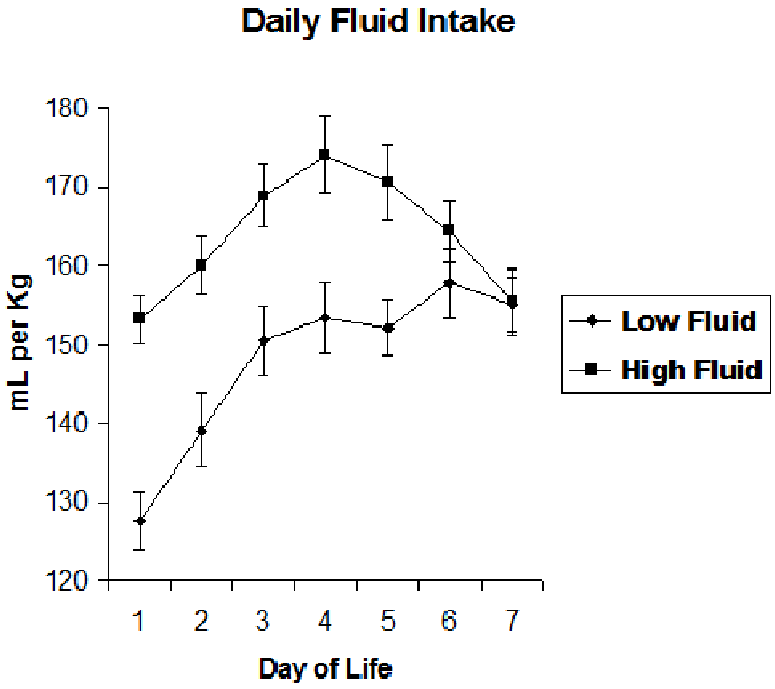

Figure 2. The daily fluid intake during first week of life. Error bars represent standard error of the mean

died within 7 days, and 5 infants had incomplete data. The remaining 38 infants comprise Group 2 (low volume fluid intake). There were no significant differences between the groups in gestational age, birth weight and sex (Table 1).

Fluid intake was found to be significantly higher over the first 5 days of life in Group 1 infants compared to Group 2 infants (Figure 2). Commensurately, at the end of 5 days, the cumulative fluid intake was significantly greater in Group 1 infants (825±17 mL/kg Group 1 *versus* 715±18 mL/kg Group 2, P <0.05). The highest fluid intake in Group 1 infants occurred on day 4 (174±5 mL/kg/day); whereas in Group 2 infants, the highest volume intake occurred on day 6 (158±4 mL/kg).

There was no significant difference in weight loss on any day between the two groups. Group 1 infants had a nadir in their weights on day 5 of life (643±14 grams), while in Group 2 infants it occurred on day 4 (629±18 grams). Despite the earlier nadir in the low volume intake group, there was no significant difference in weights between the two groups on any day (Figure 3). The mean cumulative percentage of weight loss was also not different between the two groups (Figure 4). Infants in the two groups had a similar mean cumulative percentage of weight loss by day 4: 13%±2% (Group 1) *versus* 16.8%±3.5% (Group 2), p >0.05.

There were no differences between the two groups in oxygen requirement at 28 days of life or at 36 weeks postmenstrual age, medically or surgically treated PDA, pulmonary hemorrhage, duration of mechanical ventilation, length of hospital stay for survivors, or mortality (Table 2). Mortality during first week of life was 13.9% in group 1 compared to 18.9% in group 2. The numbers of intraventricular hemorrhage and cystic periventricular leucomalacia were very small in study infants. There was no significant difference in the

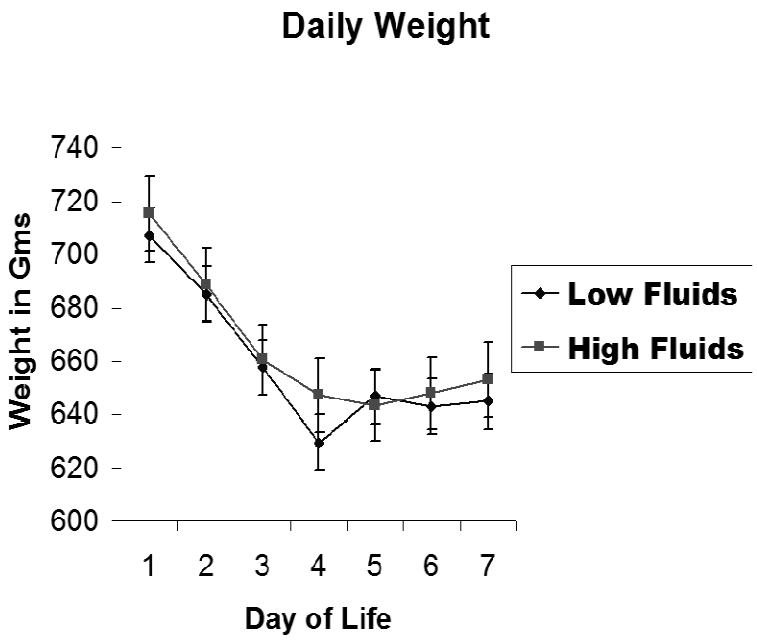

Figure 3. Daily weights during the first week of life. Error bars represent standard error of the mean

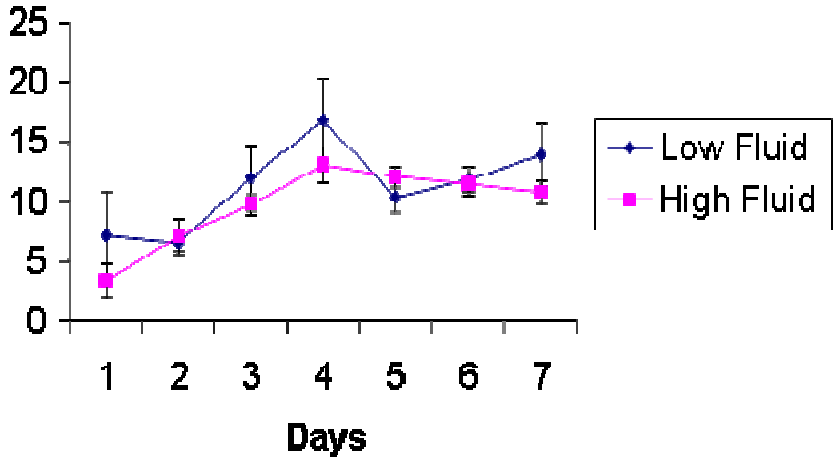

Figure 4. Daily cumulative percent weight loss during first week of life. Error bars represent standard error of the mean

Table 2: Morbidity and mortality outcomes

Outcomes	Group 1 (High Fluid)	Group 2 (Low Fluid)	P value
O_2 at 28 days of life	63/72 (87.5%)	31/36 (86.1%)	>0.50
O_2 at 36 weeks PMA	28/71 (39.4%)	12/36 (33.3%)	>0.50
Symptomatic PDA	35/75 (46.7%)	17/38 (44.7%)	>0.50
PDA closed surgically (failed medical treatment)	6/35 (17.1%)	4/17 (23.5%)	>0.50
Pulmonary hemorrhage	6/75 (8.0%)	5/38 (13.2%)	>0.20
Ventilation days	30.5 $\pm$ 3.1	38.7 $\pm$ 5.3	0.13
LOS of survivors	90.9 $\pm$ 3.1	92.0 $\pm$ 6.0	0.80
Mortality	4/75 (5.3%)	3/38 (7.9%)	>0.50

incidence of intraventricular hemorrhage and cystic periventricular leucomalacia in two groups.

DISCUSSION

The more stringent fluid management period from 2000-2001 resulted in no demonstrable reduction in BPD or PDA, complications of extreme prematurity that are often attributed to excessive fluid. Moreover, there was no significant difference in mortality. Our findings agree with those of Lorenz et al., (1982), who found no statistically significant differences between two fluid intake groups in the occurrences of clinically significant PDA, BPD, duration of respiratory support, length of stay, or neonatal mortality. Spahr et al., (1980), also found no effect of fluid intake on the subsequent development of BPD. Recently Stephens et al., (2008) found increased fluid intake was not significantly related to BPD. On other hand, some observational studies have implicated excess parenterally administered fluid as a risk factor for chronic lung disease (Brown et al., 1978; Tooley, 1979; Marshall et al., 1999; Hartnoll et al., 2000). Van Marter et al (1990) found that neonates in whom chronic lung disease developed had received a higher intake of colloids, crystalloids, and total fluid and had gained weight during the first 4 days of life. Oh et al (2005) found that higher fluid intake and less weight loss during the first 10 days of life were associated with increased risk of BPD in ELBW infants. Similarly Wadhawan et al., (2007) found that early postnatal weight loss was associated with lower risk of BPD or death in ELBW infants. Our infants in the higher fluid group had the same weight loss as those in the low intake group. More recently Baumgart (2009) concluded from Cochrane review that careful fluid restriction reduced death, PDA, BPD, necrotizing enterocolitis in infants of birth weight 1000 to 1500 grams and may be reasonable for ELBW infants, however he did not suggest an early fluid restriction for treatment of ELBW infants.

There was no significant difference between the two groups in development of PDA requiring pharmacologic or surgical closure. This finding was concordant with the results of Lorenz et al (1982), who found no significant differences in fluid intake during first 5 days of life between infants with or without clinically significant PDA, but not with the findings of Stevenson (1990) and Bell *et al* (1980). Recently Stephens et al (2008) found that high fluid intake more than 170 mL/kg/day on day 3 of life was associated with increased risk of PDA among infants of birth weight equal or less than 1250 gms. Their study sample included infants with higher gestational age and birth weight compared to our study infants.

We did not find significant difference in pulmonary hemorrhage, length of hospital stay of survivors, or neonatal mortality between our two study groups, findings similar to the results of Lorenz *et* al.,(1982) and Tammela et al (1992).

There are several possible explanations for the lack of significant differences in outcome of ELBW infants in the two time periods of our study despite more restrictive fluid administration during the second period. First, there may be truly no effect of fluid restriction on outcome, despite other reports (Bell et al., 1979; Bell et al., 1980; Bell and Acarregui, 2008; Tammela and Koivisto, 1992; Tammela et al., 1992). Second, the restriction of fluid intake during the second period may have been inadequate to demonstrate the hypothesized effects. Third, the sample size may have been inadequate. Fourth, there may have been other, unrecognized changes in practice between the first and second periods that offset the effects of more restrictive fluid management. Another possibility is that the analysis was hampered by its focus on fluid intake without consideration of urine and other outputs; a more comprehensive look at fluid balance may have been more informative.

While our practice of fluid management has changed in recent years towards favoring a less aggressive fluid replacement and a relative fluid volume restriction, we found no significant differences in weight loss or percent weight loss. This finding suggests that the higher fluid intake may not have been physiologically necessary and more importantly, that it may have been excessive. ELBW infants may have maintained their total body water and body weight by adjusting urine output to compensate for the fluid intake. Indeed, others have found that infants who received the higher fluid input regimen tended to have higher urine outputs than those on the restricted regimen (Kavvadia et al., 1999; Kavvadia et al., 2000). We did not evaluate renal function or electrolyte concentrations in the two groups. We assessed only the outcomes in infants with liberal fluid intake compared to those with restrictive intake.

Our data indicate that a more restrictive approach to fluid intake applied in our NICU in recent years has not had significant effect on the major neonatal outcomes of ELBW infants. Whether either of these approaches is more beneficial to the long-term developmental outcome is unknown and needs to be evaluated.

As a retrospective observational study, this study has limitations compared to randomized controlled trials. Lack of data on serum electrolytes and urine output is a limitation of this study. Small study sample size may have affected the differences in outcomes.

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