Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants (Review)

Bell EF, Acarregui MJ

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[Intervention Review]

Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Edward F Bell[1], M J Acarregui[1]

[1]Department of Pediatrics, University of Iowa, Iowa City, Iowa, USA

Contact address: Edward F Bell, Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, Iowa, 52242, USA. edward-bell@uiowa.edu.

Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2008.
Review content assessed as up-to-date: 25 August 2007.

Citation: Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD000503. DOI: 10.1002/14651858.CD000503.pub2.

ABSTRACT

Background

Most premature infants are not sufficiently mature physiologically to ingest all of their required water and nutrients orally. Therefore, premature infants rely on their caregivers to regulate their volume of water intake. Thus, the caregiver must determine the amount of water to be given each day to such infants.

Objectives

The objective of this review is to examine the effects of water intake on postnatal weight loss and on the risks of dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death in premature infants.

Search strategy

Randomized clinical trials identified in previous versions of this review were re-examined and, in each case, retained. Additional trials were sought that compared the outcomes of interest in groups of premature infants who were given different levels of water intake according to experimental protocol. Such trials were sought in a list of trials provided by the Cochrane Neonatal Review Group, with a PubMed search, and in the authors' personal files.

Selection criteria

Only randomized clinical trials of varying water intake in premature infants are included. The review was limited to trials that included infants whose water intake was provided mainly or entirely by intravascular infusion. Included studies reported at least one of the following outcomes: postnatal weight loss, dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death.

Data collection and analysis

Standard methods of the Cochrane Collaboration were used. The studies to be included were selected by two reviewers, each of whom also assessed the methodological quality of each trial. Data were independently extracted by the reviewers, who agreed on the key details. The data were then entered into tables using RevMan 4.3.1. The adverse event rates were calculated for the restricted and liberal water intake groups for each dichotomous outcome, and the relative risk and risk difference were computed. In addition, the maximal weight loss results were recorded, and the weighted mean difference was computed. The analyses - including calculation of relative risk, risk difference, and weighted mean difference - and tests of heterogeneity were accomplished using RevMan 4.3.1 software.

Main results

The analysis of the five studies taken together indicates that restricted water intake significantly increases postnatal weight loss and significantly reduces the risks of patent ductus arteriosus and necrotizing enterocolitis. With restricted water intake, there are trends toward increased risk of dehydration and reduced risks of bronchopulmonary dysplasia, intracranial hemorrhage, and death, but these trends are not statistically significant.

Authors' conclusions

Based on this analysis, the most prudent prescription for water intake to premature infants would seem to be careful restriction of water intake so that physiological needs are met without allowing significant dehydration. This practice could be expected to decrease the risks of patent ductus arteriosus and necrotizing enterocolitis without significantly increasing the risk of adverse consequences.

PLAIN LANGUAGE SUMMARY

Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Most babies born before 37 weeks of pregnancy (preterm babies) are not developed enough to take all the water and nutrients they need by mouth. As a result, they are unable to regulate their intake of water. Inadequate water intake can cause the baby to become dehydrated. Excessive water intake can cause heart and lung problems or intestinal damage. Systematic review of trials related to this issue leads to the conclusion that careful restriction of water for preterm babies, to amounts that meets their physical needs without causing dehydration, reduces the risk of certain complications. More research on this topic is needed.

BACKGROUND

Premature infants are generally too ill or immature to be fed by breast or bottle. Therefore, the premature infant depends on his physicians and nurses to determine the rate of water administration by infusion into the infant's veins and arteries or by tube feeding into the stomach or intestine.

Estimation of the desirable intake of water each day is based on incomplete knowledge of the consequences of varying the rate of water intake. Moreover, the margin of error is smaller in managing the premature infant for several reasons. First, the premature infant's water losses to the environment are large (per kg body weight) and highly variable compared to larger, more mature infants or to children and adults. Second, the premature infant's kidneys are limited in their ability to compensate for varying water and solute intake by adjusting the concentration of the urine.

Several clinical trials have been conducted to examine the impact of varying the premature infant's water intake on clinical outcomes. These outcomes have included dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death. Dehydration may lead to hyperkalemia, cardiac arrhythmia, renal failure, and death. Patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, and intracranial hemorrhage are serious complications that may lead to death or disability in premature infants, and the first two of these have been found by some investigators to be more likely if the water intake is excessive.

OBJECTIVES

The objective of this review is to examine the effects of water intake on postnatal weight loss and on the risks of dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death in premature infants. The following questions were examined in premature infants:

1. Does restriction of water intake result in greater maximal postnatal weight loss?

2. Does restricted water intake increase the risk of dehydration?

3. Does restricted water intake decrease (or increase) the risk of patent ductus arteriosus?

4. Does restricted water intake decrease (or increase) the risk of necrotizing enterocolitis?

5. Does restricted water intake decrease (or increase) the risk of bronchopulmonary dysplasia?

6. Does restricted water intake decrease (or increase) the risk of intracranial hemorrhage?

7. Does restricted water intake decrease (or increase) the risk of death?

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized clinical trials were included.

Types of participants

Only studies whose participants consisted entirely or mainly of premature infants (infants born before 37 weeks gestation) were included.

Types of interventions

Studies of varying water intake were included. Trials were excluded if the subjects received water mainly or entirely as enteral feedings. Because we wished to examine the effects of water per se rather than feedings, our review was limited to trials that included infants whose water intake was provided mainly or entirely by parenteral means, i.e. intravascular infusion.

Types of outcome measures

The studies that were included reported at least one of the following outcomes as defined and reported by the authors: postnatal weight loss, dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death prior to hospital discharge.

Search methods for identification of studies

Randomized clinical trials identified in previous versions of this review were reexamined and, in each case, retained. These included trials identified from multiple sources, including a previous review by one of the authors (Bell EF. Fluid therapy. In: Effective Care of the Newborn Infant, eds JC Sinclair, MB Bracken. Oxford: Oxford University Press, 1992: 59-72, Bell 1992) and a Medline search. Additional trials were sought that compared the outcomes of interest in groups of premature infants who were given different levels of water intake according to experimental protocol. Such trials were sought in a list of trials provided by the Cochrane Neonatal Review Group, in the authors' personal files, and with a PubMed search using the following strategy:
1 infant, low birth weight (18196 sources identified)
2 infant, premature (40795 sources identified)
3 1 or 2 (52832 sources identified)
4 water intake (14417 sources identified)
5 fluid intake (5979 sources identified)
6 4 or 5 (18998 sources identified)
7 3 and 6 (176 sources identified)

Data collection and analysis

Two reviewers (EFB, MJA) independently selected the trials to be included in the review. Disagreements, had they occurred, would have been resolved by discussion.
The standard methods of the Cochrane Collaboration (Cochrane Reviewers' Handbook, version 4.2.6, September 2006; RevMan User Guide, version 4.3.1) for conducting a systematic review were used.
The methodological quality of each trial was assessed by the reviewers, who did not use a scoring system to assess quality, but simply recorded details of randomization method, blinding, whether intention to treat analyses were possible from the published data, and the number of patients lost to follow-up. The data were then entered into tables using RevMan 4.3.1.
The adverse event rates were calculated for the restricted and liberal water intake groups for each dichotomous outcome; the relative risk and risk difference were computed for each outcome. In addition, the maximal weight loss results were recorded, and the weighted mean difference was computed. The analyses - including calculation of relative risk, risk difference, and weighted mean difference - and tests of heterogeneity were accomplished using RevMan 4.3.1 software and fixed effects models.

RESULTS

Description of studies

See: Characteristics of included studies.

Five studies were included in this analysis. All were randomized clinical trials of varying water intake in premature infants. Each study compared two groups, one of whom received liberal water intake (this is considered the standard or control therapy) and the other restricted water intake. The principal difference among the studies was the timing and duration of the period when the subjects' water intake was determined by study protocol. In the Bell study, the prescribed water intake was begun before 72 hours of age and continued up to age 30 days (unless any of certain criteria was met first). In the Kavvadia study, the prescribed water intake was given only during the first 7 days of life; this study was limited to infants who required assisted ventilation starting within 6 hours of birth. In the Lorenz study, the prescribed water intake was given only during the first 5 days of life. In the Tammela study, the prescribed water intake was begun within 24 hours of birth and continued until age 28 days. In the von Stockhausen study, the prescribed water intake was given only during the first 3 days of life.

Various clinical outcomes were reported for each study as described in the "Table of Included Studies."

Risk of bias in included studies

Bell 1980:
Prognostic stratification*?: yes
Pre-randomization blinding of investigators to allocation?: yes
Blinding of caretakers to treatment?: no
Observer who categorized outcome blinded to treatment?: no
All subjects included in analysis?: yes

Kavvadia 2000:
Prognostic stratification?: no
Pre-randomization blinding of investigators to allocation?: yes
Blinding of caretakers to treatment?: no
Observer who categorized outcome blinded to treatment?: no
All subjects included in analysis?: yes

Lorenz 1982:
Prognostic stratification?: yes
Pre-randomization blinding of investigators to allocation?: cannot determine
Blinding of caretakers to treatment?: no
Observer who categorized outcome blinded to treatment?: no
All subjects included in analysis?: no

Tammela 1992:
Prognostic stratification?: no
Pre-randomization blinding of investigators to allocation?: yes
Blinding of caretakers to treatment?: no
Observer who categorized outcome blinded to treatment?: no
All subjects included in analysis?: yes

von Stockhausen 1980:
Prognostic stratification?: no
Pre-randomization blinding of investigators to allocation?: cannot determine
Blinding of caretakers to treatment?: no
Observer who categorized outcome blinded to treatment?: no
All subjects included in analysis?: not stated

*Prognostic stratification assures balance between treatment groups of other factors known or suspected to influence the outcomes of interest.

Effects of interventions

RESTRICTED VS. LIBERAL WATER INTAKE (COMPARISON 01):

Weight loss (Outcome 01.01):
Postnatal weight loss (expressed as a percentage of birth weight) was significantly higher with restricted water intake in the trials of Bell and Tammela. It was also higher with restricted water intake in the meta-analysis of the three trials of Bell, Tammela, and von Stockhausen (overall weighted mean difference 1.94% of birth weight, 95% confidence interval [CI] 0.82 to 3.07).

Dehydration (Outcome 01.02):
There was a nonsignificant trend toward increased risk of dehydration with restricted water intake in the trial of Bell. The meta-analysis, which included the trials of Bell and Lorenz, revealed a similar trend toward increased dehydration with restricted water intake (typical relative risk [RR] 2.43, 95% CI 0.71 to 8.28; typical risk difference [RD] 0.04, 95% CI -0.01 to 0.09), but this trend was not significant.

Patent ductus arteriosus (Outcome 01.03):
The risk of patent ductus arteriosus was significantly lower with restricted water intake in the trial of Bell and in the meta-analysis (typical RR 0.52, 95% CI 0.37 to 0.73; typical RD -0.14, 95% CI -0.21 to -0.07), which included the trials of Bell, Kavvadia, Lorenz, and Tammela. Based on this analysis, the number needed to treat with restricted water intake to prevent one case of patent ductus arteriosus is 7 (95% CI 5 to 14).

Necrotizing enterocolitis (Outcome 01.04):
The risk of necrotizing enterocolitis was significantly lower with restricted water intake in the trial of Bell and in the meta-analysis (typical RR 0.43, 95% CI 0.21 to 0.87; typical RD -0.05, 95% CI -0.09 to -0.01), which included the trials of Bell, Kavvadia, Lorenz, and Tammela. Based on this analysis, the number needed to treat with restricted water intake to prevent one case of necrotizing enterocolitis is 20.0 (95% CI 11 to 100).

Bronchopulmonary dysplasia (Outcome 01.05):
The risk of bronchopulmonary dysplasia was not significantly affected by water intake in any of the four trials in which this was reported (Bell, Kavvadia, Lorenz, and Tammela), nor in the meta-analysis (typical RR 0.85, 95% CI 0.63 to 1.14; typical RD -0.04, 95% CI -0.11 to 0.03). The direction of effect in all four trials

and in the meta-analysis was toward reduced risk of bronchopulmonary dysplasia with restricted water intake.

Intracranial hemorrhage (Outcome 01.06):

The risk of intracranial hemorrhage (all grades) was not significantly affected by water intake in any of the three trials in which this was analyzed (Kavvadia, Lorenz, and Tammela), nor in the meta-analysis (typical RR 0.74, 95% CI 0.48 to 1.14; typical RD -0.06, 95% CI -0.13 to 0.02). However, the trend in two of the trials (Kavvadia and Tammela) and in the meta-analysis was toward reduced risk of intracranial hemorrhage with restricted water intake.

Death (Outcome 01.07):

The risk of death was significantly lower with restricted water intake in the trial of Tammela but not in the other four trials nor in the meta-analysis (relative RR 0.81, 95%CI 0.54 to 1.23; relative RD -0.03, 95%CI -0.08 to 0.03), which included all five trials.

Summary:

The analysis of the five studies taken together indicates that restricted water intake significantly increases postnatal weight loss and significantly reduces the risks of patent ductus arteriosus and necrotizing enterocolitis. With restricted water intake, there are trends toward increased risk of dehydration and reduced risks of bronchopulmonary dysplasia, intracranial hemorrhage, and death, but these trends are not statistically significant.

DISCUSSION

This analysis shows what appear to be significant advantages to a restrictive strategy for managing the water intake of premature infants. When considered collectively using meta-analysis, the infants in these five trials who were in the restricted groups were at lower risk of patent ductus arteriosus and necrotizing enterocolitis with no significant increase in adverse effects. There were trends toward increased risk of dehydration and decreased risk of bronchopulmonary dysplasia, intracranial hemorrhage, and death with restricted water intake, but these trends were not significant. It is important to use caution in extrapolating these results to extremely premature infants, who were underrepresented in these studies.

AUTHORS' CONCLUSIONS

Implications for practice

Based on this analysis, the most prudent prescription for water intake to premature infants would seem to be careful restriction of water intake so that physiological needs are met without allowing significant dehydration. This practice could be expected to decrease the risks of patent ductus arteriosus and necrotizing enterocolitis without a significant increase in adverse consequences.

Implications for research

Future research in this area might be directed toward refining the critical period during which water intake must be controlled in order to achieve the desired reduction in complications of prematurity. It would also be valuable to develop models for predicting optimal water intakes that take into account the most important determinants of water requirement, such as birth weight, gestational age, postnatal age, and ambient humidity. Finally, future studies should target the most vulnerable group: extremely premature infants.

ACKNOWLEDGEMENTS

None

REFERENCES

References to studies included in this review

Bell 1980 *{published data only}*

* Bell EF, Warburton D, Stonestreet BS, Oh W. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *New England Journal of Medicine* 1980;**302**:598–604. [MEDLINE: 1980099478]

Bell EF, Warburton D, Stonestreet BS, Oh W. High-volume fluid intake predisposes premature infants to necrotising enterocolitis. *Lancet* 1979;**2**:90. [MEDLINE: 1979198572]

Kavvadia 2000 *{published data only}*

Kavvadia V, Greenough A, Dimitriou G, Forsling ML. Randomized trial of two levels of fluid input in the perinatal period -- effect on fluid balance, electrolyte and metabolic disturbances in ventilated VLBW infants. *Acta Paediatrica* 2000;**89**:237–41. [MEDLINE: 20173131]

Kavvadia V, Greenough A, Dimitriou G, Hooper R. Comparison of the effect of two fluid input regimens on perinatal lung function in ventilated very low birthweight infants. *European Journal of Pediatrics* 1999;**158**:917–22. [MEDLINE: 20009459 20009459]

Kavvadia V, Greenough A, Dimitriou G, Hooper R. Randomised trial of fluid restriction in ventilated very low birthweight infants. *Archives of Disease in Childhood Fetal Neonatal Ed* 2000;**83**:F91–6. [MEDLINE: 20409236]

Lorenz 1982 *{published data only}*

* Lorenz JM, Kleinman LI, Kotagal UR, Reller MD. Water balance in very low-birth-weight infants: relationship to water and sodium intake and effect on outcome. *Journal of Pediatrics* 1982;**101**:

423–32. [MEDLINE: 1982268391]
Reller MD, Lorenz JM, Kotagal UR, Meyer RA, Kaplan S. Hemodynamically significant PDA: an echocardiographic and clinical assessment of incidence, natural history, and outcome in very low birth weight infants maintained in negative fluid balance. *Pediatric Cardiology* 1985;**6**:17–24. [MEDLINE: 1985242348]

Tammela 1992 ***{published data only}***
Tammela OKT, Koivisto ME. Fluid restriction for preventing bronchopulmonary dysplasia?Reduced fluid intake during the first weeks of life improves the outcome of low-birth-weight infants. *Acta Paediatrica* 1992;**81**:207–12. [MEDLINE: 1992379368]
Tammela OKT, Lanning FP, Koivisto ME. 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. *European Journal of Pediatrics* 1992; **151**:295–9. [MEDLINE: 1992362652]
Tammela OKT, Lanning FP, Koivisto ME. 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. *European Journal of Pediatrics* 1992; **151**:367–71. [MEDLINE: 1993011369]

von Stockhausen 1980 ***{published data only}***
von Stockhausen HB, Struve M. Die Auswirkungen einer stark unterschiedlichen parenteralen Flussigkeitszufuhr bei Fruh- und Neugeborenen in den ersten drei Lebenstagen. *Klinische Pädiatrie* 1980;**192**:539–46. [MEDLINE: 1981171265]

Additional references

Bell 1992
Bell EF. Fluid therapy. In: Sinclair JC, Bracken MB editor(s). *Effective Care of the Newborn Infant*. Oxford: Oxford University Press, 1992:59–72.

References to other published versions of this review

Bell 1998
Bell EF, Acarregui M. Restricted versus liberal water intake for the prevention of morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD000503]

Bell 2001
Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD000503]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bell 1980

Methods	Water intake was controlled by study protocol until one of six criteria was met: significant patent ductus arteriosus (PDA), dehydration, death, full enteral feedings, transfer to another hospital, or age 30 days. This was a randomized, unblinded clinical trial. Enrolled infants were divided into eight groups (prognostic stratification)according to three factors thought to influence the risk of PDA: birth weight below or above 1.25 kg, size for gestational age (AGA vs SGA), and respiratory status (presence or absence of significant RDS). Within each of the resulting eight groups, subjects were randomly assigned to either of two treatment groups ("low" and "high" volume water intake) by opening the next opaque, sealed envelope from the pile for the corresponding prognostic group; the envelope contained the designation of "low" or "high" volume group as determined from a table of random numbers prior to enrollment of the first subject in the study. Within each of the eight prognostic groups, the randomization was balanced so that the number of low and high volume infants was equal after every second infant was enrolled into that group. Consecutively enrolled infants in each group were paired for analysis. A two-sided sequential plan was used, and the outcomes for discordant pairs of infants were plotted on this plan. No confounding variables were identified. No infants were withdrawn from the study. Infants were cared for in unhumidified single-walled incubators.
Participants	The participants were 170 infants with birth weight ranging from 751 to 2000 g. They were enrolled within the first three days of life. Complete accounting is given for infants in this weight range who contemporaneously were not enrolled in the study. Infants were excluded who by the third day of life had died, were receiving more than half of their water intake enterally, had evidence of PDA or other congenital heart defect, were suspected of having renal anomaly or injury or elevated intracranial pressure, or were clinically dehydrated. Of the 384 consecutive infants admitted with birth weight between 751 and 2000 g, 123 were excluded according to one or more of the aforementioned criteria. Of the remaining 261 eligible infants, consent was not sought in 39 cases and was denied in 52 cases. The remaining 170 infants were enrolled in the study. The mean birth weight was 1.4 kg in both groups, and the mean gestational age was 31 weeks.
Interventions	The subjects' total water intake (enteral plus parenteral)was determined by study protocol. An upper limit was set for the "low" volume group, and a lower limit was set for the "high" volume group. These limits depended on birth weight and varied with postnatal age and were raised by 10 ml/kg/d during phototherapy. The mean daily water intake for all subjects throughout the study was 122 ml/kg/d for the low volume group and 169 ml/kg/d for the high volume group.
Outcomes	The outcomes compared between the treatment groups included maximum weight loss, PDA, PDA with signs of congestive heart failure, necrotizing enterocolitis, bronchopulmonary dysplasia, and death.
Notes	The results of this study were reported in the New England Journal of Medicine (1980; 302:598-604) except for the detailed limits for water intake in all subgroups, which were published only in a letter in the Lancet (1979; 2:90).

Risk of bias

Item	Authors' judgement	Description

Bell 1980 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Kavvadia 2000

Methods	Water intake was determined by study protocol for first seven days. This was a randomized, unblinded clinical trial.
Participants	The participants were 168 infants with birth weight 1500 g or less with required assisted ventilation within 6 hours of birth.
Interventions	Subjects were randomly assigned to receive one of two fluid regimens. The water intake prescribed for the infants in the restricted intake group was lower than the liberal group by 20-40 ml/kg/d. The water intake could be adjusted according to specific guidelines if an infant in either group developed renal failure, hypotension, or hyperbilirubinemia requiring phototherapy. Overall, the infants in the restricted intake group received 11% less water than the infants in the liberal group.
Outcomes	The outcomes compared between groups were death or survival, duration of assisted ventilation, duration of supplemental oxygen, oxygen dependence at 28 d, oxygen dependence at 36 weeks postmenstrual age, pneumothorax, pulmonary interstitial emphysema, intracranial hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, renal failure, and treatment with pancuronium, inhaled nitric oxide, high-frequency ventilation, diuretic drugs, and corticosteroids.
Notes	The results of this study were reported in three papers: European Journal of Pediatrics (1999; 158:917-22) , Acta Paediatrica (2000; 89:237-41), and Archives of Disease in Childhood Fetal and Neonatal Edition (2000; 83:F91-6).

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Lorenz 1982

Methods	The duration of study (control of water intake according to study criteria) was for five days after birth. This was a randomized, unblinded clinical trial. The details of randomization are not given, but the subjects were first stratified according to birthweight group (750-999 g, 1000-1249 g, and 1250-1500 g), 5-minute Apgar score (6 or less vs more than 6), presence of respiratory distress syndrome (RDS), and hospital of birth (inborn vs outborn). No confounding variables were identified in a comparison of demographic features in the two groups. Deviations from protocol were allowed for infants with patent ductus arteriosus (PDA), but the number for whom this occurred is not stated. Seven of 108 infants were withdrawn from the study. Two infants in the liberal water intake group were subsequently found to have non-PDA congenital heart defects; two in the restricted water intake group were withdrawn because of intestinal obstruction or perforation requiring surgery; and three infants in the restricted water intake group died within 24 hours of enrollment. In addition, 13 infants were excluded from analysis because they had no matching infant (according to the above stratification criteria) who received the other treatment. Infants were cared for in maximally humidified, single-walled incubators.
Participants	The participants included in the analysis were 88 AGA infants with birth weight between 750 and 1500 g. The "exclusion" criteria given in the report were actually withdrawal criteria: non-PDA congenital heart disease, conditions requiring surgery, and death within 24 hours after entry into the study. The mean birth weight in both groups was 1.2 kg, and the mean gestational age was 29 weeks. Thirty-four infants had 5-minute Apgar scores of 6 or less; 64 had RDS; and 30 infants were inborn. The gender distribution is not given.
Interventions	The water intake of infants in the restricted water intake group was managed to allow a 3 to 5% loss of weight per day to a maximum of 15%. Their water intake began at 65 to 70 ml/kg/d and increased to 80 ml/kg/d by day 5. In the liberal water intake group, the water intake was managed to allow a 1 to 2% loss of weight per day to a maximum loss of 10%. The water intake in the liberal intake group began at 80 ml./kg on the first day and increased gradually to 140 ml/kg/d by day 5. The actual mean weight losses were 12.9% and 8.8% in the restricted and liberal groups, respectively.
Outcomes	The outcomes examined were maximum weight loss as a percentage of birth weight, water intake and urine output, sodium intake, serum sodium concentration, hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, significant PDA, bronchopulmonary dysplasia, intracranial hemorrhage, necrotizing enterocolitis, dehydration, acute renal failure, and death.
Notes	The results of this study were published in two papers: Journal of Pediatrics (1982; 101:423-32)and Pediatric Cardiology (1985; 6:17-24).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Tammela 1992

Methods	The duration of the study--i.e. determination of water intake according to study protocol--was for 28 days beginning on the day of birth. This was a randomized, unblinded clinical trial. Randomization was by ordered opening of sealed envelopes containing the assignment to "dry" or "control" group as determined from a table of random numbers. There was no prognostic stratification. No confounding variables were identified in a comparison of demographic features in the two groups. No information was given about dropouts or deviations from study protocol except to say that water intake was increased by 10 ml/kg/d for infants in either group who lost more than 5% of their body weight in a day or more than 15% in total since birth. All infants were initially cared for in incubators with 50% relative humidity.
Participants	The participants were 100 infants with birth weight below 1751 g who were admitted to the NICU during the first 24 h of life. During a two-year period, 100 of 103 consecutive eligible infants were enrolled. Two were excluded because of extreme prematurity (gestational age <24 weeks), and one was excluded because of failure to obtain parental consent. The mean birthweight in both groups was 1.3 kg, and the mean gestational age was 31 weeks. Thirty-four infants (34%) were SGA, 31% were delivered by cesarean section, 49% were males, and 91% had endotracheal tubes placed for respiratory assistance.
Interventions	The subjects' total water intake (enteral plus parenteral except replacement of phlebotomy losses with transfused erythrocytes)was determined by study protocol. The "dry" group was targeted to receive 50 ml/kg on day 1, 60 ml/kg on day 2, 70 ml/kg on day 3, 80 ml/kg on day 4, 90 ml/kg on day 5, 100 ml/kg on day 6, 120 ml/kg on day 7, and 150 ml/kg thereafter. The "control" group was targeted to receive 80 ml/kg on day 1, 100 ml/kg on day 2, 120 ml/kg on day 3, 150 ml/kg on days 4 through 7, and 200 ml/kg thereafter. The volumes actually delivered varied slightly from these targets but differed highly significantly between the groups, as planned.
Outcomes	The outcomes compared between the treatment groups included maximum weight loss, age to recovery of birth weight, weight at 28 days (as % of birth weight), hypotension, volume of erythrocytes transfused, hypoglycemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, need for phototherapy, patent ductus arteriosus requiring treatment, necrotizing enterocolitis, intraventricular hemorrhage, duration of assisted ventilation, duration of intubation, need for high ventilator pressures, pulmonary air leak, bronchopulmonary dysplasia, and death.
Notes	The results of this study were reported in three published papers: Acta Paediatrica (1992; 81:207-12)and two identical papers in the European Journal of Pediatrics (1992; 151:295-99 and 1992; 151:367-71).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

von Stockhausen 1980

Methods	The duration of the study--i.e. determination of water intake according to study protocol--was the first three days of life. This was a randomized, unblinded clinical trial. The subjects were randomly assigned to "low" or "high" volume of water intake for the first three days of life. The details of randomization are not given, and there was no prognostic stratification. Males outnumbered females in both groups, but the preponderance of males was greater in the low volume group (23/28 vs 17/28). The low group also had slightly higher mean birth weight (2.0 vs 1.9 kg) and gestational age (34.6 vs 34.2 weeks). No information was given about dropouts or deviations from study protocol. All infants were cared for in incubators with maximal humidity.
Participants	The participants were 56 newborn infants, most of whom were premature, all enrolled on first day of life. Five of these infants required intermittent positive-pressure ventilation, and six others required continuous positive airway pressure. No information is given on exclusion criteria.
Interventions	The subjects' total intake was determined by study protocol for the first three days of life. The "low" volume group was given 60 ml/kg/d, and the "high" volume group was given 150 ml/kg/d.
Outcomes	The outcomes reported include death, maximum weight loss, urine volume, osmolal clearance, creatinine clearance, free water clearance, net acid excretion, sodium clearance, chloride clearance, and a number of laboratory values, including urinary osmolality, sodium, potassium, chloride, calcium, phosphate, creatinine, urea, and uric acid. Also reported were hematocrit, blood osmolality, and serum concentrations of sodium, chloride, calcium, phosphate, creatinine, urea, and bilirubin.
Notes	No information is given on the incidence of PDA, NEC, or BPD.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

DATA AND ANALYSES

Comparison 1. Restricted versus liberal water intake

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight loss (%)	3	326	Mean Difference (IV, Fixed, 95% CI)	1.94 [0.82, 3.07]
2 Dehydration	2	258	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.71, 8.28]
3 Patent ductus arteriosus	4	526	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.37, 0.73]
4 Necrotizing enterocolitis	4	526	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.21, 0.87]
5 Bronchopulmonary dysplasia	4	526	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.14]
6 Intracranial hemorrhage (all grades)	3	356	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.14]
7 Death	5	582	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.23]

Analysis 1.1. Comparison 1 Restricted versus liberal water intake, Outcome 1 Weight loss (%).

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 1 Weight loss (%)

Study or subgroup	Restricted N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bell 1980	85	14 (5.7)	85	11.5 (6.3)		38.9 %	2.50 [0.69, 4.31]
Tammela 1992	50	8.8 (5.2)	50	6.2 (6.3)		24.8 %	2.60 [0.34, 4.86]
von Stockhausen 1980	28	5.3 (3.9)	28	4.4 (3.2)		36.3 %	0.90 [-0.97, 2.77]
Total (95% CI)	**163**		**163**			**100.0 %**	**1.94 [0.82, 3.07]**

Heterogeneity: Chi² = 1.89, df = 2 (P = 0.39); I² =0.0%

Test for overall effect: Z = 3.38 (P = 0.00072)

Analysis 1.2. Comparison 1 Restricted versus liberal water intake, Outcome 2 Dehydration.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 2 Dehydration

Study or subgroup	Restricted n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1980	6/85	0/85		14.3 %	13.00 [0.74, 227.20]
Lorenz 1982	2/44	3/44		85.7 %	0.67 [0.12, 3.80]
Total (95% CI)	**129**	**129**		**100.0 %**	**2.43 [0.71, 8.28]**

Total events: 8 (Restricted), 3 (Liberal)

Heterogeneity: Chi^2 = 3.44, df = 1 (P = 0.06); I^2 =71%

Test for overall effect: Z = 1.42 (P = 0.16)

Analysis 1.3. Comparison 1 Restricted versus liberal water intake, Outcome 3 Patent ductus arteriosus.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 3 Patent ductus arteriosus

Study or subgroup	Restricted n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1980	9/85	35/85		44.3 %	0.26 [0.13, 0.50]
Kavvadia 2000	18/84	22/84		27.8 %	0.82 [0.47, 1.41]
Lorenz 1982	9/44	13/44		16.5 %	0.69 [0.33, 1.45]
Tammela 1992	5/50	9/50		11.4 %	0.56 [0.20, 1.54]
Total (95% CI)	**263**	**263**		**100.0 %**	**0.52 [0.37, 0.73]**

Total events: 41 (Restricted), 79 (Liberal)

Heterogeneity: Chi^2 = 7.53, df = 3 (P = 0.06); I^2 =60%

Test for overall effect: Z = 3.81 (P = 0.00014)

Analysis 1.4. Comparison 1 Restricted versus liberal water intake, Outcome 4 Necrotizing enterocolitis.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 4 Necrotizing enterocolitis

Study or subgroup	Restricted n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1980	3/85	16/85		65.3 %	0.19 [0.06, 0.62]
Kavvadia 2000	4/84	3/84		12.2 %	1.33 [0.31, 5.78]
Lorenz 1982	3/44	1/44		4.1 %	3.00 [0.32, 27.74]
Tammela 1992	0/50	4/50		18.4 %	0.11 [0.01, 2.01]
Total (95% CI)	**263**	**263**		**100.0 %**	**0.43 [0.21, 0.87]**
Total events: 10 (Restricted), 24 (Liberal)					
Heterogeneity: Chi^2 = 7.91, df = 3 (P = 0.05); I^2 =62%					
Test for overall effect: Z = 2.35 (P = 0.019)					

Analysis 1.5. Comparison 1 Restricted versus liberal water intake, Outcome 5 Bronchopulmonary dysplasia.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 5 Bronchopulmonary dysplasia

Study or subgroup	Restricted n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1980	5/85	8/85		11.9 %	0.63 [0.21, 1.83]
Kavvadia 2000	21/84	22/84		32.8 %	0.95 [0.57, 1.60]
Lorenz 1982	10/44	12/44		17.9 %	0.83 [0.40, 1.73]
Tammela 1992	21/50	25/50		37.3 %	0.84 [0.55, 1.29]
Total (95% CI)	**263**	**263**		**100.0 %**	**0.85 [0.63, 1.14]**
Total events: 57 (Restricted), 67 (Liberal)					
Heterogeneity: Chi^2 = 0.51, df = 3 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 1.08 (P = 0.28)					

Analysis 1.6. Comparison 1 Restricted versus liberal water intake, Outcome 6 Intracranial hemorrhage (all grades).

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 6 Intracranial hemorrhage (all grades)

Study or subgroup	Restricted n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kavvadia 2000	12/84	21/84		55.3 %	0.57 [0.30, 1.09]
Lorenz 1982	14/44	11/44		28.9 %	1.27 [0.65, 2.49]
Tammela 1992	2/50	6/50		15.8 %	0.33 [0.07, 1.57]
Total (95% CI)	**178**	**178**		**100.0 %**	**0.74 [0.48, 1.14]**
Total events: 28 (Restricted), 38 (Liberal)					
Heterogeneity: Chi^2 = 4.16, df = 2 (P = 0.12); I^2 =52%					
Test for overall effect: Z = 1.37 (P = 0.17)					

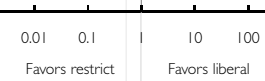
Analysis 1.7. Comparison 1 Restricted versus liberal water intake, Outcome 7 Death.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 7 Death

Study or subgroup	Restricted n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1980	6/85	8/85		18.6 %	0.75 [0.27, 2.07]
Kavvadia 2000	21/84	16/84		37.2 %	1.31 [0.74, 2.33]
Lorenz 1982	5/44	7/44		16.3 %	0.71 [0.25, 2.08]
Tammela 1992	1/50	11/50		25.6 %	0.09 [0.01, 0.68]
von Stockhausen 1980	2/28	1/28		2.3 %	2.00 [0.19, 20.82]
Total (95% CI)	**291**	**291**		**100.0 %**	**0.81 [0.54, 1.23]**
Total events: 35 (Restricted), 43 (Liberal)					
Heterogeneity: Chi^2 = 7.87, df = 4 (P = 0.10); I^2 =49%					
Test for overall effect: Z = 0.98 (P = 0.33)					



WHAT'S NEW

Last assessed as up-to-date: 25 August 2007.

11 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 4, 1998

26 August 2007	New search has been performed	This review updates the review "Restricted versus liberal water intake for the prevention of morbidity and mortality in preterm infants", published in The Cochrane Library , Issue 3, 2001 (Bell 2001). New trials were sought using the same search strategy and selection criteria employed in the previous review. One new trial was identified and incorporated into the review.
26 August 2007	New citation required but conclusions have not changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

The contact reviewer (EFB) corresponded with the editors, compiled the studies to be considered for inclusion in the review, identified studies meeting the search criteria, assessed the methodological quality of the included studies, and composed the text of the review.

The co-reviewer (MJA) identified studies meeting the search criteria, assessed the methodological quality of the included studies, and reviewed the text.

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Drinking; *Infant, Premature; *Water; Bronchopulmonary Dysplasia [prevention & control]; Dehydration [etiology]; Ductus Arteriosus, Patent [prevention & control]; Enterocolitis, Necrotizing [prevention & control]; Infant, Newborn; Infant, Premature, Diseases [mortality; *prevention & control]; Intracranial Hemorrhages [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans