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Bell EF, Acarregui MJ.
Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants.
Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD000503.
DOI: [10.1002/14651858.CD000503.pub3](https://doi.org/10.1002/14651858.CD000503.pub3).

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[Intervention Review]

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

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ABSTRACT

Background

Most premature infants are physiologically not sufficiently mature to orally ingest all of their required water and nutrients. 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

To determine the effect of water intake on postnatal weight loss and the risks of dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death in premature infants.

Search methods

Randomized clinical trials (RCTs) 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 an 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.

This search was updated in 2014.

Selection criteria

Only RCTs of varying water intake in premature infants were included. The review was limited to trials that included infants whose water intake was provided mainly or entirely by intravascular infusion.

Data collection and analysis

The standard methods of The Cochrane Collaboration were used. Study selection and data abstraction were performed independently by each review author. 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.

Main results

The analysis of the five studies taken together indicated that restricted water intake significantly increased postnatal weight loss and significantly reduced the risks of patent ductus arteriosus and necrotizing enterocolitis. With restricted water intake, there were trends

toward increased risk of dehydration and reduced risks of bronchopulmonary dysplasia, intracranial hemorrhage, and death but these trends were 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 meet their physical needs without causing dehydration, reduces the risk of certain complications. More research on this topic is needed.

BACKGROUND

Description of the condition

Premature infants are generally too ill or immature to be fed by the 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.

Description of the intervention

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 small 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. 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 was to determine the effects of water intake on postnatal weight loss and 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 (RCTs) were included. Quasi-randomized trials were searched for and eligible for inclusion in the 2014 update.

Types of participants

Only studies where 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 participants 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, that is intravascular infusion.

Types of outcome measures

Primary outcomes

1. Postnatal weight loss
2. Dehydration

Secondary outcomes

1. Patent ductus arteriosus (PDA) (as defined in the study)
2. Necrotizing enterocolitis (Bells Stage II or greater, or as defined by the authors) ([Bell 1978](#))
3. Bronchopulmonary dysplasia
4. Oxygen requirement at 28 to 30 days of life
5. Oxygen requirement at 36 weeks postmenstrual age
6. Intraventricular hemorrhage (IVH), defined using Papile criteria (any grade or severe (grades III or IV)) ([Papile 1978](#))
7. Death prior to hospital discharge

Search methods for identification of studies

Electronic searches

RCTs identified in previous versions of this review were re-examined and, in each case, retained. These included trials were identified from multiple sources, including a previous review by one of the authors ([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 an 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 (18,196 sources identified);
2. infant, premature (40,795 sources identified);
3. 1 or 2 (52,832 sources identified);
4. water intake (14,417 sources identified);
5. fluid intake (5979 sources identified);
6. 4 or 5 (18,998 sources identified);

7. 3 and 6 (176 sources identified).

In April 2010, we updated the search as follows: CENTRAL (*The Cochrane Library*), MEDLINE (search via PubMed), EMBASE and CINAHL were searched from 2007 to 2010. Search terms: fluid intake OR water intake. Limits: human, newborn infant and clinical trial. No language restrictions were applied.

In October 2014 we updated the search as follows: MEDLINE (search via PubMed), CINAHL, EMBASE and CENTRAL (*The Cochrane Library*) were searched from 2010 to 2014. Search terms: fluid intake OR water intake. Limits: human, newborn infant and clinical trial. No language restrictions were applied.

Searching other resources

Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictpr).

Data collection and analysis

The standard methods of The Cochrane Collaboration for conducting a systematic review were used.

Selection of studies

All randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section were included. Both review authors reviewed the results of the search and separately selected the studies for inclusion. The review authors resolved any disagreement by discussion.

Data extraction and management

The data were then entered into tables using RevMan software.

Assessment of risk of bias in included studies

The standard methods of the Cochrane Neonatal Review Group were employed. The methodological quality of each trial was reviewed independently by the two review authors. Each identified trial was assessed for methodological quality with respect to: a) masking of allocation, b) masking of intervention, c) completeness of follow-up, and d) masking of outcome assessment. This information is included in the 'Characteristics of included studies' table.

For the updated review in 2010 and 2014, the 'Risk of bias' table was completed. The two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion.

The risk of bias table addressed the following questions.

1. Sequence generation: was the allocation sequence adequately generated?

For each included study, we described the method used to generate the allocation sequence as: adequate (any truly random process for example a random number table, computer random number generator); inadequate (any nonrandom process for example odd or even date of birth, hospital or clinic record number); or unclear.

2. Allocation concealment: was allocation adequately concealed?

For each included study, we described the method used to conceal the allocation sequence as: adequate (for example telephone or central randomization, consecutively numbered sealed opaque envelopes); inadequate (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth); or unclear.

3. Blinding of participants, personnel and outcome assessors: was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

For each included study, we described the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: adequate, inadequate or unclear for participants; adequate, inadequate or unclear for study personnel; and adequate, inadequate or unclear for outcome assessors and specific outcomes assessed.

4. Incomplete outcome data: were incomplete outcome data adequately addressed?

For each included study, and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We assessed methods as: adequate (< 20% missing data), inadequate ($\geq 20\%$ missing data) or unclear.

5. Selective outcome reporting: were reports of the study free of suggestion of selective outcome reporting?

For each included study, we assessed the possibility of selective outcome reporting bias as: adequate (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported), inadequate (where not all the study's pre-specified outcomes have been reported, one or more reported primary outcomes were not pre-specified, outcomes of interest were reported incompletely and so could not be used, study failed to include results of a key outcome that would have been expected to have been reported) or unclear.

6. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns regarding other possible sources of bias (for example whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as: yes, no or unclear.

Measures of treatment effect

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, weighted mean

difference and tests of heterogeneity were accomplished using RevMan software and a fixed-effect model.

Assessment of heterogeneity

We examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic.

Data synthesis

Meta-analysis was carried out using the Review Manager software (RevMan 5, The Cochrane Collaboration). For estimates of typical relative risk and risk difference we used the Mantel-Haenszel method. For measured quantities we used the inverse variance method. All meta-analyses were done using the fixed effect model.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were performed.

RESULTS

Description of studies

Five studies were included in this analysis. All were RCTs of varying water intake in premature infants. Each study compared two groups, one of whom received liberal water intake (this was 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 infants' water intake was determined by the study protocol. In the Bell study (Bell 1980), the prescribed water intake was begun before 72 hours of age and continued up to age 30 days (unless any of certain criteria were met first). In the Kavvadia study (Kavvadia 2000), the prescribed water intake was given only during the first seven days of life; this study was limited to infants who required assisted ventilation starting within six hours of birth. In the Lorenz study (Lorenz 1982), the prescribed water intake was given only during the first five days of life. In the Tammela study (Tammela 1992), the prescribed water intake was begun within 24 hours of birth and continued until age 28 days. In the von Stockhausen study (von Stockhausen 1980), the prescribed water intake was given only during the first three days of life.

Various clinical outcomes were reported for each study, as described in the table 'Characteristics of included studies'.

One study was identified in the search of the literature for the 2014 update and was excluded from the review. Stroustrup 2012 sought to determine the effect of mild fluid restriction on the series of events in hospital (course) of neonates with transient tachypnea of the newborn (TTN). Most infants were late preterm and term neonates diagnosed with TTN. Infants were randomized to receive standard fluid management or mild fluid restriction. Studies in this population will be addressed by the planned review 'Fluid restriction in the management of transient tachypnea of the newborn' by Gupta and colleagues.

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 participants included in the 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 participants included in the analysis?: yes

Lorenz 1982

Prognostic stratification?: yes
Pre-randomization blinding of investigators to allocation?: could not determine
Blinding of caretakers to treatment?: no
Observer who categorized outcome blinded to treatment?: no
All participants included in the 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 participants included in the 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 participants 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 versus liberal water intake (Comparison 1)

Weight loss (Outcome 1.1)

Postnatal weight loss (expressed as a percentage of the birth weight) was significantly higher with restricted water intake in the trials of Bell 1980 and Tammela 1992. It was also higher with restricted water intake in the meta-analysis of the three trials (Bell 1980; Tammela 1992; von Stockhausen 1980) (overall weighted mean difference 1.94% of birth weight, 95% confidence interval (CI) 0.82 to 3.07).

Dehydration (Outcome 1.2)

There was a nonsignificant trend toward increased risk of dehydration with restricted water intake in the trial of Bell 1980. The meta-analysis, which included the trials of Bell 1980 and Lorenz 1982, 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 1.3)

The risk of patent ductus arteriosus was significantly lower with restricted water intake in the trial of Bell 1980 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 four trials (Bell 1980; Kavvadia 2000; Lorenz 1982; Tammela 1992). Based on this analysis, the number needed to treat with restricted water intake to prevent one case of patent ductus arteriosus was 7 (95% CI 5 to 14).

Necrotizing enterocolitis (Outcome 1.4)

The risk of necrotizing enterocolitis was significantly lower with restricted water intake in the trial of Bell 1980 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 1980; Kavvadia 2000; Lorenz 1982 and Tammela 1992. Based on this analysis, the number needed to treat with restricted water intake to prevent one case of necrotizing enterocolitis was 20.0 (95% CI 11 to 100).

Bronchopulmonary dysplasia (Outcome 1.5)

The risk of bronchopulmonary dysplasia was not significantly affected by water intake in any of the four trials in which this was reported (Bell 1980; Kavvadia 2000; Lorenz 1982; Tammela 1992), 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.

Intraventricular hemorrhage (Outcome 1.6)

The risk of intraventricular hemorrhage (all grades) was not significantly affected by restricted water intake in any of the three trials in which this was analyzed (Kavvadia 2000; Lorenz 1982; Tammela 1992) 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 2000; Tammela 1992) and in the meta-analysis was toward reduced risk of intracranial hemorrhage with restricted water intake.

Death (Outcome 1.7)

The risk of death was significantly lower with restricted water intake in the trial of Tammela 1992 but not in the other four trials, nor in the meta-analysis (typical RR 0.81, 95% CI 0.54 to 1.23; typical RD -0.03, 95% CI -0.08 to 0.03) which included all five trials.

Summary

The analysis of the five studies taken together indicated that restricted water intake significantly increased postnatal weight loss and significantly reduced the risks of patent ductus arteriosus and necrotizing enterocolitis. With restricted water intake there were trends toward increased risk of dehydration and reduced risks of

bronchopulmonary dysplasia, intracranial hemorrhage and death, but these trends were 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 under-represented in these studies.

AUTHORS' CONCLUSIONS

Implications for practice

Based on this analysis, the most prudent prescription for water intake of 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, which 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

The Cochrane Neonatal Review Group has been funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN267200603418C.

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* 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 versus 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 versus SGA), and respiratory status (presence or absence of significant RDS)

Bell 1980 (Continued)

Allocation concealment (selection bias)	Low risk	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.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded clinical trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No infants were withdrawn from the study
Selective reporting (reporting bias)	Low risk	

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 to 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

Bias	Authors' judgement	Support for judgement
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Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants (Review)

Kavvadia 2000 (Continued)

Random sequence generation (selection bias)	Unclear risk	This was a randomized, unblinded clinical trial The methods of allocation and randomization were unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded clinical trial

Lorenz 1982

Methods	The duration of the 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 to 999 g, 1000 to 1249 g, and 1250 to 1500 g), 5-minute Apgar score (6 or less versus more than 6), presence of respiratory distress syndrome (RDS), and hospital of birth (inborn versus outborn). No confounding variables were identified in a comparison of demographic features in the two groups. Deviations from the 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
Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants (Review)

Lorenz 1982 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, unblinded clinical trial. The details of randomization are not given, but the subjects were first stratified according to birthweight group (750 to 999 g, 1000 to 1249 g, and 1250 to 1500 g), 5-minute Apgar score (6 or less versus more than 6), presence of respiratory distress syndrome (RDS), and hospital of birth (inborn versus outborn)
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded clinical trial
Incomplete outcome data (attrition bias) All outcomes	High risk	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.

Tammela 1992

Methods	The duration of the study, that is 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 the 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.

Tammela 1992 (Continued)

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: <i>Acta Paediatrica</i> (1992; 81:207-12) and two identical papers in the <i>European Journal of Pediatrics</i> (1992; 151:295-99 and 1992; 151:367-71)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	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
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded clinical trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was given about dropouts or deviations from the 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

von Stockhausen 1980

Methods	The duration of the study, that is 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 versus 17/28). The low group also had slightly higher mean birth weight (2.0 versus 1.9 kg) and gestational age (34.6 versus 34.2 weeks). No information was given about dropouts or deviations from the 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 the 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

von Stockhausen 1980 (Continued)

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	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
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded clinical trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was given about dropouts or deviations from study protocol

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Stroustrup 2012	Prospective randomized controlled trial of 64 late preterm and term neonates diagnosed with TTN at a single tertiary care hospital in the United States. Infants were randomized to receive standard fluid management or mild fluid restriction

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]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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 Intraventricular 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 (%).

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

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

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

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

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

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

WHAT'S NEW

Date	Event	Description
22 October 2014	New search has been performed	This review updates the existing review "Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants" published in the Cochrane Database of Systematic Reviews (Bell 2008).
22 October 2014	New citation required but conclusions have not changed	Search updated October 2014. No new studies identified for inclusion. One study in late preterm and term infants was excluded (Stroustrup 2012). No changes to conclusions.

HISTORY

Protocol first published: Issue 4, 1997
Review first published: Issue 4, 1998

Date	Event	Description
23 April 2010	New search has been performed	<p>This review updates the existing review "Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants" published in the Cochrane Database of Systematic Reviews (Bell 2008).</p> <p>Updated search found no new trials.</p> <p>No changes to conclusions.</p>
11 June 2008	Amended	Converted to new review format.
26 August 2007	New citation required but conclusions have not changed	Substantive amendment
26 August 2007	New search has been performed	<p>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).</p> <p>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.</p>

CONTRIBUTIONS OF AUTHORS

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

The 2010 review and the 2014 update were conducted centrally by the Cochrane Neonatal Review Group staff (Yolanda Montagne, Diane Haughton, Colleen Ovelman and Roger Soll). This update was reviewed and approved by EFB.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchopulmonary Dysplasia [*prevention & control]; Dehydration [*etiology]; Drinking Water [*administration & dosage] [adverse effects]; Ductus Arteriosus, Patent [*prevention & control]; Enterocolitis, Necrotizing [*prevention & control]; Infant, Premature;

Infant, Premature, Diseases [mortality] [*prevention & control]; Intracranial Hemorrhages [*prevention & control]; Randomized Controlled Trials as Topic; Weight Loss

MeSH check words

Humans; Infant, Newborn