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Fluid restriction for treatment of preterm infants with chronic lung disease (Review)

Barrington KJ, Fortin-Pellerin E, Pennaforte T

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[Intervention Review]

Fluid restriction for treatment of preterm infants with chronic lung disease

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ABSTRACT

Background

Fluid restriction is often recommended as part of the management of infants with early or established bronchopulmonary dysplasia (BPD).

Objectives

To determine whether fluid restriction as part of the therapeutic intervention for early or established BPD improves clinical outcomes.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1) in the Cochrane Library (searched 16 February 2016), MEDLINE via PubMed (1966 to 16 February 2016), Embase (1980 to 16 February 2016), and CINAHL (1982 to 16 February 2016). We also searched clinical trials' databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Prospective randomised clinical trials comparing two distinct fluid administration volumes in preterm infants with early or established BPD.

Data collection and analysis

We used the standard methods of Cochrane Neonatal. For the included trial, we extracted data and assessed the risk of bias, and used GRADE methods to assess the quality of the evidence. The outcomes considered in this review are effects on mortality or requirement for oxygen at 36 weeks' postmenstrual age (primary outcome measure), the duration of supplemental oxygen therapy, proportion of infants discharged from hospital on oxygen, duration of assisted ventilation, duration of hospitalisation, weight gain, feeding tolerance, apnoea, necrotizing enterocolitis, renal dysfunction or nephrocalcinosis, lung mechanics, and use of diuretic therapy (secondary outcome measures).

Main results

One trial was found, including 60 preterm infants at 28 days of age with persistent oxygen requirements. Infants were randomised to either 180 mL/kg/day of standard formula or 145 mL/kg/day of concentrated formula. This single study did not provide data regarding our primary outcome. No effects of the intervention were found on any of our secondary outcomes. The quality of the evidence from this study was graded low.

Authors' conclusions

There is no evidence to support the practice of fluid restriction in infants with early or established BPD.

PLAIN LANGUAGE SUMMARY

Fluid restriction as a treatment for preterm infants developing chronic lung disease

Background
Babies born prematurely are at risk of developing a form of chronic lung disease which is defined as persistent need for oxygen once the child has reached a corrected gestational age of 36 weeks. As fluid accumulation in the lung is one of the processes involved in the early phases of lung disease in premature babies, low fluid intake might halt the progression of the insult and result in lower rates of chronic lung disease of prematurity.

Study characteristics
Our search identified only one study comparing two volumes of fluid intake in preterm infants with early signs of chronic lung disease. Unfortunately, this study did not report progression to established chronic lung disease. Hence, no infant could be included in this analysis.

Other outcomes, including days that the baby needed extra oxygen, proportion of infants discharged from hospital on oxygen, days of assisted ventilation, duration of hospital stay, weight gain and serious apnoeas were not affected by the volume of fluid received (from the evidence graded as low quality). The evidence is current to February 2016.

Key results
There is no study comparing low to high fluid intake in a population of preterm babies with early signs of chronic respiratory disease to prevent progression to full blown chronic lung disease or death. Other outcomes were not improved by fluid restriction.

Quality of evidence
Not applicable.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fluid restricted compared to liberal fluids compared to placebo for treatment of preterm babies with chronic lung disease

Fluid restricted compared to liberal fluids compared to placebo for treatment of preterm babies with chronic lung disease

Participant or population: treatment of preterm babies with chronic lung disease
Setting:
Intervention: Fluid restricted compared to liberal fluids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with fluid restricted compared to liberal fluids				
Duration of oxygen therapy	The mean duration of oxygen therapy was 27.5 days	median 0.5 days higher (0 to 0)	-	60 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Duration of hospitalisation	The mean duration of hospitalisation was 85 days	MD 3 Days higher (7.64 lower to 13.64 higher)	-	60 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Daily weight gain	The mean daily weight gain was 14.8 g/kg/d	MD 0.5 g/kg/d higher (1.22 lower to 2.22 higher)	-	60 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Proportion with apnoea	Study population		RR 1.35 (0.98 to 1.86)	60 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
	630 per 1000	850 per 1000 (617 to 1000)				
	Moderate					
	630 per 1000	850 per 1000 (617 to 1000)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Unmasked study
[2] Wide confidence limits

BACKGROUND

Description of the condition

Bronchopulmonary dysplasia (BPD), often referred to as chronic lung disease (CLD) of prematurity, is a frequent complication of neonatal intensive care. It occurs more frequently in the very immature infant and leads to persistent respiratory distress and a long-term oxygen requirement. An inflammatory interstitial pulmonary oedema was described as part of the pathogenesis of early CLD in the preterm infant (Northway 1967; Brown 1978). It is not known if this is still the case in more recently treated infants in whom a reduction in alveolar development seems to be paramount in the development of "the new BPD" (Jobe 2011).

Description of the intervention

Because of the presence of excess lung water, diuretics have been investigated as a therapeutic option. They are now used frequently in the treatment of preterm infants with BPD. Physiological studies of diuretics have demonstrated short-term effects on lung mechanics but no long-term clinical benefits have been proven (Kao 1983; McCann 1985).

Possibly by extrapolation from the use of diuretics came the practice of restricting fluid intake as a treatment for preterm infants with CLD. Some neonatal textbooks recommend restricting fluid as a treatment for BPD (Niermeyer 1988; Bancalari 2002). By the time fluid restriction is contemplated, most infants are receiving enteral nutrition, either totally or at least partially.

Fluid restriction requires limiting total (enteral and parenteral) fluid intake to less than the amount usually recommended (i.e. to less than 150 mL/kg/day), with the goal of improving pulmonary function.

How the intervention might work

Fluid restriction is used in the hope that it will reduce pulmonary oedema and thus improve pulmonary function, and perhaps lessen lung injury.

Why it is important to do this review

There are concerns with the practice of fluid restriction as it may interfere with the delivery of adequate nutrition. It seems likely that restricting fluid intake will lead to a decrease in urine output; within clinically acceptable limits of fluid intake it is questionable whether fluid restriction will lead to changes in total body water, lung fluid balance or pulmonary function. In addition, the reduction of free water intake will probably lead to an increase in renal solute load and potentially to a greater incidence of renal dysfunction and nephrocalcinosis. On the other hand, larger fluid volumes could be associated with an increase in feeding intolerance or with a risk of necrotizing enterocolitis (Viswanathan 2015).

Randomised comparisons of differing levels of fluid intake in early life of the preterm infant as a means of preventing BPD have been performed and systematically reviewed (Bell 1998). These studies showed that reduced fluid intakes led to a non-significant trend toward reduction in the risk of BPD and a significant reduction in death (Bell 1998).

Once BPD has developed or is developing, fluid restriction as part of treatment of the disease is sometimes considered by physicians, and continues to be recommended as a part of treatment. Review articles recommending fluid restriction usually provide no references, or refer solely to other review articles.

We wished to determine if there is adequate evidence to support this practice. Recommended fluid intake can be defined as 150 ml/kg/day or more (Gregory 2005); we therefore considered a fluid intake less than 150 ml/kg/day as 'restricted'. For the purpose of this review, we defined BPD as oxygen requirement at 28 postnatal days, and CLD as oxygen requirement at 36 weeks' postmenstrual age.

OBJECTIVES

To determine whether fluid restriction as part of the therapeutic intervention for early or established BPD improves clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised and quasi-randomised trials. We excluded short-term cross-over studies as not being informative for our primary outcome measure.

Types of participants

Preterm infants (< 34 weeks) with early or established BPD. Established BPD was defined as oxygen need and evidence of respiratory insufficiency at 28 days of age. Early BPD was defined as a persistent oxygen need, respiratory insufficiency and high predicted likelihood of development of established BPD after a minimum of 21 days of age. Maximum age of enrolment into the study was 36 weeks' postmenstrual age.

Types of interventions

We searched for studies comparing two different levels of fluid intake. Because there is a wide range of possible fluid intakes in such infants, in order to group the studies we assumed that normal fluid intake is 140 to 150 ml/kg/day, and we intended to group the subjects into unrestricted (≥ 150 ml/kg/day) and fluid restricted (< 150 ml/kg/day).

Types of outcome measures

Primary outcomes

Mortality or requirement for oxygen at 36 weeks' postmenstrual age (CLD).

Secondary outcomes

1. Duration of supplemental oxygen in days from enrolment until discharge.
2. Proportion of infants discharged from hospital on oxygen.
3. Duration of assisted ventilation in days from enrolment until discharge.
4. Duration of hospitalisation in days from enrolment until discharge.
5. Daily weight gain from enrolment until the end of the intervention.

6. Apnoea: number (proportion) of infants with problematic apnoea.
7. Feeding intolerance: number (proportion) of infants with feeding intolerance requiring alteration in feeds.
8. Necrotizing enterocolitis (NEC): number (proportion) of infants with NEC defined as Bell stage two or more.
9. Renal dysfunction: mean changes in serum creatinine between enrolment and the end of the intervention.
10. Nephrocalcinosis: proportion of infants with nephrocalcinosis on renal ultrasound or CT scan.
11. Lung mechanics: percentage change in dynamic compliance between enrolment and the end of the intervention.
12. Need for diuretics: number of doses of diuretic (loop diuretic or thiazide) needed per participant since the start of intervention.

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1) in the Cochrane Library (searched 16 February 2016); MEDLINE via PubMed (1966 to 16 February 2016); Embase (1980 to 16 February 2016); and CINAHL (1982 to 16 February 2016) using the following search terms: (fluid OR food, formulated) AND (bronchopulmonary dysplasia OR BPD OR chronic lung disease OR CLD), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials' registries for ongoing or recently completed trials (ClinicalTrials.gov; the World Health Organization's International Clinical Trials Registry Platform www.who.int/ictrp/search/en/; and the ISRCTN Registry).

Searching other resources

We examined the references in all studies identified as potentially relevant.

Data collection and analysis

We used the standard methods of Cochrane and Cochrane Neonatal (Higgins 2011). Review authors independently assessed trials for inclusion and methodological quality. Differences were resolved by discussion. We planned to contact study authors if we needed additional information.

Selection of studies

All three review authors screened the title and abstract of all studies identified by the above search strategy. We assessed the full text of any potentially eligible reports and excluded those studies that did not meet all of the inclusion criteria. We discussed any disagreements until consensus was achieved.

Data extraction and management

All three review authors extracted the data separately. Any disagreements were discussed until consensus was achieved. We contacted trial authors for further information if data from the trial reports was insufficient.

Assessment of risk of bias in included studies

We used the criteria and standard methods of Cochrane Neonatal. The methodological quality of the studies was assessed using the following key criteria: allocation concealment (blinding of randomisation), blinding of intervention, completeness of follow-up, and blinding of outcome measurement/assessment. For each criterion, assessment was 'yes', 'no' or 'unclear'. Additional information from the trial authors was requested to clarify methodology and results as necessary. This information was included in the table 'Characteristics of included studies'.

In addition, the 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).

The methodological quality of the studies was assessed using the following criteria.

1. Sequence generation (evaluating possible selection bias). For each included study, we described the method used to generate the allocation sequence as: adequate (any truly random process e.g. random number table; computer random number generator); inadequate (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or unclear.
2. Allocation concealment (evaluating possible selection bias). For each included study, we described the method used to conceal the allocation sequence as: adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth); or unclear.
3. Blinding (evaluating possible performance bias). For each included study, we described the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. 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.
4. Incomplete outcome data (evaluating possible attrition bias through withdrawals, dropouts, protocol deviations). 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 total randomised 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 (> 20% missing data); or unclear;
5. Selective reporting bias. For each included study where the protocol is available (through trials' registers), we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as: adequate (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported); inadequate (where not all the study's prespecified outcomes had been reported; one or more reported primary

outcomes were not prespecified; 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. We noted 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 owing 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.
7. Funding sources: when reported we divided funding sources into funding from local funds (hospital, research centre, or university), charitable foundations, government agencies, or from industry. If funding was from industry, and industry also had substantial input into study design or conduct or analysis, then that was determined to be a high risk of bias. Funding from sources that had no potential financial benefit from the results was considered to be a low risk of bias. Unclear or partial funding was considered unclear risk of bias.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). When it was deemed appropriate to combine two or more study arms, we obtained the treatment effects from the combined data using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We determined the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for a statistically significant difference in the RD.

Unit of analysis issues

The only trial included was an individually randomised parallel group trial.

Dealing with missing data

We requested additional data from the trial investigators for data on important outcomes which were missing.

Assessment of heterogeneity

If more than one trial was included in a meta-analysis, we planned to examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We planned to calculate the I^2 statistic for each analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. The I^2 statistic was to be analysed as follows: less than 25% = no heterogeneity; 25% to 49% = low heterogeneity; 50% to 74% = moderate heterogeneity; and 75%+ = high heterogeneity. If moderate or high heterogeneity was detected (I^2 statistic > 50%), we would have explored the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments) in sensitivity analyses.

Assessment of reporting biases

We planned to investigate publication bias by using funnel plots if at least 10 clinical trials were included in the systematic review (Higgins 2011).

Data synthesis

We used the standard methods of the Cochrane Neonatal Review Group. For categorical outcomes, typical estimates for relative risk (RR) and risk difference (RD) were calculated along with their 95% confidence intervals. For significant results, we planned on reporting the number needed to treat for an additional beneficial outcome or number needed to treat for an additional harmful outcome (NNTB/NNTH). A fixed-effect model was assumed. Continuous outcomes were analysed using weighted mean difference, assuming a fixed-effect model.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: death, chronic lung disease at 36 weeks, duration of invasive and non-invasive assisted ventilation and duration of oxygen therapy.

Two authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised controlled trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the GRADEpro Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis for the severity of the disease, the different levels of fluid restriction and the duration of the intervention were planned but could not be performed as only one study was found and data for these subgroups was unavailable.

Sensitivity analysis

Sensitivity analysis was planned to eliminate trials considered of low quality, but only one trial was found.

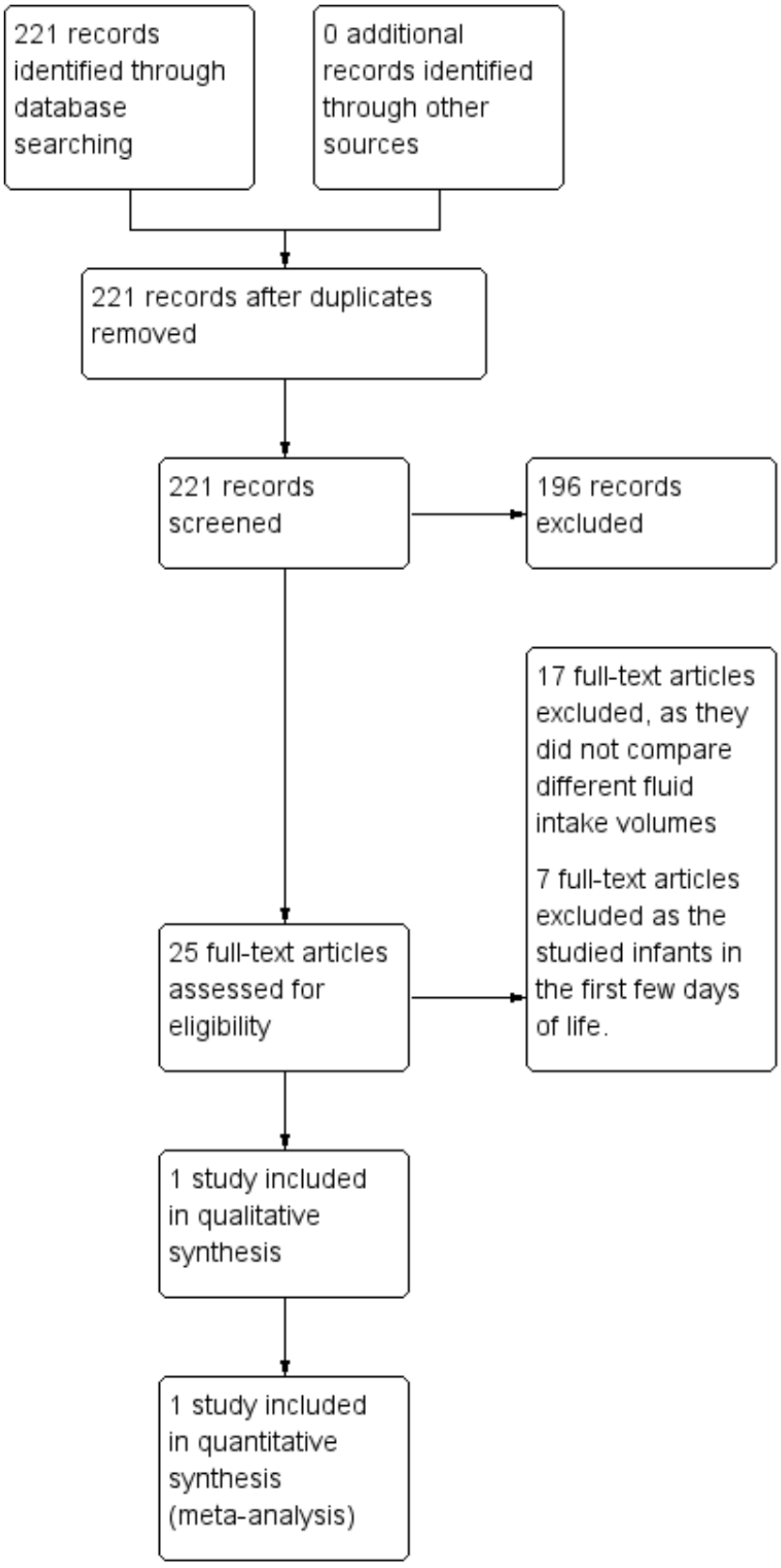
RESULTS

Description of studies

Results of the search

The initial search as described found 221 articles, Figure 1.

Figure 1. Study flow diagram.



Twenty-five of the articles were reports of randomised controlled trials. Seventeen were randomised comparisons of maternal milk with artificial milk; maternal milk with or without fortification; or of different formulas or fortification of feeds given after discharge from the neonatal intensive care unit.

There were eight reports of trials comparing different fluid intakes in preterm infants in which one outcome reported was either BPD or CLD. Seven of those reports were of RCTs comparing fluid intakes in the first week of life.

There was only one relevant study in which two volumes of fluid intake were compared in infants with early or established BPD.

Included studies

The only relevant study was Fewtrell 1997, a randomised comparison of two different diet/fluid regimes in 60 preterm infants below 1500 grams' birth weight and less than 32 weeks' gestation, who were enrolled as they still required oxygen at 28 days of age. Infants received either standard formula (24 kcal/oz) at 180 mL/kg/day (n = 27) or a high nutrient-density formula (30 kcal/oz) at 145 mL/kg/day (n = 33). The primary outcomes are listed as growth rate; duration and severity of respiratory disease; and energy and protein intake.

Excluded studies

The reasons for excluding studies are summarized in Figure 1.

Risk of bias in included studies

The 'Risk of bias' table revealed a moderate risk of bias in this trial. The intervention was not masked, as it was not feasible to do so; also the research staff performing some of the assessments were not masked. The trial was smaller than originally planned as there were more mothers providing breast milk than expected.

Allocation

Randomisation assignments held in sealed envelopes.

Blinding

Unblinded study.

Incomplete outcome data

All infants accounted for.

Selective reporting

No published or registered protocol was found.

Other potential sources of bias

Funded by industry (Ross Laboratories).

Effects of interventions

See: **Summary of findings for the main comparison** Fluid restricted compared to liberal fluids compared to placebo for treatment of preterm babies with chronic lung disease

Restricted compared with liberal fluid intake (comparison 1)

Primary outcomes

Mortality or CLD

This outcome was not reported.

Secondary outcomes

Duration of supplemental oxygen in days from enrolment until discharge

All but one infant in each group required oxygen during the study. The median duration of supplemental oxygen was 27.5 days (range 2 to 71) in the high-fluid group, and 28 days (range 2 to 79) in the restricted group. The standard deviations are not reported.

Proportion of infants discharged from hospital on oxygen

Not reported.

Duration of assisted ventilation in days from enrolment until discharge

More of the fluid-restricted infants were on assisted ventilation during the study period, and the median duration of assisted ventilation was longer in the fluid-restricted group (27 days (range 5 to 48) compared to 1 day (range 1 to 16)), but was reported to be not statistically significant.

Duration of hospitalisation

There was no significant effect of restricted compared with liberal fluids on duration of hospitalisation; mean difference three days (95% CI −7.64 to 13.64). Tests for heterogeneity were not applicable (Analysis 1.1).

Daily weight gain from enrolment until the end of the intervention

There was no significant effect of restricted compared with liberal fluids; mean difference 0.50 g/day (95% CI −1.22 to 2.22). Tests for heterogeneity were not applicable (Analysis 1.2).

Apnoea: number (proportion) of infants with problematic apnoea

There was no significant effect of restricted compared with liberal fluids; relative risk 1.35, 95% CI 0.98 to 1.86. Risk difference 0.22, 95% CI 0.00 to 0.44. Tests for heterogeneity were not applicable (Analysis 1.3).

Feeding intolerance: number (proportion) of infants with feeding intolerance requiring alteration in feeds

The authors report that there was no significant effect of restricted compared with liberal fluids in the incidence of vomiting, abdominal distension or the volume of gastric aspirate but do not give the figures.

Necrotizing enterocolitis: number (proportion) of infants with NEC defined as Bell stage two or more

Not reported.

Renal dysfunction: mean changes in serum creatinine between enrolment and the end of the intervention

Not reported.

Nephrocalcinosis: proportion of infants with nephrocalcinosis on renal ultrasound or CT scan

Not reported.

Lung mechanics: percentage change in dynamic compliance between enrolment and the end of the intervention

Not reported.

Need for diuretics: number of doses of diuretic (loop diuretic or thiazide) needed per participant since the start of intervention

The median number of days of treatment with furosemide were 12 (interquartile range 2 to 41) days in the fluid restricted group versus 31 (interquartile range 6 to 60) days in the liberal fluid group, (P = 0.09).

There were no statistically significant differences between the restricted and liberal fluid regime in any of the primary or secondary outcomes.

The clinically important primary outcomes (death and CLD at 36 weeks) for the 'Summary of findings' tables were either not reported or were reported as median and range. Some data were presented about secondary outcomes that are indirectly related to the primary outcomes, and they are presented in the 'Summary of findings' table.

DISCUSSION

Despite the frequent recommendation to restrict fluid intake in infants with evolving (early) or established BPD there is no evidence to support the practice. The one available trial did not provide data on the primary outcome and showed no statistically significant effect on the secondary outcomes which were reported. It seems unlikely that modest changes in fluid intake have any effect on pulmonary function. Only a drastic reduction in intake, with a reduction in total body water (i.e. dehydration) might be postulated to potentially have an effect. Adverse effects of fluid restriction may include nutritional inadequacy (avoided in Fewtrell 1997 by study design) and an increase in effective renal osmotic load, which was not investigated by Fewtrell and colleagues.

Summary of main results

The only applicable trial showed no benefit of restricting fluid intake to preterm infants who still required oxygen at, or after, 28 days of life. But our primary outcome was not reported.

Overall completeness and applicability of evidence

The power of this analysis is low because of the small number of infants studied.

Quality of the evidence

The quality of the evidence from the one trial was low, quality was downgraded for lack of blinding, imprecision of results, and indirectness for our primary outcomes.

Potential biases in the review process

We have no financial or other conflicts of interest.

AUTHORS' CONCLUSIONS

Implications for practice

Fluid intake in BPD should be adequate to provide sufficient nutrients for growth and lung repair. Calorie requirements of infants with early or established BPD are increased compared to infants with normal lungs. There is no proven advantage of supplying highly concentrated, lower volume feeds. Available evidence is insufficient to either support or refute the use of fluid restriction for BPD.

Implications for research

In order to provide a rationale for future RCTs of fluid restriction, physiological studies of short-term fluid restriction (controlled and with adequate masking) are required. if such studies do demonstrate a physiological benefit on lung function or lung fluid content then further RCTs, adequately powered to detect clinically important differences in outcomes, may be justifiable.

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CHARACTERISTICS OF STUDIES

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

Fewtrell 1997

Methods	Randomised controlled trial
Participants	60 preterm infants < 1500 grams and < 32 weeks, dependent on oxygen at more than 28 days of age
Interventions	Standard formula (24 kcal/oz) at 180 mL/kg/day compared to high nutrient-density formula (30 kcal/oz) at 145 mL/kg/day
Outcomes	Growth variables, respiratory outcomes.
Notes	

Fewtrell 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pre-determined randomisation sequence in block of 4 and 6.
Allocation concealment (selection bias)	Low risk	Randomisation sequences maintained in opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to mask the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome measures done by a research nurse not blind to the dietary randomisation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All subjects accounted for in the results.
Selective reporting (reporting bias)	Unclear risk	No published or registered protocol was found.
Other bias	Unclear risk	The lack on concealment may have had an impact on the intervention itself: the medical staff were apparently reluctant to increase daily fluids, so the high-volume group did not receive as much fluid as planned.
Funding Source	Unclear risk	Study was funded by industry (Ross Laboratories) who also created the formulae. No indication is given about other roles of the funding source.

DATA AND ANALYSES

Comparison 1. Fluid restricted compared to liberal fluids

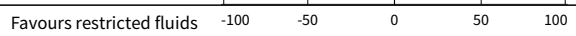
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospitalisation	1	60	Mean Difference (IV, Fixed, 95% CI)	3.0 [-7.64, 13.64]
2 Daily weight gain	1	60	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.22, 2.22]
3 Proportion with apnoea	1	60	Risk Difference (M-H, Fixed, 95% CI)	0.22 [-0.00, 0.44]

Analysis 1.1. Comparison 1 Fluid restricted compared to liberal fluids, Outcome 1 Duration of hospitalisation.

Study or subgroup	Restricted Fluids N	Restricted Fluids Mean(SD)	Liberal Fluids N	Liberal Fluids Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Fewtrell 1997	33	88 (22)	27	85 (20)		100%	3[-7.64,13.64]
Total ***	**33**		**27**			**100%**	**3[-7.64,13.64]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							

Analysis 1.2. Comparison 1 Fluid restricted compared to liberal fluids, Outcome 2 Daily weight gain.

Study or subgroup	Restricted Fluids N	Restricted Fluids Mean(SD)	Liberal Fluids N	Liberal Fluids Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Fewtrell 1997	33	15.3 (3.9)	27	14.8 (2.9)		100%	0.5[-1.22,2.22]
Total ***	**33**		**27**			**100%**	**0.5[-1.22,2.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.57(P=0.57)							



Analysis 1.3. Comparison 1 Fluid restricted compared to liberal fluids, Outcome 3 Proportion with apnoea.

Study or subgroup	Restricted Fluids n/N	Liberal Fluids n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Fewtrell 1997	28/33	17/27		100%	0.22[-0,0.44]
Total (95% CI)	**33**	**27**		**100%**	**0.22[-0,0.44]**
Total events: 28 (Restricted Fluids), 17 (Liberal Fluids)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					

APPENDICES

Appendix 1. Standard search methodology

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomised controlled trial or controlled clinical trial or randomised or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

HISTORY

Protocol first published: Issue 3, 2005
Review first published: Issue 2, 2017

Date	Event	Description
22 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

KB designed the protocol and wrote the first draft.

All three authors reviewed the articles found by the literature search.

All three authors edited the review.

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.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The search strategy was updated to include a search of CINAHL and clinical trial registries.

The methods for the assessment of risk of bias were altered to match current Cochrane standards.

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Apnea [epidemiology]; Bronchopulmonary Dysplasia [*therapy]; Chronic Disease; Fluid Therapy [*methods]; Infant, Premature; Length of Stay [statistics & numerical data]; Lung Diseases [therapy]; Oxygen Inhalation Therapy; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; Weight Gain

MeSH check words

Humans; Infant, Newborn