

Aerosolized diuretics for preterm infants with (or developing) chronic lung disease

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Title

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Reviewers

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Dates

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What's new

This review updates the previously published review "Aerosolized diuretics for preterm infants with (or developing) chronic lung disease", The Cochrane Library, Issue 2, 2001.

A search of MEDLINE in April 2003 and of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 1, 2003) did not yield any additional eligible studies.

No substantive changes were made to the review. We added a reference to a published summary of the three Cochrane reviews about diuretics and chronic lung disease (Brion 2001).

Dates

Date review re-formatted: 07/09/1999

Date new studies sought but none found: //

Date new studies found but not yet included/excluded: 01/04/2003

Date new studies found and included/excluded: //

Date reviewers' conclusions section amended: //

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Date response to comment/criticisms added: //

Text of review

Synopsis

Still no evidence of benefit from routine use of inhaled diuretics in preterm babies at risk of chronic lung disease.

Lung disease in babies born early (preterm) is often complicated with excess of water. Medications which reduce body water (diuretics) might help the baby recover from lung disease. In theory, giving the diuretic as an inhaled mist (aerosol) could drain water from the lung more than from the rest of the body, which could reduce adverse effects. The review found several small trials of a single type of diuretic (furosemide). A single dose improved lung function, but only temporarily. No information was available about longterm outcome.

Abstract

Background

Lung disease in preterm infants is often complicated with lung edema.

Objectives

The aim of this review is to assess the risks and benefits of aerosolized diuretic administration in preterm infants with or developing chronic lung disease (CLD). Primary objectives are to assess effects on short term outcome (changes in need for oxygen or ventilatory support) and effects on long-term outcome. Secondary objectives are to assess changes in pulmonary mechanics and potential complications of therapy.

Search strategy

We used the standard search method of the Cochrane Neonatal Review Group. We used the following keywords: {<bronchopulmonary dysplasia> or <chronic lung disease>} and <explode diuretics>, limited to <human> and limited to <infant, newborn> or <infant>. We searched MEDLINE (1966-1998), EMBASE (1974-1998) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2003). In addition, we hand searched several abstract books of national and international American and European Societies. The search of MEDLINE was updated in January 2001 and April 2003.

Selection criteria

We included in this analysis trials in which preterm infants with or developing chronic lung disease and at least five days of age were all randomly allocated to receive an aerosolized loop diuretic. Eligible studies needed to assess at least one of the outcome variables defined a priori for this systematic review. Primary outcome variables included important clinical outcomes, and secondary outcome variables included pulmonary mechanics and potential complications of therapy.

Data collection & analysis

We used the standard method for the Cochrane Collaboration which is described in the Cochrane Collaboration Handbook. Two investigators extracted, assessed and coded separately all data for each study, using a form that was designed specifically for this review. Any disagreement was resolved by discussion. We combined parallel and cross-over trials and, whenever possible, transformed baseline and final outcome data measured on a continuous scale into change scores using Follmann's formula.

Main results

We identified eight studies which met selection criteria. Most studies focused on pathophysiological parameters and did not assess effects on important clinical outcomes defined in this review or the potential complications of diuretic therapy. No study assessed the amount of diuretic effectively delivered to the patient. Furosemide was the only diuretic used in the eight studies included in this review.

Among preterm infants < 3 weeks of age developing CLD, not enough information is available to assess the effect of aerosolized furosemide on outcome or lung function.

Among infants > 3 weeks with CLD, a single aerosolized dose of 1 mg/kg of furosemide may transiently improve

pulmonary mechanics. Not enough information is available to assess the effect of chronic administration of aerosolized furosemide on oxygenation and pulmonary mechanics.

Reviewers' conclusions

In preterm infants > 3 weeks with CLD administration of a single dose of aerosolized furosemide improves pulmonary mechanics. In view of the lack of data from randomized trials concerning effects on important clinical outcomes, routine or sustained use of aerosolized loop diuretics in infants with (or developing) CLD cannot be recommended based on current evidence.

More double-blinded randomized trials are needed (1) to analyze factors likely to affect the response to aerosolized furosemide, e.g., washout period and delivery of furosemide to distal airways, and (2) to assess the effects of chronic administration of aerosolized furosemide on mortality, O₂ dependency, ventilator dependency, length of hospital stay and long-term outcome.

Background

This review is part of a group of three closely related reviews on diuretics in preterm infants with CLD, developing CLD or at high risk of CLD (Brion 1999 a,b). The present review will describe the evidence about administration of aerosolized diuretics in preterm infants with CLD, developing CLD or at high risk of CLD. The other two reviews ([Brion 1999a,b](#)) will discuss the use of systemic loop diuretics and the use of diuretics acting on distal segments of the renal tubule (thiazides and spironolactone).

1. Rationale for administering aerosolized diuretics to neonates with CLD:

1.1. Reduction of lung edema:

Early stages of chronic lung disease (CLD) of prematurity are associated with lung edema. Factors involved in this edema include increased capillary permeability resulting from lung injury, congestive heart failure due to patent ductus arteriosus, and fluid overload ([Brown 1978](#), [Zimmerman 1995](#)). This edema could not only reduce pulmonary compliance (and thus tidal volume if using a pressure-limited ventilator) but also increase airway resistance by narrowing terminal airways ([Northway 1967](#)). Diuretics may accelerate lung fluid reabsorption and improve pulmonary mechanics in patients with lung edema via two types of mechanisms: (1) an immediate, diuresis-independent lung fluid reabsorption, and (2) a delayed increase in urine output ([Brion 1999a](#)). It is possible that the incidence of lung edema in preterm infants may have decreased as a result of changes in therapy introduced in the last decade (Gortner 1991, [Sonntag 1996](#)).

1.2. Reduction of bronchoconstriction:

Reactive airway disease may result from narrowing of the terminal airways secondary to interstitial edema (see 1.1) and from bronchial smooth muscle hypertrophy ([Northway 1967](#)). Infants with BPD may develop reactive airway disease ([Denjean 1992](#)) and benefit from bronchodilator therapy. Reactive airway disease in those infants may persist into childhood ([Bader 1987](#)).

Both in children and in adults, aerosolized diuretic administration (furosemide, acetazolamide and amiloride) has been shown to alleviate reactive airway disease mediated by various stimuli (exercise, fog, metabisulfite, antigen) but not bronchoconstriction at rest or that secondary to metacholine challenge ([Editorial 1990](#), [O'Donnell 1992](#), [Mochizuki 1995](#)). In contrast, a randomized double-blind, placebo-controlled trial with parallel design failed to show any therapeutic effect of aerosolized furosemide in wheezing infants ([Van Bever 1995](#)).

Furosemide decreases smooth muscle contractility in vitro whether applied to the intraluminal (mucosal) or extraluminal side of the airway ([Iwamoto 1997](#)). Several possible mechanisms of diuretic action (specifically, furosemide) on airway smooth muscle contractility have been proposed. First, furosemide, by inhibiting the basolateral Na-K-2Cl cotransporter of the epithelial cells ([Frizzell 1979](#), [Welsh 1983](#), [Lavallee 1997](#)), could modify the osmotic and ionic environment, thereby possibly affecting the activation of mast cells and sensory epithelial nerves ([Bienenstock 1988](#)). Second, furosemide has been shown to decrease the release of inflammatory mediators, including leukotrienes and histamine produced by lung tissue in vitro ([Anderson 1991](#)) and interleukin-6 by peripheral blood mononuclear cells ([Yuengsigul 1996](#)). Third, furosemide could release bronchodilator prostaglandins from airway epithelium, as shown with vascular endothelium ([Lundergan 1988](#)) or kidney (see [Brion 1998](#)). The action of furosemide on bronchospasm has been shown to be reduced by indomethacin by some ([Pavord 1992](#)) but not all authors ([Rodwell 1997](#)). Finally, loop diuretics could inhibit cholinergic and excitatory non-cholinergic non-adrenergic contraction of bronchial muscle ([Elwood 1991](#)).

Therefore, one may speculate that aerosolized diuretic administration might decrease bronchoconstriction in those infants with BPD who also have reactive airway disease.

2. Pharmacokinetics and pharmacodynamics of diuretics:

So far, the only diuretic administered to neonates in aerosolized form is furosemide. Because of the long half-life of loop diuretics in immature infants ([Peterson 1980](#), [Vert 1982](#)), a prolonged washout period (without diuretic administration) is needed if one wishes to eliminate any residual diuretic activity before initiating a clinical trial or between exposures in cross-over trials.

Only a small fraction of aerosolized furosemide reaches the terminal bronchioles and alveoli. Medication deposition in the lung may range between 1 and 15% (Fok 1994, [O'Riordan 1994](#)). Critical components may include (1) the type of nebulizer, which affects the size of the droplets (2) characteristics of the tubing, including length and temperature gradient, (3) the side flow which if too high will lead to bypassing the patient into the expiratory limb of the tubing, (4) humidity of inhaled gas and (5) whether the patient is ventilated or not ([Cameron 1990](#), Fok 1994, [Kugelman 1997](#); [O'Riordan 1994](#), [Prabhu 1997](#)).

Unless all these characteristics are provided, it may be difficult to estimate the amount of medication effectively received by the patient. Thus, negative data might result from either lack of efficacy of the medication on the lung, lack of delivery to the distal airway, or both.

Some of the effects on lung function may result from systemic absorption, as shown by increased urine output in some (Aufricht 1997, [Seidenberg 1992](#)) but not all studies.

3. Potential toxicity of diuretic administration include the following:

- (1) hypovolemia, increased drug-induced nephrotoxicity (resulting at least in part from hypovolemia), hyponatremia, hypokalemia, hypochloremia, hyperuricemia and metabolic alkalosis.
- (2) hypercalciuria (leading to nephrolithiasis, nephrocalcinosis and bone demineralization) and hyperphosphaturia (leading to osteopenia)
- (3) increased incidence of patent ductus arteriosus
- (4) cholelithiasis
- (5) neurosensory hearing loss, resulting from high serum levels of furosemide associated with long half-life in immature infants.

4. Summary and rationale for aerosolized diuretic administration in CLD in preterm infants:

Diuretic administration could improve pulmonary mechanics by three separate mechanisms:

- immediate diuresis-independent reabsorption of lung fluid
- decrease in bronchospasm in patients with reactive airway disease
- delayed reabsorption of lung fluid mediated by a decrease in extracellular volume secondary to increased diuresis

The first two mechanisms would be expected to improve lung mechanics by local action, whereas the third mechanism requires systemic absorption. The rationale for using aerosolized diuretics is to try to alleviate lung disease without causing side effects secondary to systemic absorption.

This review incorporates minor additions in updating the existing review which was published in The Cochrane Library, Disk Issue 3, 1999 (Brion 1999d).

Objectives

The aim of this review is to assess risks and benefits of aerosolized diuretic administration in preterm infants with or developing chronic lung disease.

Primary objectives are to assess:

- (1) short-term improvement: changes in mean airway pressure, need for artificial ventilation, need for continuous positive airway pressure, failure to tolerate extubation, and oxygen supplementation
- (2) long-term improvement: mortality, duration of need for oxygen supplementation and respiratory support, bronchopulmonary dysplasia (BPD) defined as need for oxygen supplementation at 28 days of life, death or BPD, chronic lung disease at 36 weeks of postconceptional age (gestational age + postnatal age), length of stay, and number of rehospitalizations during the first year of life.

Secondary objectives are to assess changes in pulmonary mechanics after treatment and potential complications of diuretic administration.

Criteria for considering studies for this review

Types of studies

We included in this analysis only randomized controlled studies. Randomization needed to involve the allocation of all patients either to a specific treatment (patients on diuretic vs controls on placebo or another therapy), or to a specific time of administration of the diuretic (diuretic first vs placebo first).

Types of participants

Participants needed to be:

- (1) Preterm infants
- (2) With oxygen dependency (>21% O₂ to maintain pulse oximetry >90% or paO₂ > 50 mm Hg) or ventilator dependency secondary to lung disease beyond five days of life.

Although BPD is usually defined by the need for oxygen supplementation at four weeks of age, CLD already starts during the first few days of life in patients with RDS ([Northway 1967](#)). For the present study, we only included studies with entry criteria of oxygen or ventilator dependence beyond five days, to avoid overlap with a systematic review of the use of diuretics in patients with RDS ([Brion 1999c](#)). Thus, patients eligible for this study included those with CLD, those developing CLD and those at high risk of CLD.

Types of interventions

The intervention needed to include the randomized administration of an aerosolized loop diuretic. Eligible studies were those that assessed either the administration of an aerosolized diuretic compared to placebo (or no treatment), the administration of an additional aerosolized diuretic compared to a single diuretic in controls, the administration of a different diuretic from that in controls, or administration of a diuretic using another mode compared to control therapy (typically enteral or intravenous furosemide).

Types of outcome measures

Outcome measures had to include an assessment of the effect of diuretic administration on at least one of the following variables:

1. Primary outcome variables:

1.1. Short-term improvement: changes in mean airway pressure, need for artificial ventilation, need for continuous positive airway pressure, failure to tolerate extubation, and oxygen supplementation

1.2. Long-term improvement: mortality, duration of need for oxygen supplementation and respiratory support, BPD, death or BPD, chronic lung disease at 36 weeks of postconceptional age (gestational age + postnatal age), length of stay, and number of rehospitalizations during the first year of life.

2. Secondary outcomes:

2.1. Potential complications: Alkalosis, hyponatremia, hypochloremia, bone demineralization, nephrocalcinosis, nephrolithiasis, cholelithiasis, neurosensory hearing loss.

2.2. Pulmonary function: resistance, compliance, tidal volume for patients on pressure-limited ventilation, expiratory flow.

Search strategy for identification of studies

See: Collaborative Review Group search strategy

1. Published manuscripts:

We searched MEDLINE (1966-1998), EMBASE (1974-1998) and the Cochrane Controlled Trials Register (CCTR) from The Cochrane Library (Issue 3, 1998) in August 1998. We did not limit the search to any language.

We used the following keywords:

{<bronchopulmonary dysplasia> or <chronic lung disease>}

and <diuretics>,

limited to <human> and

limited to <infant, newborn> or <infant>.

Additional searches of MEDLINE done using {<bronchopulmonary dysplasia> or <chronic lung disease>} and <diuretic> in January 2001 and April 2003 did not yield any additional eligible studies. A search of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2003) did not yield any additional eligible studies.

2. Published abstracts:

We searched the abstracts of the following national or international societies (1991-1998 unless otherwise specified):

American Academy of Pediatrics 90-98 (published in American Journal of Perinatology [90-95] and in Pediatrics [96-

98])

American Society of Nephrology (published in Journal of the American Society of Nephrology)

American Thoracic Society 91-98 (published in American Review of Respiratory Disease [91-93] and in American Journal of Respiratory and Critical Care Medicine [94-98])

British Paediatric Association (now Royal College of Paediatrics and Child Health [RCPCH] Annual Scientific Meeting)

European Respiratory Society

European Society for Pediatric Research (published in Pediatric Research)

Neonatal Society [UK]

Society for Pediatric Research [US] (published in Pediatric Research).

Details of the search can be found in a related review ([Brion 1999a](#)).

3. Database of the Neonatal CRG of the Cochrane Collaboration:

We screened all publications coded under diuretics as intervention in September, 1998.

4. Selection process:

We only kept randomized controlled trials fulfilling the selection criteria described in the previous section. Selection was done separately by two investigators (LPB and RP); any disagreement was resolved by discussion.

Methods of the review

We used the standard method for the Cochrane Collaboration which is described in the Cochrane Collaboration Handbook.

1. Data extraction and entry:

Two investigators extracted, assessed and coded separately all data for each study, using a form that had been designed specifically for this review. We transformed graphical data into numerical data using a millimetric ruler and an electronic spreadsheet. We replaced any standard error of the mean by the corresponding standard deviation (SD). As much as possible we homogenized units among studies; in some cases this required using a specific formula to estimate the SD of a ratio or a product ([Baird 1995](#), [Armitage 1994](#)).

In December 1998, we sent to each author an itemized letter requesting additional information about design, patients, methods, or original outcome data (if missing, incomplete or presented in graphical form). We obtained additional data from three authors: Dr. Ohki, Dr. Kugelman and Dr. Stefano (c/o Ms. Leef). Dr. Ohki kindly provided us with additional data, specifically, mean and standard deviation of measurements of pulmonary mechanics at baseline, 1 hr and 2 hr, as well as mean and standard deviation of the values at 1 hr and 2 hr expressed as percent of baseline. Dr. Kugelman provided us with description of methods, other medications received by the patients, and the order of medication administered. Dr. Stefano provided us with information on prior exposure to diuretics, method of aerosolization and ventilator parameters.

All calculations within the spreadsheet and entries into Revman were done by one reviewer (LPB) and subsequently checked for accuracy by another reviewer (WY and RP). Any disagreement was resolved by discussion.

Conversion of values into SI units:

To obtain gas pressure in kPa, we multiplied the value in cm H₂O by 0.10 or that in mm Hg by 0.13

To obtain calcium:creatinine ratio in mM:mM, we multiplied the ratio in mg:mg by 2.84

To obtain calcium in mM/L, we multiplied the value in mg/dl by 0.25

2. Planned comparisons and subgroup analyses:

2.1. We planned the following comparisons based on type of intervention:

2.1.1. Comparison of aerosolized diuretic administration versus placebo

2.1.2. Comparison of aerosolized diuretic administration versus intravenous administration

2.1.3. Comparison of various doses of furosemide by aerosol

For studies in which controls did not receive placebo but another intervention, we arbitrarily considered as 'control' 1) intravenous administration of furosemide, or 2) intermittent administration of a single diuretic.

2.2. Mean postnatal age:

Within each of the above groups, subgroups were determined based on mean postnatal age. The initial plan was to use a cut-off value of four wks, based on the usual definition of bronchopulmonary dysplasia. However, using this value would have made it impossible to classify two of the twenty studies included in this group of three related reviews on diuretics in preterm infants with (or developing) CLD ([Singhal 1983](#), [Robbins 1993](#)). Therefore, we selected a mean postnatal age of 3 wk as the cut-off for all three reviews.

2.3. Mean gestational age:

We planned to use subcategories based on mean gestational age if mean values in various studies were observed to differ by more than four weeks.

2.4. Presence of an endotracheal tube:

Pre-determined sub-categories were used for intubated patients vs. non-intubated patients. The presence of an endotracheal tube is expected to increase total resistance and to decrease dead space. Patients requiring an endotracheal tube are likely to be sicker and thus to have lower pulmonary compliance and to require more oxygen than the other patients.

3. Criteria for assessing the methodological quality of the studies:

We used the standard method of the Cochrane Neonatal Review Group. We assessed the methodological quality of the studies by assessing the risk for four types of bias (selection, performance, attrition and detection). Each study was assessed separately by two reviewers; disagreements were resolved by discussion with the other reviewers.

4. Statistical analysis:

We used the standard method of the Cochrane Neonatal Review Group, using a fixed effect model. We combined parallel trials with cross-over trials using Metaview. For trials with a cross-over design we used as number in each arm the total number of patients entered into the trial.

For dichotomous variables we analyzed the relative risk (RR) and the risk difference (RD) with their 95% confidence intervals (CI). For continuous variables we obtained the weighted mean difference (WMD) and its CI between change scores in the treatment group and in the control group. Change scores were obtained either from the mean of individual differences between baseline and final values, from mean and SD (or standard error) values of change (or percent of baseline) provided by the authors, or from the means and SD of baseline and final values. In the latter case, the variance (var) of change was estimated using Follmann's ([Follmann 1992](#)) method, described in version 3.0.2 of the Cochrane Collaboration Handbook (page 213):

$$\text{Var}(\text{change}) = \text{Var}(\text{pretest}) + \text{Var}(\text{posttest}) - 2 \times \text{SD}(\text{pretest}) \times \text{SD}(\text{posttest}) \times \text{pretest-posttest correlation coefficient}.$$

We searched the literature for values of pretest-posttest correlation coefficient (r) for each test, interval and patient group. If such data were not available, we assumed a value of 0.4, and conducted a sensitivity analysis by successively using $r = 0.3$ and $r = 0.5$.

For those studies providing mean and SD of baseline values and of the percent change from baseline, we obtained the mean change by multiplying percent change by the average baseline. Variance of change was calculated using established guidelines ([Baird 1995](#), [Armitage 1994](#)), as described elsewhere ([Brion 1999a](#)).

Description of studies

A total of nine studies were considered for this review. One was eliminated because it did not involve random allocation to diuretic administration ([Suresh 1992](#)). Thus, eight studies were included in the present review. Details reported by the authors are provided in the table.

Almost all studies included in this review included dynamic measurements of pulmonary mechanics with or without an esophageal balloon. Static measurements were done in only one study ([Ohki 1997](#)). Main categories (intervention) are shown as first entry in the column labeled 'Interventions.' No subcategories were used based on gestational age, because the maximum range of gestational age within each intervention group was four weeks. Main categories (based on intervention) and subcategories (based on postnatal age and mechanical ventilation) are described below:

1. Administration of furosemide by aerosol versus placebo:

This group included four studies, one with parallel design ([Robbins 1993](#)), and three with cross-over design ([Raval 1994](#), [Ohki 1997](#), [Kugelman 1997](#)). Average gestational age ranged between 25 and 29 weeks, so that only one group was considered for the analysis. All patients required mechanical ventilation at study entry.

1.1. Average postnatal age < 3 weeks

[Raval 1994](#): cross-over design with pooled data.

This study was available as abstract only; additional data were provided by the authors. Six infants did not receive any diuretics before the study period. One patient in the control group had received diuretics 2 weeks before the study, and three patients had received one dose of furosemide during the last 5 days preceding the study (two in the control group and one in the treated group). Patients were randomized to receive either a daily dose of 1 mg/kg of furosemide for two days followed by placebo, or vice-versa. There was no washout period between the two phases. An 'acorn' nebulizer with a capillary was placed in line on the ventilator circuit and the medication was mixed with 2 ml of normal saline and delivered at 6 L/min flow. The authors measured dynamic pulmonary mechanics. Change scores for tidal volume were estimated using Follmann's formula.

1.2. Average postnatal age > 3 weeks

[Kugelman 1997](#): cross-over design with pooled data.

Patients were randomized to receive either a single dose of 1 mg/kg of furosemide followed by placebo, or vice-versa. The washout period before the study was only six hours for thiazides, spironolactone, and furosemide. A 24 hour-washout period was documented at the time of cross-over. Change scores for tidal volume were estimated using Follmann's formula; those for compliance, resistance and transcutaneous pO₂ were calculated from the authors' primary data.

[Ohki 1997](#): cross-over design with pooled data.

Patients were randomized to receive either a single dose of 1 mg/kg of furosemide followed by a 48-hour washout period and then placebo, or vice-versa. A washout period of 48 hours was documented both before the study and at the time of crossover.

In patients on furosemide, change scores for pulmonary function tests were estimated by the mean of two results. First we used Baird and Armitage's method with the exact unpublished average and SD baseline values (see table of included studies) and percent values of baseline provided by Y. Ohki. Second, we calculated the mean of change scores for individual data extracted from figures 4-6. For patients in the control group, only the first method was available. Change scores for blood pH were estimated using Follmann's formula.

[Robbins 1993](#): parallel design.

This study was available as abstract only. Patients were randomized to receive either 1 mg/kg of furosemide (the interval is not mentioned in the abstract) for seven days, or placebo. No washout period was documented. Change scores for tidal volume were estimated using Follmann's formula.

2. Administration of furosemide by aerosol versus intermittent intravenous furosemide administration in controls:

This group included two studies (Rastogi 92, Prabhu 97), both with a cross-over design. Patients in these studies had similar gestational ages (26-27 weeks) and postnatal ages (~ four weeks). All patients required mechanical ventilation at study entry.

[Prabhu 1997](#): cross-over design with pooled data.

Patients were randomized to receive either 1 mg/kg of furosemide followed by placebo, or vice-versa. No patients had received any diuretics before the study. Bronchodilators were held for 4 hr before the study. Change scores for tidal volume were estimated using Follmann's formula.

[Rastogi 1992](#): cross-over design with pooled data.

Patients were randomized to receive either 1 mg/kg of furosemide followed by placebo, or vice-versa. No washout period was documented. Change scores for tidal volume were estimated using Follmann's formula.

3. Comparison of various doses of aerosolized furosemide:

This group includes two studies (Prabhu 98 and Rastogi 94). They had similar gestational ages and postnatal ages. One study compared a dose of 1 mg/kg furosemide with lower doses (Rastogi 94). The other study compared a dose of 1 mg/kg with 2 mg/kg (Prabhu 98). Therefore, we did not combine these two studies.

[Prabhu 1998](#): cross-over design with pooled data.

Patients were randomized to receive either 1 mg/kg followed by 2 mg/kg of furosemide, or vice-versa. No diuretics or glucocorticosteroids were used before study in any patient. Bronchodilators were held for four hours before the study. Change scores for tidal volume were estimated using Follmann's formula.

[Rastogi 1994](#): cross-over design with pooled data.

Patients received furosemide at doses of 0.1, 0.25 and 0.5 mg/kg in random order. A washout period of 72 hr was documented before the study. Serial values were only provided after a dose of 1 mg/kg, so that change scores could not be calculated for any of the lower doses.

Methodological quality of included studies

1. Administration of furosemide by aerosol versus placebo:

1.1. Average postnatal age < 3 weeks:

[Raval 1994](#):

This study was exempt of any of the four types of bias analyzed.

1.2. Average postnatal age > 3 weeks:

[Kugelman 1997](#):

This study was exempt of any of the four types of bias analyzed.

[Ohki 1997](#):

Randomization and outcome, but not intervention (nurses prepared the medication), were blinded.

[Robbins 1993](#):

This study was exempt of any of the four types of bias analyzed.

2. Administration of furosemide by aerosol versus intermittent intravenous furosemide administration in controls:

[Prabhu 1997](#):

Blinding is not documented.

[Rastogi 1992](#):

Blinding is not documented.

3. Comparison of various doses:

[Prabhu 1998](#):

Blinding is not documented.

[Rastogi 1994](#):

Blinding was not documented.

Results

1. Limitations of the scope of available studies:

Most studies focused on short-term pathophysiological parameters (pulmonary mechanics) and failed to assess the primary outcomes defined in this review (e.g., mean airway pressure or percent inspiratory oxygen) or the potential complications of diuretic therapy. No studies reported on need for or duration of mechanical ventilation or oxygen supplementation, need for continuous positive airway pressure, BPD, death or BPD, chronic lung disease at 36 weeks of postconceptional age, mortality, length of stay, or number of rehospitalizations during the first year of life.

Furthermore, for most outcomes, only one or two studies provided data that could be merged into a meta-analysis, so that only a small number of patients was included in each analysis. Therefore, it is possible that real differences due to furosemide administration could have been missed. For each analysis we report the studies and the number of patients in which the particular outcome is reported.

No study assessed the amount of diuretic effectively delivered to the patient.

2. Estimation of the pretest-posttest correlation coefficient (r):

For most variables, r was assumed to be 0.4. Unless specified otherwise, sensitivity analysis using a value of 0.3 or 0.5 did not significantly alter the CI and the summary results.

Limited data on dynamic measurements in preterm infants ([Kugelman 1997](#)) suggest that r is higher for dynamic compliance (0.8 for a 1-hour or a 2-hour period) than for resistance (0.4 for a 2-hour, 0.7 for a 1-hour period). We used these values in our calculations of change scores with the Follmann's formula for several studies that analyzed the evolution of dynamic pulmonary mechanics over a period of maximum two hours ([Prabhu 1997](#), [Prabhu 1998](#), [Rastogi 1992](#), [Robbins 1993](#)). Sensitivity analysis was done using $r=0.4$ (vs 0.7-0.8 as the expected value) or 0.3 (vs 0.4 as the expected value) .

Serial data in patients on furosemide ([Ohki 1997](#)) yielded a higher value of r for static compliance (0.84 for 1-hour and 0.90 for a 2-hour period) and resistance (0.87 for a 1-hour and 0.91 for a 2-hour period) than for tidal volume (0.48 for a 1-hour and 0.32 for a 2-hour period). We did not use these values of r for calculating change scores; we used instead additional original data provided by Dr. Ohki.

3. Effects of aerosolized furosemide:

3.1. Administration of furosemide by aerosol versus placebo:

The effect of a single dose of furosemide on pulmonary mechanics in patients > 3 weeks of age was analyzed in three studies ([Kugelman 1997](#), [Ohki 1997](#), [Robbins 1993](#)).

Measurements of pulmonary mechanics 30 minutes after furosemide administration were obtained in only five patients > 3 weeks of age ([Robbins 1993](#)). Furosemide did not significantly affect compliance (WMD -0.13 ml/cm H₂O/kg, CI -0.29, +0.03 using $r=0.8$, CI -0.40, +0.14 using $r=0.4$) and resistance (WMD +28 cm/L/sec, CI -5, + 62 using $r=0.7$, CI -18, +75 using $r=0.4$). This cross-over study, available in abstract form only, did not provide documentation of a washout period.

Seventeen patients were assessed one hour and two hours after aerosol administration ([Kugelman 1997](#), [Ohki 1997](#)). Furosemide administration did not significantly affect transcutaneous pO₂ after one and two hours (n=9 patients) ([Kugelman 1997](#)) or blood pH after one hour (n=8 patients) ([Ohki 1997](#)). WMD for tidal volume ([Kugelman 1997](#)) was calculated using Follmann's formula while assuming $r=0.4$ for tidal volume, whereas WMDs for compliance and resistance were calculated from individual differences between baseline and final values. WMDs for Ohki's data were calculated using original mean and SD of percent values from baseline provided by the author.

Meta-analysis showed that furosemide significantly improved tidal volume after one hour (WMD 1.87 ml/kg, CI 0.95, 2.79) and two hours (1.21 ml/kg, CI 0.19, 2.24) but failed to improve compliance and resistance at either time point. One study ([Ohki 1997](#)) showed a significant improvement in compliance and in tidal volume with furosemide whereas the other one ([Kugelman 1997](#)) showed no significant improvement in either variable.

The test for heterogeneity (chi-square) was statistically significant for compliance (chi-square = 10.66, $p < 0.005$, $df=1$ at one hour and chi-square = 9.75, $p < 0.005$ at 2 hours) but not for tidal volume (chi-square = 2.99, $p = 0.084$, $df = 1$ at one hour and chi-square = 3.82, $p = 0.051$ at two hours). Heterogeneity of response to furosemide could have resulted from differences in (1) washout period at study entry (48 hours for Ohki's study vs 6 hours for Kugelman's study) or at the time of cross-over (48 hours vs 24 hours, respectively), (2) blinding of intervention (only in the second study), (3) method of measuring mechanics of the total respiratory system (static for Ohki's study vs dynamic without esophageal balloon for Kugelman's study), and (4) method of furosemide delivery (ultrasonic nebulizer [Ohki] vs neonatal nebulizer with a relatively high side flow of 5-6 L/min [Kugelman]). Method of furosemide delivery is unlikely to account for heterogeneity, because the neonatal nebulizer used in the second study has been successfully used to deliver other medications, including B₂ agonists, ipratropium bromide, and beclomethasone in ventilated infants with BPD ([Kugelman 1997](#)). Washout period is unlikely to account to heterogeneity because subgroup analysis of patients randomized to furosemide first and those randomized to placebo first in Kugelman's study (using data kindly provided

by Dr. Kugelman) showed similar results.

Lack of significance of the test for heterogeneity for tidal volume might have resulted from overestimating the CI of the WMD for tidal volume in Kugelman's study by using $r=0.4$ in Follmann's formula. Severity of lung disease was similar in both studies (FiO₂ 0.30 vs 0.35, peak inspiratory pressure 20 vs 22 cm H₂O).

Although furosemide tended to increase resistance in Kugelman's study and to decrease it in Ohki's study, the test for heterogeneity was not significant. Subgroup analysis of patients randomized to furosemide first and those randomized to placebo first in Kugelman's study (using data kindly provided by Dr. Kugelman) showed that furosemide tended to increase resistance at two hours in patients randomized to furosemide first (WMD +11.8 cm/L/sec, CI -13.8, +37.4, $n=5$) and to decrease it in patients randomized to furosemide on the second day (WMD -3.3 cm/L/sec, CI -39.3, +32.8, $n=5$). It may be possible that this trend might have resulted from the longer washout period after cross-over (24 hours) than at the time of entry into the study (six hours).

The effects of a two-day treatment with aerosolized furosemide on pulmonary mechanics were assessed in 22 patients < 3 weeks of age enrolled in one study ([Raval 1994](#)). Furosemide tended to reduce compliance, resistance, tidal volume and minute ventilation 20 minutes after therapy ($n=22$ patients) ([Raval 1994](#)). None of these trends reached statistical significance. Data on ventilatory support ($n=19$ measurements in each group, provided by Dr. Stefano) showed identical values at the time of entry into the study and trends toward higher peak pressure, higher PEEP and higher FiO₂ after furosemide administration than after placebo.

The single study ([Robbins 1993](#)) assessing a seven-day treatment with a daily dose of aerosolized furosemide in patients > 3 weeks of age showed no significant difference between change scores of dynamic compliance or resistance in the treatment group and in the placebo group ($n=10$ patients). This cross-over study was available in abstract form only and did not provide documentation of a washout period.

3.2. Administration of furosemide by aerosol versus intermittent intravenous furosemide administration in controls: Aerosolized furosemide tended to decrease the percent inspiratory oxygen and to improve transcutaneous hemoglobin saturation after two hours ($n=19$) ([Prabhu 1997](#)). Aerosolized furosemide did not affect peak inspiratory pressure, positive end expiratory pressure or ventilatory rate two hours after treatment ($n=19$) ([Prabhu 1997](#)).

Compared with intravenous furosemide, aerosolized furosemide tended to increase compliance at 30 minutes (WMD 0.07 ml/cm H₂O/kg, CI 0.00, 0.14 using $r=0.8$, and CI -0.05, +0.19 using $r=0.4$, $n=24$ patients) ([Prabhu 1997](#), [Rastogi 1992](#)). Aerosolized furosemide significantly improved compliance at one hour (WMD 0.15 ml/cm H₂O/kg, CI 0.06, 0.24 using $r=0.8$, and CI 0.00, 0.30 using $r=0.4$) and at two hours (WMD 0.18 ml/cm H₂O/kg, CI 0.07, 0.29 using $r=0.8$, and CI 0.02, 0.35 using $r=0.4$, $n=24$ patients) ([Prabhu 1997](#), [Rastogi 1992](#)). Lack of significance at 4 hours (WMD 0.23, CI -0.36, +0.82) may have resulted from the small number of patients available ($n=5$ patients) ([Rastogi 1992](#)), from lack of a washout period, from overestimating the CI by using $r=0.4$ in Follmann's formula, or from other factors that could not be analyzed in this study available as an abstract only.

Compared with intravenous furosemide, aerosolized furosemide tended to improved tidal volume at 30 min (WMD 0.8 ml/kg, CI -0.5, +2.1, $n=24$); a trend toward improvement was observed in one study ([Prabhu 1997](#)) and a trend toward worsening was observed in the other one ([Rastogi 1992](#)). Aerosolized furosemide tended to improve tidal volume at one hour (WMD 1.3 ml/kg, CI -0.2, +2.9, $n=24$ patients) ([Prabhu 1997](#), [Rastogi 1992](#)) and significantly improved tidal volume at two hours (WMD 1.8 ml/kg, CI 0.2, 3.4, $n=24$) but not at four hours ($n=5$) ([Rastogi 1992](#)). Lack of significance at four hours may have resulted from the same factors as described in the previous paragraph.

Meta-analysis showed no significant effect of aerosolized furosemide compared with intravenous furosemide on resistance between 30 min and four hours (n=24). However, at 30 min, the statistical test for heterogeneity was significant (chi-square = 5.43, p = 0.020, df = 1) using $r=0.7$, but not using $r=0.4$ (chi-square = 3.5, p = 0.061, df = 1). Aerosolized furosemide significantly improved resistance in one study (WMD -30 cm/L/sec, CI -7, -53 using $r=0.7$ and CI -0.01, -60.0, =19) ([Prabhu 1997](#)) but had no effect in the other study (WMD +16 cm/L/sec, CI -15, +48 using $r=0.7$ and CI -22, +55 using $r=0.4$, n=5) ([Rastogi 1992](#)). Heterogeneity could have resulted from lack of a washout period in one study ([Rastogi 1992](#)) but not the other one ([Prabhu 1997](#)), or from overestimating the CI using $r=0.4$ in Follmann's formula. Other potential differences could not be analyzed or detected because Rastogi's study is only available as an abstract.

3.3. Comparison of various doses:

[Rastogi 1994](#):

One study compared the effects of 1 mg/kg of furosemide with those of lower doses (n=8 patients) ([Rastogi 1994](#)). The authors found no effect of low doses of furosemide on pulmonary function, in contrast with a standard dose of 1 mg/kg. For this review, we arbitrary limited data entry into Metaview to data corresponding to 1.0 mg/kg (treatment) vs. 0.1 mg/kg (control). Results on pulmonary function would have been similar with any of the other low doses. In comparison with the lower dose, the standard dose of 1 mg/kg of furosemide significantly decreased the risk of failure to improve compliance within 30 minutes (RR 0.12, CI 0.02, 0.78; RD -0.88, CI -1.20, -0.55) and 4 hours (RR 0.25, CI 0.08, 0.83; RD -0.75, CI -1.12, -0.38). The dose of 1 mg/kg decreased the risk of failure to improve resistance within 30 minutes (RR 0.12, CI 0.02, 0.78; RD -0.88, CI -1.20, -0.55) and four hours (RR 0.12, CI 0.02, 0.78; RD -0.88, CI -1.20, -0.55). The dose of 1 mg/kg decreased the risk of failure to improve tidal volume within 30 minutes (RR 0.06, CI 0.00, 0.87; RD -1.00, CI -1.24, -0.76) and four hours (RR 0.25, CI 0.08, 0.83; RD -0.75, CI -1.12, -0.38). Administration of a 1 mg/kg dose of aerosolized furosemide did not increase 24-hour calciuria or urine calcium:creatinine ratio compared with a lower dose of furosemide.

[Prabhu 1997](#):

A single study analyzed the effects of the standard dose of 1 mg/kg with a higher dose of 2 mg/kg on pulmonary mechanics (n=13 patients) ([Prabhu 1998](#)). Changes in compliance, tidal volume and resistance at two, four and six hours after 2 mg/kg furosemide were similar to those observed after 1 mg/kg. Results were not significantly affected by the value of r used in Follmann's formula (WMD for 2 hr-data on compliance using $r=0.8$ with sensitivity analysis using $r=0.4$; WMD for other data using $r=0.4$ with sensitivity analysis using $r=0.3$). The higher dose tended to increase airway resistance and urine output compared with the lower dose, but this did not reach statistical significance.

Discussion

1. Limitations

1.1. Limitations of the studies included in this review:

In five of eight studies blinding was either not documented or not done. This could potentially have biased the results in favor of furosemide.

1.2. Limitations of this review:

Outcomes analyzed:

Most studies focused on pathophysiological parameters, e.g., pulmonary mechanics, and did not assess the most important outcomes defined in this review or the potential complications of diuretic therapy.

Methods used for the analysis:

We used the methods recommended by the Cochrane Neonatal Review Group. For almost all studies, we did not have access to the original data. Therefore, we used multiple transformations using formulae established by or derived from Follmann, Baird, and Armitage. Calculations using Baird and Armitage overestimate the SD of the final variable if the numerator is related to the denominator, because they assume lack of correlation between them.

For calculations using Follman's formula, we usually assumed an pretest-posttest correlation of 0.4 and did a sensitivity analysis using a correlation coefficient of 0.3-0.5. We only used other values for r if they were available for preterm infants of similar size and age, for an identical test (e.g., compliance) performed at similar time intervals and using the same method. We have found higher values of average correlation coefficient for serial dynamic measurements of tidal volume ($r=0.72$), compliance ($r=0.92$) and resistance ($r=0.80$) in full-term infants over a period of 66 hours ([Goyal 1995](#)). We are unaware of similar data in very low birth weight infants. Therefore, in this review we may have overestimated the SD of long-term change scores for pulmonary mechanics, especially compliance. Therefore, the results are likely to be conservative, i.e., confidence intervals may be wider than they should be.

Heterogeneity:

Within each subgroup, we used chi-square analysis to test for statistical evidence of heterogeneity among studies. When chi-square analysis was significant, we analyzed differences (in patient selection, baseline values, bias, design and methods) among studies that could possibly explain the heterogeneity.

Heterogeneity in response did not appear to result from differences in methods used for pulmonary function tests. Dynamic measurements were obtained in three ([Prabhu 1997](#), [Rastogi 1992](#), Rastogi 94) of four studies showing a transient improvement of pulmonary mechanics 1-2 hours after a single dose of furosemide on pulmonary mechanics and in the single study showing no effect ([Kugelman 1997](#)). Static measurements were obtained in one study, which showed a transient improvement in pulmonary mechanics after furosemide ([Ohki 1997](#)). The reader is referred elsewhere ([Brion 1999a](#)) for further discussion of methods of measuring pulmonary mechanics.

Because of the long half-life of loop diuretics in immature infants, a prolonged washout period is required to eliminate all diuretic effect before initiating a study or between exposures in a cross-over study. However, a prolonged washout period may not be possible or ethically acceptable for patients considered clinically to require diuretics. Several studies had a short or no washout period, thereby possibly decreasing the apparent effect of diuretic administration on short- and long-term outcome. All cross-over trials failed to provide information that would rule out a carry-over effect (possibly yielding an underestimation of the real effect of diuretic administration) and a period effect.

All studies failed to demonstrate actual delivery of furosemide to the distal airways. None measured the percent recovery of furosemide in the expiratory tubing or serum levels of furosemide.

Sample size:

Because of small sample size in most of the subgroups, any real effects of furosemide may have remained undetected.

2. Group-specific comments:

Studies only included intubated patients.

In infants < 3 weeks of age, available evidence (single study, pulmonary mechanics measured only after 20 minutes, abstract only) shows no benefit of a two-day course of aerosolized furosemide.

In infants > 3 weeks of age, a single aerosolized dose of 1 mg/kg of furosemide transiently (at 1-2 hours) improves compliance compared with intravenous furosemide but does not affect resistance or tidal volume. Four of five studies have shown that a single dose of 1 mg/kg of aerosolized furosemide was more effective in transiently improving

compliance than placebo, iv furosemide or a lower dose of aerosolized furosemide. The single study assessing the effect of chronic administration of a daily dose of aerosolized furosemide showed no effect on pulmonary mechanics. This study was published as an abstract only, had no documented washout period, and included only 10 patients.

Double-blinded studies are needed (1) to analyze factors likely to affect the response to aerosolized diuretics, e.g., washout period and delivery of furosemide to distal airways, and (2) to assess the effects of chronic administration of aerosolized diuretics on O₂- and ventilator-dependency and long-term outcome.

Reviewers' conclusions

Implications for practice

Most studies focused on pathophysiological parameters and did not assess the most important outcomes defined in this review or the potential complications of diuretic therapy.

In infants > 3 weeks of age with CLD, a single aerosolized dose of 1 mg/kg of furosemide may transiently improve pulmonary mechanics. There is no evidence to support any benefit of aerosolized diuretic administration on need for ventilatory support, length of stay, survival or long-term outcome. In view of the lack of data from randomized trials concerning effects on important clinical outcomes, routine or sustained use of aerosolized loop diuretics in infants with (or developing) CLD cannot be justified based on current evidence.

Implications for research

Investigators planning randomized trials should consider (1) using double-blinded design (2) analyzing factors likely to affect the response to aerosolized furosemide, e.g., washout period and delivery of furosemide to distal airways, and (3) assessing, in addition or instead of short-term outcome, the effects of chronic administration of aerosolized furosemide on mortality, O₂ dependency, ventilator dependency, length of hospital stay and long-term outcome.

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We would like to thank Dr. Ohki, Dr. Kugelman and Dr. Stefano (c/o Ms. Leaf) for providing us with additional data about their studies included in this review ([Ohki 1997](#), [Kugelman 1997](#), [Raval 1994](#)).

Potential conflict of interest

None

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment

Kugelman 1997	<p>Blinding of randomization: yes Blinding of intervention: yes Complete follow up: yes Blinding of outcome: yes Randomized clinical trial, cross-over design with pooled data Washout period (thiazides, spironolactone, furosemide, albuterol, aminophylline): 6 hr before the study; 24 hours at cross-over</p>	<p>Number of patients entered into the study: n=9 Mechanical ventilation Entry criteria: birth weight 500-2500 g, gestational age maximum 32 weeks, persistent respiratory failure requiring mechanical ventilation and > 30% O₂ at 21 days of life, radiographic changes consistent with BPD. Exclusion criteria: proven sepsis, cardiac disease (except patent ductus arteriosus), unstable clinical status. Average birth weight was 1.1±0.3 kg, gestational age 29±3 weeks, postnatal age 47 ±18 days, postconceptional age 35.7±4.0 weeks and study weight 1.8±0.6 kg. Serum electrolyte concentrations were normal. Six patients were receiving albuterol aerosols and one was receiving aminophylline. Seven were being treated with iv furosemide, one of whom was also receiving thiazide and spironolactone.</p>	<p>Aerosolized furosemide vs placebo Diuretics and bronchodilators were held for 6 hours before the study. Patients were randomly allocated to receive either 1 dose of aerosolized furosemide 1 mg/kg in 2 ml of normal saline followed by placebo within 24 hours, or vice versa.</p>	<p>Main outcome: Pulmonary mechanics Secondary outcome: transcutaneous pO₂ and pCO₂ Measurements of compliance, resistance, pO₂ and pCO₂ obtained after furosemide were not statistically significant from those after placebo.</p>	<p>Nebulization was done using a neonatal nebulizer (Adaptor Kit, Hudson RCI, Temecula, CA) (providing 1-2.1 µm-droplets) placed 10-12 cm from the endotracheal tube on the inspiratory limb of the ventilator, using a side flow of 5-6 L/min. Ventilator conditions were kept constant during treatment. Pulmonary mechanics were assessed at baseline, and 1 hour and 2 hours after the aerosol. The authors measured dynamic compliance and resistance using the two-factor least mean square analysis, without an esophageal balloon.</p>	A
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		<p>All these medications were stopped at least 6 hours before the study. No patients received dexamethasone for prevention or treatment of BPD. Ventilatory settings were similar on each day of the study: FiO₂ 0.35 ±0.06 vs 0.36 ±0.09, on day of furosemide administration and on the day of placebo administration, respectively. Peak inspiratory pressure was 22.8±2.4 and 22.4±2.4 cm H₂O, positive end expiratory pressure 3.8±0.6 cm H₂O in both groups, and ventilator rate 19.7 ±10.5 and 19.3 ±11.7 breaths per minute.</p>				
Ohki 1997	<p>Blinding of randomization: yes Blinding of intervention: no (nurses prepared the medication) Complete follow up: yes Blinding of outcome: yes Randomized clinical trial, cross-over design with pooled data Washout 48 hours before the study and 48 hours at</p>	<p>Number of patients entered into the study: n=8 Mechanical ventilation Entry criteria: Birthweight < 1500 g, respiratory distress requiring mechanical ventilation for > 14 days, chest radiographic evidence of chronic lung disease, no administration of diuretics for at least</p>	<p>Aerosolized furosemide versus placebo Patients were randomly allocated to receive either a single dose of aerosolized furosemide 2 mg/kg diluted in 3 ml of normal saline, followed after 48 hours by placebo, or vice versa.</p>	<p>Main outcome: static compliance, resistance and tidal volume. Furosemide administration was followed by a significant increase in compliance from 0.77 ±0.22 ml/cm/kg initially to 0.94±0.24 ml/</p>	<p>Nebulization was done using an ultrasonic nebulizer placed in the inspiratory limb of the ventilator circuit. Pulmonary mechanics were measured at baseline and at 1 and 2 hours after</p>	A

crossover	<p>48 hour before the start of the study. Exclusion criteria: evidence of congenital malformations, patent ductus arteriosus, congenital heart disease, sepsis or pneumonia. Eight infants were randomized, 6 girls and 2 boys. Average birth weight was 798 \pm225 g and gestational age 26.5 \pm1.9 weeks. Six of 8 patients had received surfactant for RDS. At the time of study postnatal age was 32\pm15 days, postconceptional age 29.3\pm1.5 weeks, weight 807 \pm236 g, peak pressure 20\pm7 cm H₂O, ventilatory rate 20\pm7, FiO₂ 0.30\pm0.08, paO₂ 65.0\pm13.2 mm Hg and paCO₂ 50.5 \pm4.5 mm Hg.</p>		<p>m/kg after 1 hour and 0.92 \pm0.18 after 2 hours; compliance did not change after placebo (corresponding values, 0.86 \pm0.21 ml/cm/kg, 0.84\pm0.16 and 0.85\pm0.20 ml/cm/kg). Furosemide was also followed by an increase in tidal volume from 7.51 \pm1.26 ml/kg to 9.71\pm1.70 after 1 hour and 9.59\pm2.05 after 2 hours. Tidal volume did not change after placebo (corresponding values, 8.71 \pm1.83, 8.70 \pm1.88 and 8.50 \pm1.63). Neither furosemide nor placebo induced any change in resistance; baseline value in the furosemide group was 276.2\pm96.7 cm H₂O/L/sec, and that for the control group was 250.8\pm95.0 cm H₂O/L/sec.</p>	<p>aerosol administration. The authors measured static pulmonary mechanics using the passive occlusion technique.</p>
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Prabhu 1997	Blinding of randomization: no Blinding of intervention: no Complete follow up: yes Blinding of outcome: no Randomized clinical trial, cross-over design with pooled data Washout period: bronchodilators 4 hr before study; no diuretics used before study	Number of patients entered into the study: n=19 Mechanical ventilation. Entry criteria: (1) neonate ventilated and O ₂ -dependent for 14 or more days since birth for primary lung disease, (2) decision by physician caring for the infant to initiate diuretic treatment with furosemide. Exclusion criteria: glucocorticosteroids or diuretics before or during the study. Nineteen patients were randomized, including 6 girls and 13 boys. Eleven were randomized to receive iv furosemide first. Average birth weight was 800 ±170 g, gestational age 26.2±2.1 weeks, postnatal age 27±11 days, postconceptional age 30.0±2.4 weeks and weight at the time of the study 910±180 g. FiO ₂ before aerosolized furosemide was 0.45±0.13 vs 0.37 ±0.13 before intravenous furosemide. Peak pressure was 17.7 ±2.5 and 17.8±2.7	Aerosolized furosemide vs iv furosemide Patients were randomized to receive either 1 dose of aerosolized furosemide 1 mg/kg followed within 24 hours by 1 dose of intravenous furosemide 1 mg/kg, or vice versa. Nebulized bronchodilator (adrenergic) therapy was withheld for 4 hours before and during the 2 hours after furosemide administration. Infants who were receiving theophylline continued to receive it during the study. However, no infant was started on theophylline during the study.	Main outcome: pulmonary function, fluid and electrolyte balance. Administration of aerosolized furosemide did not affect ventilatory settings or FiO ₂ compared to intravenous administration, but significantly reduced urine output (p<0.01) and excretion of Na (p<0.01) and Cl (p<0.01). Repeated measures analysis of variance showed significant increase in tidal volume and in compliance but no change in resistance in after nebulized furosemide; no significant change from baseline was observed after intravenous furosemide. The % change in tidal volume from	Furosemide was provided by using a commercial nebulizer connected to the inspiratory limb of ventilatory circuit. The entire dose was administered at a flow of 2 l/min over 5-10 min. Pulmonary function tests were obtained at baseline and at 30 min, 1hr and 2 hr after furosemide administration, whereas the other variables were obtained at baseline and 2 hours after furosemide administration. Pulmonary mechanics were measured using the two-factor, least mean square technique without an esophageal balloon.	D
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		cm H ₂ O, respectively, PEEP was 5.0±0.7 cm for both, and rate of mechanical ventilation was 26 ±13 and 29±17 breaths/ min.		baseline was higher after aerosolized furosemide than after intravenous administration, both at 30 min (p<0.05) and at 120 min (p<0.01) but not at 60 min. Compliance was higher after aerosolized furosemide than after intravenous administration at 60 min (p<0.05) and 120 min (p<0.01) but not at 30 min.		
Prabhu 1998	Blinding of randomization: not documented Blinding of intervention: not documented Complete follow up: yes Blinding of outcome: not documented Randomized clinical trial, cross-over design with pooled data Washout period: bronchodilators 4 hr before study; no diuretics or glucocorticosteroids used before study in any patient	Number of patients entered into the study: n=13 Mechanical ventilation Entry criteria: Prematurity, requirement of oxygen and mechanical ventilation for primary lung disease for at least 14 days Exclusion criteria: major congenital anomalies Mean birth weight was 713±132 g, gestational age 25.4 ±1.5 weeks, postnatal age 24 ±9.5 days and postconceptional	Aerosolized furosemide 2 mg/kg vs 1 mg/kg Patients were randomized to receive either aerosolized furosemide 1 mg/kg once, followed by a 2 mg/kg dose after 24 hours, or vice versa.	Main outcome: magnitude and duration (beyond 2 hours) of the effects of furosemide on pulmonary mechanics. Secondary outcome: urine output and urinary excretion of electrolytes. Repeated measures ANOVA showed that both doses significantly increased compliance	Furosemide was nebulized via the inspiratory limb of the ventilator circuit, using a flow of 2 L/ min and a nebulizer (MiniHeart, Vortran Medical Technology). Pulmonary function tests were obtained at baseline and at 2,4 and 6 hours after administration of the aerosol. Pulmonary mechanics	D

		age 28.8±2.0 weeks. Baseline values of compliance, tidal volume, resistance and urine output before the 2 mg/kg dose were similar to those before the 1 mg/kg dose.		and tidal volume for up to 6 hours. The 2 doses of furosemide yielded non significantly different values of compliance and tidal volume at 2, 4 and 6 hours. Furosemide administration was not followed by any significant change in urinary output or urinary electrolyte excretion after either dose of furosemide.	were measured using the two-factor, least mean square technique without an esophageal balloon. Urine was collected for six hours before and six hours after aerosol administration. Theophylline was continued in those infants already on this medication before the study; no infant was started on theophylline during the 2-day study period.	
Rastogi 1992	Blinding of randomization: no Blinding of intervention: no Complete follow up: yes Blinding of outcome: no Randomized clinical trial, cross-over design with pooled data No washout period documented	Number of patients entered into the study: n=5 Mechanical ventilation Inclusion criteria: Infant with BPD, ventilator dependent Mean birth weight was 743±168 g, gestational age 27 ±1.8 weeks, postnatal age 30.6 ±4.3 days and postconceptional age 31.4±1.9 weeks. Baseline compliance before nebulized furosemide tended	Aersolized furosemide vs iv furosemide Patients were randomly allocated to receive either nebulized furosemide 1 mg/kg followed by intravenous furosemide 1 mg/kg, or vice versa.	Main outcome: pulmonary function tests Resistance was not affected by the route of administration of furosemide. Compliance 2 hours (but not at other times) after nebulized furosemide was significantly higher than after	Abstract form only; incomplete information available. Pulmonary function tests were measured 1/2, 1, 2 and 4 hours after aerosol administration. Units and methods are not provided; they were assumed to be the same as in one	D

		to be 18% higher than baseline before iv furosemide. Baseline tidal volume and resistance had baselines before nebulized furosemide that were similar to those before iv furosemide.		intravenous furosemide. Tidal volume 4 hours (but not at other times) after nebulized furosemide was significantly higher than after intravenous furosemide. However, average % changes from baseline after nebulized furosemide were not significantly different from those after intravenous furosemide.	manuscript (Rastogi 1994), in which dynamic compliance (ml/cm H ₂ O/kg) and resistance (cm/L/sec) were measured by the least mean square method.	
Rastogi 1994	Blinding of randomization: no. Randomization was obtained using a table of random numbers. Blinding of intervention: no. Complete follow-up: yes. Of 11 eligible infants, informed consent was denied in 3. All of 8 enrolled infants were followed throughout the study. Blinding of outcome: no. Randomized clinical trial, cross-over design with	Number of patients entered into the study: n=8 Mechanical ventilation Entry criteria: history of RDS requiring mechanical ventilation at birth, postnatal age > 14 days, persistence of respiratory failure and dependence on O ₂ and mechanical ventilation, radiographic evidence of chronic pulmonary parenchymal disease, no drug therapy other than vitamins for at least	Aerosolized furosemide 0.1 vs 0.25, 0.5 ,1 mg/kg Patients successively received in random order four different doses of aerosolized furosemide: 0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg and 1 mg/kg. Furosemide was made up to a final volume of 2 ml with 0.9% NaCl.	Compliance improved in 0/8 patients after a low dose of furosemide, compared to 7/8 at 30 minutes and 6/8 at 4 hours after a dose of 1 mg/kg. Resistance decreased in 0/8 patients after a low dose of furosemide, compared to 7/8 at 30 minutes and at 4 hours after a dose of 1 mg/	There is no information about efficacy of the method of nebulization, so that the exact amount of drug reaching the distal airways is not sure. Pulmonary function was measured at baseline, then at 30 min, 1,2 and 4 hours after aerosol administration. Pulmonary mechanics were	D

pooled data.
Washout: 72 hr
before delivery; 24
hr at cross-over

72 hours before the
start of the study
Exclusion criteria:
evidence of
congenital
malformations,
infection,
congenital heart
defect, or
congenital heart
disease.
Mean birth weight
was 815 ± 297 g and
mean gestational
age was 27.4 ± 1.6
weeks. At the time
of the study,
postnatal age was
 33 ± 13 days,
postconceptional
age 32.1 ± 2.5 weeks
and weight 1013
 ± 331 g. Mean peak
inspiratory pressure
was 19.3 ± 1.0 cm
H₂O, mean airway
pressure 7.9 ± 1.5
cm, FiO₂ 0.45
 ± 0.17 , and
ventilatory rate 30
 ± 12 per minute.
Blood pH was 7.33
 ± 0.07 and pCO₂
was 44 ± 8 mm Hg.

kg. Tidal
volume
increased in
0/8 patients
after a low
dose of
furosemide,
compared to
8/8 at 30
minutes and
6/8 at 4 hours
after a dose of
1 mg/kg.
Urine output,
urinary
calcium,
calcium/
creatinine
ratio,
fractional
excretion of
sodium and
creatinine
clearance
were similar
after each of
the 4 doses of
furosemide,
suggesting
that
aerosolized
furosemide
had no effect
on the kidney.

measured
using the least
mean square
method. The
FiO₂ was
adjusted
during
measurement
of pulmonary
mechanics to
maintain
hemoglobin
saturation >94
%. Patients
did not
receive
sedation; most
were in quiet
but active
sleep state
during testing.
Urine was
collected for
24 hours after
each dose of
diuretic.
The authors
state that
doses of 0.1-
0.5 mg/kg had
no effect on
pulmonary
function;
however, no
data are
provided, so
this
information
cannot be
used for meta-
analysis.
Furthermore,
no data are
provided to
support that a
dose of
furosemide of
0.1 mg/kg had
no effect on

					urine output. For this meta-analysis, we assumed that 0.1 mg/kg of furosemide had no significant effect on any of the variables and thus can be considered as a placebo.	
Raval 1994	Blinding of randomization: yes Blinding of intervention: yes Complete follow up: yes Blinding of outcome: yes Randomized clinical trial, cross-over design with pooled data No washout period documented	Number of patients entered into the study: n=11 Mechanical ventilation Inclusion criteria: BPD, ventilator-dependent premature infant with postnatal age at least 14 days Average birth weight was 780 ±207 g, gestational age 25±1 wk, postnatal age 19 ±10 days and postconceptional age 27.7±1.7 weeks. Baseline values of compliance, resistance, tidal volume and minute ventilation before furosemide were similar to those before placebo.	Aerosolized furosemide vs placebo Patients were randomly allocated to receive aerosolized furosemide 1 mg/kg in 2 ml of normal saline twice q 24 hours followed by placebo twice q 24 hours, or vice versa.	Main outcome: pulmonary mechanics: compliance, resistance, tidal volume, minute ventilation. There was no significant difference in any of the variables after furosemide versus after placebo.	Abstract form only; no information available about type of nebulizer, flow, and other medications. Dynamic pulmonary function tests were obtained 20 minutes before and 20 minutes after treatment.	A

Robbins 1993	Blinding of randomization: yes Blinding of intervention: yes Complete follow up: yes Blinding of outcome: yes Randomized clinical trial, parallel design No washout period documented	Number of patients entered into the study: n=10 Mechanical ventilation Inclusion criteria: BPD Of 10 patients, five were allocated to each group. There was no significant difference between the two groups in any of the variables analyzed. Average birth weight was similar in furosemide-treated patients and in those on placebo, 671±136 g and 786±242, g respectively. Mean gestational age was, respectively, 26.2±1.8 and 26.2±1.3 weeks, mean weight at entry 850±179 and 944±293 g, mean postnatal age 31±13 and 24±7 days, and postconceptional age 30.6±2.6 and 29.6±1.6 weeks, respectively. Peak inspiratory pressure was similar in both groups (20.2±1.8 vs 19.6±1.8 cm H ₂ O), so were positive end expiratory pressure (5.2±1.1 and 5.0±1.0 cm) and FiO ₂ (0.41±0.25 and 0.41±0.20).	Aerosolized furosemide vs placebo Patients were randomly allocated to receive either aerosolized furosemide 1 mg/kg in 2 ml normal saline or placebo (normal saline) for seven days. The interval of administration is not stated in the abstract.	Main outcome: pulmonary mechanics. There was no significant difference in compliance or in resistance between the two groups.	Abstract form only; no information available about frequency of administration, type of nebulizer, flow, other medications. Pulmonary function tests (dynamic compliance and resistance) were obtained 15 minutes before aerosol, 30 minutes after the first dose and again on day 7 before the aerosol.	A
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± always precedes SD

Characteristics of excluded studies

Study	Reason for exclusion
Suresh 1992	Not a randomized study

References to studies

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Comparisons and data

01 Aerosolized furosemide vs control

01.01 [Change in transcutaneous pO₂ \(mm Hg\), patients > 3 weeks of age](#)

01.02 [Change in blood pH, 1 hour after 1 dose, patients > 3 weeks of age](#)

01.03 [Change in compliance \(ml/cm H₂O/kg\)](#)

01.04 [Change in resistance \(cm/L/sec\)](#)

01.05 [Change in tidal volume \(ml/kg\)](#)

01.06 [Change in minute ventilation \(ml/kg/min\) 20 min after dose, on second day, patients > 3 weeks of age](#)

01.07 [Change in resistance \(cm/L/sec\) at 2 hours](#)

02 Aerosolized furosemide vs intravenous furosemide

02.01 [Change in % inspiratory O₂ 2 hours after 1 dose](#)

02.02 [Change in transcutaneous O₂ saturation \(%\) 2 hours after 1 dose](#)

02.03 [Change in peak inspiratory pressure \(cm H₂O\) 2 hours after 1 dose](#)

02.04 [Change in positive end expiratory pressure \(cm H₂O\) 2 hours after 1 dose](#)

02.05 [Change in ventilator rate \(cycles per minute\) 2 hours after 1 dose](#)

02.06 [Change in compliance \(ml/cm H₂O/kg\)](#)

02.07 [Change in resistance \(cm/L/sec\)](#)

02.08 Change in tidal volume (ml/kg)**03 1 mg/kg aerosolized furosemide (Treatment) vs lower dose (Control)****03.01 Failure to improve compliance****03.04 Failure to improve resistance****03.07 Failure to improve tidal volume****03.10 Urinary calcium (mg/kg/day) over 24 hours****03.11 Calcium:creatinine ratio (mg:mg)****04 2 mg/kg aerosolized furosemide (Treatment) with 1 mg/kg (Control)****04.01 Change in compliance (ml/cm H2O/kg)****04.02 Change in resistance (cm/L/sec)****04.03 Change in tidal volume (ml/kg)****04.04 Change in urine output (ml/kg/hr)**

Comparison or outcome	Studies	Participants	Statistical method	Effect size
01 Aerosolized furosemide vs control				
01 Change in transcutaneous pO ₂ (mm Hg), patients > 3 weeks of age			WMD (fixed), 95% CI	Subtotals only
02 Change in blood pH, 1 hour after 1 dose, patients > 3 weeks of age	1	16	WMD (fixed), 95% CI	0.00 [-0.03, 0.03]
03 Change in compliance (ml/cm H ₂ O/kg)			WMD (fixed), 95% CI	Subtotals only
04 Change in resistance (cm/L/sec)			WMD (fixed), 95% CI	Subtotals only
05 Change in tidal volume (ml/kg)			WMD (fixed), 95% CI	Subtotals only
06 Change in minute ventilation (ml/kg/min) 20 min after dose, on second day, patients > 3 weeks of age	1	22	WMD (fixed), 95% CI	-52.00 [-144.04, 40.04]
07 Change in resistance (cm/L/sec) at 2 hours	3	36	WMD (fixed), 95% CI	-1.26 [-19.80, 17.29]
02 Aerosolized furosemide vs intravenous furosemide				
01 Change in % inspiratory O ₂ 2 hours after 1 dose	1	38	WMD (fixed), 95% CI	-6.00 [-16.03, 4.03]
02 Change in transcutaneous O ₂ saturation (%) 2 hours after 1 dose	1	38	WMD (fixed), 95% CI	2.00 [-0.11, 4.11]
03 Change in peak inspiratory pressure (cm H ₂ O) 2 hours after 1 dose	1	38	WMD (fixed), 95% CI	0.00 [-1.80, 1.80]

04 Change in positive end expiratory pressure (cm H ₂ O) 2 hours after 1 dose	1	38	WMD (fixed), 95% CI	-0.10 [-0.62, 0.42]
05 Change in ventilator rate (cycles per minute) 2 hours after 1 dose	1	38	WMD (fixed), 95% CI	1.00 [-9.73, 11.73]
06 Change in compliance (ml/cm H ₂ O/kg)			WMD (fixed), 95% CI	Subtotals only
07 Change in resistance (cm/L/sec)			WMD (fixed), 95% CI	Subtotals only
08 Change in tidal volume (ml/kg)			WMD (fixed), 95% CI	Subtotals only
03 1 mg/kg aerosolized furosemide (Treatment) vs lower dose (Control)				
01 Failure to improve compliance			RR (fixed), 95% CI	Subtotals only
04 Failure to improve resistance			RR (fixed), 95% CI	Subtotals only
07 Failure to improve tidal volume			RR (fixed), 95% CI	Subtotals only
10 Urinary calcium (mg/kg/day) over 24 hours	1	16	WMD (fixed), 95% CI	-0.10 [-2.01, 1.81]
11 Calcium:creatinine ratio (mg:mg)	1	16	WMD (fixed), 95% CI	0.00 [-0.20, 0.20]
04 2 mg/kg aerosolized furosemide (Treatment) with 1 mg/kg (Control)				
01 Change in compliance (ml/cm H ₂ O/kg)			WMD (fixed), 95% CI	Subtotals only
02 Change in resistance (cm/L/sec)			WMD (fixed), 95% CI	Subtotals only
03 Change in tidal volume (ml/kg)			WMD (fixed), 95% CI	Subtotals only
04 Change in urine output (ml/kg/hr)	1	26	WMD (fixed), 95% CI	0.70 [-0.56, 1.96]

Notes

Published notes

Amended sections

Cover sheet

Abstract

Background

Search strategy for identification of studies

Methods of the review

Discussion

Other references

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