

Furosemide for transient tachypnea of the newborn (Review)

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ABSTRACT

Background

Transient tachypnea of the newborn results from delayed clearance of lung liquid and is a common cause of admission of full term infants to neonatal intensive care units. The condition is particularly common after elective Caesarean section. Conventional treatment involves appropriate oxygen administration and continuous positive airway pressure in some cases. Most infants receive antibiotic therapy. Hastening the clearance of lung liquid should shorten the duration of the symptoms and reduce complications.

Objectives

To determine whether furosemide reduces the duration of oxygen therapy and respiratory symptoms and shortens hospital stay in term infants with transient tachypnea of the newborn.

Search strategy

We searched the Cochrane Controlled Trials Register, PubMed and EMBASE. The primary author and experts in the field were contacted.

Selection criteria

Randomised or quasi-randomised controlled trials. Infants of less than 7 days of age, born after 37 or more weeks of gestation with the clinical picture of transient tachypnea of the newborn. Intravenous, oral or nebulized furosemide compared to placebo or no diuretic in the first 7 days.

Data collection and analysis

Two reviewers assessed trial quality in each potentially eligible manuscript and two reviewers extracted data.

Main results

Searching revealed only one randomised trial which was methodologically sound. This recruited 50 infants with transient tachypnea. Infants were randomised to receive oral furosemide 2 mg/kg followed by 1 mg/kg 12 hours later, or placebo. Weight loss in the first 24 hours was greater in the furosemide treated group but there was no evidence of a difference between the groups in duration of tachypnea or severity of symptoms or length of hospitalization. The study was methodologically satisfactory.

Authors' conclusions

Oral furosemide cannot be recommended as treatment for transient tachypnea of the newborn and it should not be used unless additional data become available. The question remains as to whether intravenous furosemide given to the infant (or even to the mother before Caesarean section) might shorten the duration of the illness. As elective Caesarean section continues at a high level, these two interventions might be worthy of trials.

PLAIN LANGUAGE SUMMARY

It is common for full term infants born by elective Caesarean section to have laboured and rapid breathing (tachypnea) and to require oxygen for about 48 hours. Although transient and not usually serious, the condition requires admission to a neonatal intensive care

unit and involves separation of mother and baby and use of expensive resources. Furosemide is a powerful diuretic which, in other circumstances, can reduce fluid in the lungs. We found only one trial (involving 50 infants) that had tested furosemide in this condition. The drug was given orally and made no difference to either the severity or duration of the illness or to length of hospitalization. Giving furosemide intravenously, or even to the mother before Caesarean, might have a more powerful effect and may merit investigation.

BACKGROUND

Transient tachypnea of the newborn (TTN) was first described by Avery 1966 in infants born at term who developed rapid respiration (> 80/min), grunting and retraction at or shortly after birth. Investigations for infection were negative and the oxygen requirement did not rise above 40%. Chest X-ray showed streaky interstitial or pleural fluid, prominent interlobar fissures, perihilar vascular markings and sometimes hyperinflation. The symptoms usually resolved by 48 hours, occasionally lasting as long as 5 days. The condition is commoner in term infants born by elective caesarean section (Morrison 1995, Tudehope 1979). It may be difficult to distinguish between congenital pneumonia and TTN and many infants receive antibiotics until blood cultures are known to be negative. TTN is regarded as being synonymous with wet lung, benign unexplained respiratory distress in the newborn, neonatal tachypnea and type 2 RDS (Rennie 1999). It is attributed to the delayed clearance of fetal lung fluid with secondary air trapping. Lung liquid that has been rendered high in protein by either mild asphyxia or amniotic fluid aspiration may contribute to the problem (Avery 1966). In addition, elective caesarean section deprives the fetus of the effect of endogenous catecholamines on resorption of lung liquid.

The reported prevalence of TTN varies with some authors attributing up to 40% of neonatal respiratory distress to TTN (Tudehope 1979) and an overall incidence of around 11 per 1000 births. With a tendency to delivery by elective caesarean section for an increasing number of obstetric and fetal indications, the number of infants admitted to neonatal units with TTN is likely to rise.

There are no specific biochemical or hematological markers and the diagnosis is essentially clinical with typical radiological features on chest Xray.

The natural history is of gradual improvement of respiratory signs as fetal lung fluid is reabsorbed. Treatment is supportive with oxygen to maintain acceptable saturations and occasionally continuous positive airway pressure (CPAP) and even endotracheal ventilation to obtain adequate oxygenation and carbon dioxide clearance. TTN usually settles within 24 hours but may persist for several days and in its more severe forms may be associated with secondary surfactant deficient lung disease and in extreme cases, persistent pulmonary hypertension.

Furosemide has been shown to affect fluid dynamics in the lung by both diuretic and non-diuretic actions (Demling 1978, Belik 1987, Prabhu 1997). In theory, diuresis should increase the

plasma oncotic pressure and draw water from the lungs into the pulmonary vascular bed. This has been shown not to be the case in an adult canine model (Wickerts 1992). It seems more likely that non-diuretic effects are predominant with several authors showing improved pulmonary dynamics without demonstrable diuresis (Demling 1978, Prabhu 1997). Given the effects of furosemide on the fluid overloaded lung it is reasonable to hypothesize that it might alter the clinical course of TTN.

Although TTN is generally a benign self-limiting condition there is much to be gained from shortening its clinical course provided this can be achieved without side effects. Hastening the clearance of retained fetal lung fluid should improve oxygenation, shorten the clinical course and may reduce complication rates. Separation of mothers from their newborn infants is generally undesirable. Furthermore there are significant economic implications of reducing duration of hospital admission.

OBJECTIVES

The aim of this review was to determine whether treatment with furosemide reduces the duration of oxygen therapy and respiratory symptoms and shortens hospital stay in term infants presenting with the clinical syndrome of transient tachypnea of the newborn.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Infants of less than 7 days of age, born at 37 or more completed weeks of gestation with a clinical diagnosis of transient tachypnea of the newborn (including the synonymous conditions of wet lung, benign unexplained respiratory distress in the newborn, neonatal tachypnea and type 2 RDS).

Types of intervention

Intravenous, oral or nebulized furosemide compared to placebo or no diuretic in the first 7 days of life. Studies looking at single doses as well as multiple doses were considered.

Types of outcome measures

Duration of oxygen therapy in hours.

Duration of tachypnea (>60 breaths/min) in hours.
Length of hospital stay in days.
Number of infants receiving CPAP
Number of infants receiving positive pressure ventilation.
Patent ductus arteriosus.
Electrolyte disturbances (hyponatremia & hypokalemia).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See: Collaborative Review Group search strategy.
Standard search methods of the Neonatal Collaborative Review Group were used.

1. Published manuscripts:

Search included MEDLINE (1966-2001), EMBASE (1980-2001) and the Cochrane Controlled Trials Register (CCTR) from the Cochrane Library (2001, Issue 2). Articles in any language were considered as long as there was an abstract in English indicating content. The following were considered synonymous with transient tachypnea of the newborn: 'wet lung', 'benign unexplained respiratory distress in the newborn', 'neonatal tachypnea' and 'type 2 RDS'. The following keywords were used: 'furosemide', 'frusemide', 'diuretics', 'tachypnea', 'respiratory distress', 'wet lung', 'type 2 RDS' and 'type II RDS'. Subject heading: 'infant, newborn'

2. Published abstracts:

Search included the abstracts of the Society for Pediatric Research 1987-2001 (published in *Pediatric Research*). The search was done by hand or electronically by CD-ROM (2001). For abstract books or CD-ROMs with keywords, we used the following keywords: 'furosemide', 'respiratory distress', 'transient tachypnea'. For years 1992-3 (volumes 31 and 33 of *Pediatric Research*), no keywords are available; therefore, we hand searched the sections on Neonatal Pulmonology.

3. Database of the Neonatal Review Group of the Cochrane Collaboration:

We screened all publications with the keywords 'furosemide' OR 'frusemide'.

4. If data for review were not included in original articles then authors were contacted. Expert informants were approached to identify any relevant unpublished material.

5. Selection process:

Only randomised controlled trials fulfilling the selection criteria described in the previous sections were selected. Selection was done separately by two investigators; any disagreement was resolved by discussion.

METHODS OF THE REVIEW

Standard methods of the Neonatal Review Group were used. The one eligible study was independently assessed by each reviewer. Each reviewer assessed the methodological quality with respect to: i) masking of allocation ii) masking of intervention iii) complete follow-up iv) blinding of outcome measure.

Each reviewer extracted data separately and resolved any disparity. Additional data on randomisation methodology were requested from Wiswell et al.

The intention was to perform subgroup analysis for route of administration (oral, intravenous or nebulized). However, since only one study was identified this was not possible.

Standard methods of the Neonatal Review Group were used for data analysis. Treatment effects on categorical outcomes were analysed using relative risk, risk difference and number needed to treat. For treatment effects measured on a continuous scale, mean difference was used. 95 % confidence intervals were calculated.

DESCRIPTION OF STUDIES

See table of characteristics of included studies

Searching revealed only one randomised controlled trial examining the use of furosemide in transient tachypnea of the newborn (Wiswell 1985). No unpublished data were identified. Wiswell investigated 50 consecutive admissions to a single neonatal unit with transient tachypnea of the newborn as defined by:

- Onset of tachypnea (respiratory rate more than 60/min) within 6 hours after birth.
- Persistence of tachypnea for at least 12 hours.
- Chest roentgenogram indicating abnormalities characteristic of transient tachypnea of the newborn (hyperaeration, vascular congestion, and excessive interstitial and/or pleural fluid).
- Absence of other disorders likely to cause tachypnea (polycythemia, air dissection syndromes, hypoglycemia, pulmonary hemorrhage, aspiration syndromes, congenital heart disease, respiratory distress syndrome and pneumonitis)

After informed consent and within 6 hours of birth, the infants were randomised to receive either oral furosemide (2mg/kg body weight at time of diagnosis followed by a 1mg/kg dose 12 hours later if the tachypnea persisted) or placebo given in the form of an equal volume of coloured sterile water indistinguishable from the furosemide. They measured response to treatment in terms of;

- Weight loss as a % of birth weight at 24 hours of age and at discharge.
- Duration of hospitalization.
- Duration of tachypnea (respiratory rate >60 per minute).

METHODOLOGICAL QUALITY

See table of characteristics of included studies.

Although Wiswell 1985 did not report the method of concealment of randomisation, Dr Wiswell informed us that he used randomised opaque envelopes to allocate treatment. Power calculations were based on a 90% chance of detecting a 24-hour difference in the duration of tachypnea and estimated that 25 patients would be required. There were equal numbers of patients allocated to each group with a total of 50. The placebo preparation (coloured sterile water) was indistinguishable from the oral preparation of Furosemide. Follow-up was complete and the investigators remained blinded until the study was complete.

RESULTS

Duration of tachypnea

Wiswell 1985 found no evidence of effect (mean difference - 5.1 hours (95% CI -14.6 to 4.35 hours).

Length of hospital stay

Wiswell 1985 found no evidence of effect (mean difference 0.10 days (95% CI -0.60 to 0.80 days).

One intended primary outcome of the review was the duration of oxygen therapy. This information was not provided by Wiswell 1985. Due to the elapsed time since the study was performed, Dr Wiswell was unable to provide relevant data.

Wiswell 1985 found that none of the infants demonstrated pulmonary hypertension, needed CPAP, needed mechanical ventilation or died. There were no clinically important changes in serum electrolyte values in either group. None of the furosemide treated infants developed patent ductus arteriosus. Although weight loss at discharge was similar in the two groups, the furosemide treated group lost significantly more weight in the first 24 hours after birth.

DISCUSSION

Only one trial was found to be eligible for this review (Wiswell 1985). This study was well designed. It failed to show a statistically significant impact of oral furosemide on the duration of oxygen requirement in transient tachypnea of the newborn. The methodological quality of the study was satisfactory and the power calculations were reasonably based. Although no adverse effects

were reported in this single study it should be noted that the study was not powered to look for potential side effects. The rationale for choosing oral furosemide is not clear. Intravenous furosemide might have been more appropriate in infants with an acute respiratory disturbance and uncertain enteral absorption.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the available evidence the routine use of furosemide in infants with transient tachypnea of the newborn cannot be recommended.

Implications for research

It is plausible that with the increasing rates of elective Caesarean section (Khor 2000) the incidence of transient tachypnea of the newborn will also increase. Although not usually seriously ill, infants with transient tachypnea of the newborn may develop secondary surfactant deficient lung disease and require mechanical ventilation. No group has to date systematically investigated the role of intravenous furosemide or any other diuretic in transient tachypnea of the newborn. If shown to reduce either or both length of stay or requirement for oxygen, then diuretics could have a significant economic benefit. Such a study would almost certainly have to be multicentre in design. Furosemide has been shown to pass freely across the placenta (Beermann 1978). Intravenous administration of furosemide to the mother before elective Caesarean section might also be worthy of investigation as a way of assisting clearance of fetal lung liquid and reducing the duration of transient tachypnea.

POTENTIAL CONFLICT OF INTEREST

None.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- United Bristol Healthcare Trust UK

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References to studies included in this review

Wiswell 1985 *{published data only}*

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Wickerts 1992

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TABLES

Characteristics of included studies

Study	Wiswell 1985
Methods	Design: Randomized double blind placebo controlled trial. Setting: Single neonatal unit in Tripler Army Medical Center, Honolulu. Randomization: Method: numbered opaque sealed envelopes. 25 patients allocated to each group. Blinding of allocation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome ascertainment: yes.
Participants	Number: 50 consecutive admissions with transient tachypnea of the newborn to neonatal unit Inclusion criteria: Transient tachypnea of the newborn as defined by: 1) onset of tachypnea (respiratory rate more than 60/min) within 6 hours after birth, 2) persistence of tachypnea for at least 12 hours, 3) chest roentgenogram indicating abnormalities characteristic of transient tachypnea of the newborn (hyperaeration, vascular congestion, and excessive interstitial and/or pleural fluid), and 4) absence of other disorders likely to cause tachypnea (polycythemia, air dissection syndromes, hypoglycemia, pulmonary hemorrhage, aspiration syndromes, congenital heart disease, respiratory distress syndrome and pneumonitis)

Interventions	Oral furosemide 2mg/kg body weight, at time of diagnosis followed by a 1mg/kg dose 12 hours later if the tachypnea persisted. Placebo given in the form of an equal volume of sterile water colored with two drops of MVI solution (USV Pharmaceutical Corp, Tuckahoe, NY) indistinguishable from the furosemide.
Outcomes	Outcomes measured: 1) Weight loss as a % of birth weight at 24 hours of age and at discharge, 2) Duration of hospitalization, and 3) Duration of tachypnea. None of the infants demonstrated pulmonary hypertension, needed mechanical ventilation or died. There were no changes in serum electrolyte values in either group. None of the furosemide treated infants developed patent ductus arteriosus. There were no differences between the groups in severity or persistence of symptoms, duration of oxygen requirement, or length of hospitalization. Although weight loss at discharge was similar in the two groups, the furosemide treated group lost significantly more weight in the first 24 hours after birth.
Notes	Information on randomization obtained from authors.
Allocation concealment	A – Adequate
Information on concealment of allocation was obtained by contact with Dr Wiswell.	

ANALYSES

Comparison 01. Oral furosemide versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Duration of tachypnea in hours	1	50	Weighted Mean Difference (Fixed) 95% CI	-5.10 [-14.55, 4.35]
02 Duration of hospitalization in days	1	50	Weighted Mean Difference (Fixed) 95% CI	0.10 [-0.60, 0.80]
03 Electrolyte disturbance	1	50	Relative Risk (Fixed) 95% CI	Not estimable
04 Requirement for CPAP	1	50	Relative Risk (Fixed) 95% CI	Not estimable
05 Requirement for IPPV	1	50	Relative Risk (Fixed) 95% CI	Not estimable
06 Requirement for CPAP or IPPV	1	50	Relative Risk (Fixed) 95% CI	Not estimable
07 Persistent ductus arteriosus	1	50	Relative Risk (Fixed) 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Furosemide [*therapeutic use]; Infant, Newborn; Randomized Controlled Trials; Respiration Disorders [*drug therapy]

MeSH check words

Humans

COVER SHEET

Title	Furosemide for transient tachypnea of the newborn
Authors	Lewis V, Whitelaw A
Contribution of author(s)	VL had the idea for the review and carried out the search. AW collaborated on the structure of the review, repeated the search and advised on the use of RevMan. Both VL and AW have read the references and wrote sections of the review.
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What's New Information not supplied by author

Date new studies sought but none found Information not supplied by author

Date new studies found but not yet included/excluded Information not supplied by author

Date new studies found and included/excluded Information not supplied by author

Date authors' conclusions section amended Information not supplied by author

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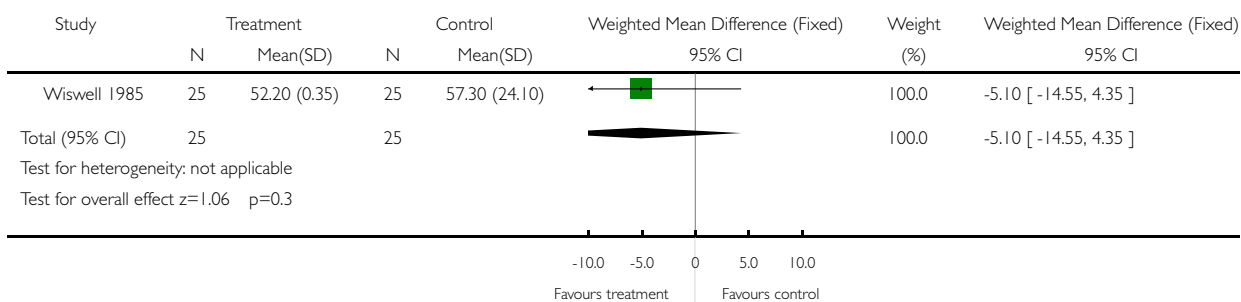
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Oral furosemide versus placebo, Outcome 01 Duration of tachypnea in hours

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 01 Duration of tachypnea in hours

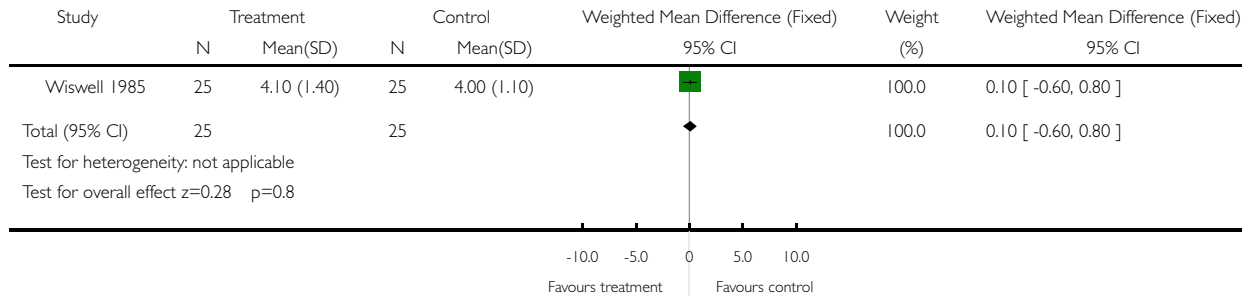


Analysis 01.02. Comparison 01 Oral furosemide versus placebo, Outcome 02 Duration of hospitalization in days

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 02 Duration of hospitalization in days

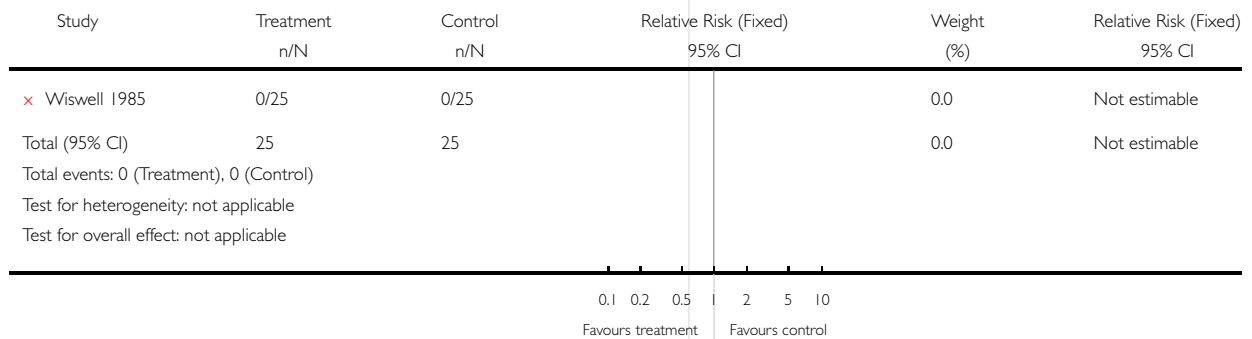


Analysis 01.03. Comparison 01 Oral furosemide versus placebo, Outcome 03 Electrolyte disturbance

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 03 Electrolyte disturbance



Analysis 01.04. Comparison 01 Oral furosemide versus placebo, Outcome 04 Requirement for CPAP

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 04 Requirement for CPAP

Study	Treatment n/N	Control n/N	Relative Risk (Fixed)		Weight (%)	Relative Risk (Fixed)	
			95% CI			95% CI	
× Wiswell 1985	0/25	0/25			0.0	Not estimable	
Total (95% CI)	25	25			0.0	Not estimable	
Total events: 0 (Treatment), 0 (Control)							
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

Analysis 01.05. Comparison 01 Oral furosemide versus placebo, Outcome 05 Requirement for IPPV

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 05 Requirement for IPPV

Study	Treatment n/N	Control n/N	Relative Risk (Fixed)		Weight (%)	Relative Risk (Fixed)	
			95% CI			95% CI	
× Wiswell 1985	0/25	0/25			0.0	Not estimable	
Total (95% CI)	25	25			0.0	Not estimable	
Total events: 0 (Treatment), 0 (Control)							
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

Analysis 01.06. Comparison 01 Oral furosemide versus placebo, Outcome 06 Requirement for CPAP or IPPV

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 06 Requirement for CPAP or IPPV

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Wiswell 1985	0/25	0/25		0.0	Not estimable
Total (95% CI)	25	25		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.07. Comparison 01 Oral furosemide versus placebo, Outcome 07 Persistent ductus arteriosus

Review: Furosemide for transient tachypnea of the newborn

Comparison: 01 Oral furosemide versus placebo

Outcome: 07 Persistent ductus arteriosus

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Wiswell 1985	0/25	0/25		0.0	Not estimable
Total (95% CI)	25	25		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					