

Nebulized racemic epinephrine for extubation of newborn infants (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	3
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	3
METHODS OF THE REVIEW	3
DESCRIPTION OF STUDIES	3
METHODOLOGICAL QUALITY	3
RESULTS	3
DISCUSSION	3
AUTHORS' CONCLUSIONS	5
POTENTIAL CONFLICT OF INTEREST	5
ACKNOWLEDGEMENTS	5
SOURCES OF SUPPORT	5
REFERENCES	5
TABLES	7
Characteristics of excluded studies	7
GRAPHS AND OTHER TABLES	7
INDEX TERMS	7
COVER SHEET	7

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ABSTRACT

Background

Following a period of mechanical ventilation, post-extubation upper airway obstruction can occur in newborn infants, especially after prolonged, traumatic or multiple intubations. The subsequent increase in upper airway resistance may lead to respiratory insufficiency and failure of extubation. The vasoconstrictive properties of epinephrine, and its proven efficacy in the treatment of croup in infants, has led to the routine use of inhaled nebulized epinephrine immediately post-extubation in some neonatal units. It is also recommended for neonates with post-extubation tracheal obstruction and stridor in neonatal and respiratory textbooks and reviews.

Objectives

The primary objective was to assess whether nebulized epinephrine administered immediately after extubation in neonates weaned from IPPV decreases the need for subsequent additional respiratory support.

Search strategy

Searches were of: MEDLINE from 1966 to September 2000; CINAHL from 1982 to September 2000; Current Contents from 1994 to September 2000; and the Cochrane Controlled Trials Register (Cochrane Library Issue 3, 2000). These searches were updated to September 2001 for this review update. Previous searches up to March 1999 included the Oxford Database of Perinatal Trials, expert informants and journal hand searching mainly in the English language, previous reviews including cross references, abstracts, and conference and symposia proceedings.

Selection criteria

All randomised and quasi-randomised control trials in which nebulized epinephrine was compared with placebo immediately post-extubation in newborn infants who have been weaned from IPPV and extubated, with regard to clinically important outcomes (i.e. need for additional respiratory support, increase in oxygen requirement, respiratory distress, stridor or the occurrence of side effects).

Data collection and analysis

No studies met our criteria for inclusion in this review.

Main results

No studies were identified which looked at the effect of inhaled nebulized epinephrine on clinically important outcomes in infants being extubated.

Authors' conclusions

Implications for practice: There is no evidence either supporting or refuting the use of inhaled nebulized racemic epinephrine in newborn infants.

Implications for research: randomised controlled trials are needed comparing inhaled nebulized racemic epinephrine with placebo in neonates post-extubation. This should be looked at both as a routine treatment post-extubation and as specific treatment for post-extubation upper airway obstruction. Study populations should include the group of infants at highest risk for upper airway obstruction from mucosal swelling because of their small glottic and sub-glottic diameters (ie those infants with birthweights less than 1000 grams).

Nebulized racemic epinephrine for extubation of newborn infants (Review)

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1

PLAIN LANGUAGE SUMMARY

The use of inhaled nebulized epinephrine after extubation in newborn infants is not supported or refuted by evidence from randomised controlled trials.

Following mechanical ventilation, airway swelling and obstruction can occur in newborn infants (especially after prolonged, traumatic or multiple intubations). This may compromise breathing and cause failure of extubation. Because epinephrine can decrease swelling and its effect has been proven in the treatment of croup in infants, it has been used immediately after extubation to prevent breathing problems. The reviewers did not identify any studies that examined clinically relevant outcomes following the use of nebulized epinephrine in newborn infants. They concluded that there is no evidence either supporting or refuting the use of inhaled nebulized epinephrine in newborn infants.

BACKGROUND

Assisted ventilation via an endotracheal tube (ETT) is a common therapy in neonates with respiratory insufficiency in the first few weeks of life. The presence of a foreign body in contact with mucosal surfaces of the larynx and sub-glottis may damage those upper airway surfaces (Phelan 1994). The delicate mucosal lining of the infant airway readily becomes oedematous in response to irritation (O'Connor 1995). Prolonged intubation, traumatic intubations and multiple intubations have been associated with a greater risk of developing post-extubation upper respiratory tract inflammation (Fan 1983, Joshi 1972, da Silva 1999) and obstruction (Koka 1977). Direct visualisation using both flexible and rigid endoscopy has demonstrated laryngeal and sub-glottic swelling and erythema in neonates post-extubation (Fan 1982).

The sub-glottis is the narrowest portion of the upper airway in infants (O'Connor 1995, Willging 1995). In neonates the upper airways contribute more to total airway resistance than peripheral airways (Wohl 1990). Whilst the specific contribution of the glottis and sub-glottis to total airway resistance is largely unknown, it is thought to be substantial (Wohl 1990). The most important determinant of resistance in airways (particularly in the small calibre upper airways in neonates) is the radius of the airway lumen (O'Brodovich 1990). Even mild oedema in these narrowest portions of the upper respiratory tract will reduce the intra-luminal cross-sectional area by more than 50% (O'Connor 1995) and result in a significant increase in airway resistance (O'Brodovich 1990). Increased airway resistance after the infant is extubated may lead to respiratory insufficiency and failure of extubation.

Four prospective series have looked at post-extubation stridor in neonates. Laing 1986 found an incidence of post-extubation stridor in neonates of 14%. The study population included all ventilated neonates in a neonatal intensive care nursery from 1978 to the mid 1980's, intubated with Cole type, 'shouldered' ETTs. The incidence of stridor post-extubation leading to reintubation was 2% - none of the infants in this series had permanent sub-glottic stenosis. Albert (Albert 1990) studied 30 consecutive infants who had been ventilated for >24 hours, intubated with Cole type ETTs, and found an incidence of stridor post-extubation of 30%. Fan

(Fan 1982) described an incidence of stridor post-extubation of 16% in 73 consecutive neonates who required intubation. These infants were intubated with McGill ETTs (i.e. with a constant external diameter). The most recent study (da Silva 1999) of ETT complications in very low birthweight infants gives an incidence of post-extubation stridor of 4.8% (11/227). Infants in this study had all been intubated with ETTs with a constant external diameter. It is also noted that some of the 227 infants had been pre-treated with systemic corticosteroids.

Epinephrine stimulates both alpha and beta adrenergic receptors and is a potent inotrope and chronotrope. It acts on vascular smooth muscle to produce vasoconstriction which markedly decreases blood flow to capillary beds, especially in the skin and mucosal surfaces. The decrease in blood flow to the surfaces of the upper respiratory tract shrinks the mucosa and reduces oedema (Hoffman 1996, Remington 1986).

When epinephrine is nebulized and inhaled the actions of the drug are largely restricted to the respiratory tract, however, systemic reactions can occur (Hoffman 1996). Side effects of epinephrine include tachycardia, arrhythmias, hypertension, peripheral vasoconstriction, hyperglycaemia, hyperkalaemia, metabolic acidosis and leucocytosis with left shift (Hoffman 1996, Solomon 1984).

Inhaled nebulized epinephrine is widely used in the treatment of infective croup in children (Couriel 1988, Skolnik 1989) and its efficacy has been well demonstrated in randomised control trials (Kuusela 1988, Kristjánsson 1994, Fanconi 1990, Corkey 1981). There is also anecdotal evidence that nebulized epinephrine can alleviate obstruction caused by laryngeal or tracheal oedema from other causes in infants (Gwinnutt 1987) and children (ASC of NYSSA 1972, Jordan 1970).

Because of the problem of post-extubation upper airway obstruction and the vasoconstrictive properties of epinephrine, inhaled nebulized epinephrine administered immediately post-extubation is used routinely in some neonatal units (Bancalari 1992). Its effects have been studied in neonates in small, uncontrolled studies (Koren 1986, Marshall 1984). It is recommended for neonates with post-extubation tracheal obstruction and stridor in neonatal

and respiratory textbooks (Phelan 1994, Greenough 1996, Corbet 1990) and reviews (Pransky 1989).

This review aimed to examine the evidence for the use of inhaled nebulized epinephrine in the prophylaxis and treatment of post-extubation upper airway obstruction in neonates.

This review updates the existing review of “nebulized racemic epinephrine for extubation of newborn infants” which was published in the Cochrane Library, Issue 1, 2001 (Davies 2001).

OBJECTIVES

The primary objective was to assess whether nebulized epinephrine administered immediately after extubation in neonates weaned from IPPV decreases the incidence of the need for subsequent additional respiratory support.

Secondary objectives included:

1. To assess whether nebulized epinephrine administered immediately after extubation decreases other post-extubation morbidity. Morbidity was considered in terms of increasing oxygen requirement or respiratory distress, or stridor.
2. To assess whether nebulized epinephrine is associated with significant side effects.

Subgroup analyses were planned to determine whether the results differ for: i. preterm neonates, ii. infants at high risk for developing post-extubation airway oedema. Infants at high risk include those intubated for 7 days or more, those who had 3 or more intubations, and those who had a traumatic intubation or attempted intubation.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised and quasi-randomised controlled trials in which nebulized epinephrine was compared with placebo immediately post-extubation.

Types of participants

Newborn infants who have been weaned from IPPV and extubated.

Types of intervention

nebulized epinephrine administered immediately post-extubation.

Types of outcome measures

1. The need for additional respiratory support (i.e. tracheal intubation and ventilation or the commencement of NCPAP) by 24 hours and 7 days.
2. An increase in oxygen (O₂) requirement post-extubation.

3. An increase in respiratory distress.

4. The occurrence of stridor post-extubation.

5. The occurrence of side effects, eg tachycardia, arrhythmias, hypertension, peripheral vasoconstriction, hyperglycaemia, hyperkalaemia, metabolic acidosis and leucocytosis with left shift.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Searches were made using MeSH search terms 'epinephrine' and 'exp infant, newborn'. Databases searched included: MEDLINE and PREMEDLINE from 1966 to September 2001; CINAHL from 1982 to September 2001; and the Cochrane Controlled Trials Register, The Cochrane Library 2001 Issue 3. Previous searches up to March 1999 included the Oxford Database of Perinatal Trials, expert informants and journal hand searching mainly in the English language, previous reviews including cross references, abstracts, and conference and symposia proceedings.

METHODS OF THE REVIEW

Criteria and methods used to assess the methodological quality of the trials: standard method of the Cochrane Collaboration and its Neonatal Review Group were used.

DESCRIPTION OF STUDIES

No studies met our criteria for inclusion in this review.

METHODOLOGICAL QUALITY

No studies met our criteria for inclusion in this review.

RESULTS

No randomised or quasi-randomised controlled trials have looked at the effect of inhaled nebulized epinephrine on clinical outcomes in newborn infants being extubated.

DISCUSSION

As of September 2001 this review has found only two randomised controlled trials (Courtney 1987, Echevarria-Ybar 1986) in which inhaled nebulized racemic epinephrine was used immediately post-extubation in neonates.

Courtney et al (1987) compared nebulized racemic epinephrine with warm humidified gases in infants immediately after extubation. The primary study outcome was ventilatory function in the first hour post-extubation. The method of randomisation was not stated. 45 infants were randomised. Neither the investigators nor attending medical and nursing staff were blinded to the treatment.

Outcomes measured in this study were ventilatory function (pulmonary mechanics) measured up to one hour post-extubation, continuous respiratory and heart rate monitoring and continuous Holter monitoring of heart rate for arrhythmias (duration not stated).

There was a statistically significant - and clinically significant - difference in mean \pm SD weight at extubation between the treatment and control groups (treatment 1.43 kg \pm 0.36 versus control 1.81 \pm 0.69).

The authors found that, whilst there was a statistically significant difference in airway resistance between the groups in males, this difference was not of any physiological significance as all measurements were still within normal range for a preterm population. This difference was not shown in the females. The authors felt that there was no consistent pattern of overall treatment effect and concluded that racemic epinephrine is not indicated as a routine in the infant post-extubation.

Whilst an attempt was made to monitor for arrhythmias with Holter monitoring, this was only possible in 16 out of 44 infants. Six infants experienced abnormalities of brief duration (2 treatment and 4 control) and no conclusions could be drawn regarding the impact of epinephrine on this side effect.

One infant who had been randomised to the control group experienced respiratory distress and stridor immediately post-extubation. The infant was withdrawn from the study, racemic epinephrine was given and no further respiratory support was required. The authors state in their discussion that no other infants developed symptoms post-extubation within 24 hours of extubation. It is unclear whether or not these symptoms were being looked for prospectively and, if so, how monitoring was performed.

This study was excluded because it did not address clinically important outcomes: the need for additional respiratory support up to a week post-extubation, an increase in oxygen requirement, or the development of stridor or respiratory distress post-extubation. In addition there was no systematic evaluation of infants for possible adverse effects of racemic epinephrine. We wrote to the first author (SEC) to see if there were any unpublished data relevant to clinically important outcome measures (as stated in our selection criteria - 'types of outcome measures'). Unfortunately there were no additional data available.

Echevarria-Ybarguengoitia et al (1986) aimed to evaluate the effect of nebulized racemic epinephrine on the incidence of post-extubation atelectasis in infants weaned from ventilation and extubated.

Because this study randomised infants to nebulized epinephrine at the time of extubation, we considered it for inclusion in our review despite the fact that its aim was specifically to study other outcomes.

43 infants (32 preterm, 11 term) were randomised to a treatment group or a control group. The treatment group received nebulized racemic epinephrine twice pre-extubation and six times post-extubation at intervals of four hours. There was no placebo used in the control group. All patients were "monitored electronically for vital signs, looking for tachycardia".

Only two of the reported outcomes were relevant to our review. Tachycardia was looked for in all patients and in the results section the authors state that "none of the 20 neonates in the treatment group presented with any clinical signs of intoxication due to racemic epinephrine".

Figures are also quoted for the number of patients re-intubated due to post-extubation atelectasis: 6/23 in the control group and 5/20 in the treatment group. It is specifically stated in both the text and the tables that the infants were re-intubated due to post-extubation atelectasis. It is not clear whether there were any other infants who were re-intubated (or required any other form of respiratory support) for other reasons.

Because the exact number of infants needing to be re-intubated is unknown and no other relevant outcomes were given we have excluded this study from our review. We have written to the authors to see if there were any unpublished data relevant to clinically important outcome measures, but we have not received a reply.

Both the above studies failed to meet our inclusion criteria mainly because no clinically important outcome measures were looked for or completely reported. No unpublished data is available from either study. Therefore, neither study can help the clinician decide whether using inhaled nebulized racemic epinephrine, as routine treatment for infants being extubated, is an efficacious treatment in preventing morbidity post-extubation.

Whilst inhaled nebulized racemic epinephrine has a theoretical basis for decreasing any laryngeal and sub-glottic swelling present post-extubation, this does not translate to proven efficacy in neonatal intensive care. Two important questions remain unanswered. Firstly, does the routine use of inhaled nebulized racemic epinephrine post-extubation prevent failure of extubation? Secondly, does inhaled nebulized racemic epinephrine successfully treat post-extubation upper airway obstruction? In addition, if the answer to these questions is yes, then do the benefits outweigh any risks of administration?

Failure of extubation may result from a number of factors including alveolar atelectasis, decreased respiratory drive associated with prematurity, or inadequate pulmonary mechanics associated with a compliant chest wall. A further factor is the increased airway resistance associated with laryngeal and sub-glottic oedema. The

increased airway resistance alone may be enough to cause failure of extubation (this may be obvious in an infant with post-extubation respiratory distress and stridor) or may act in addition to other factors. The use of inhaled nebulized racemic epinephrine in the infant without any overt symptoms of upper airway obstruction may therefore decrease airway resistance sufficiently to allow successful extubation. This may be particularly important in the in VLBW infant where a very small decrease in internal diameter of the upper airway can result in large increases in resistance.

The use of inhaled nebulized racemic epinephrine is of proven efficacy in infective croup in older children. However, it remains unstudied in neonates with upper airway obstruction post-extubation.

Given the theoretical basis for using inhaled nebulized racemic epinephrine as routine treatment in neonates post-extubation and the fact that it is currently used routinely in some neonatal units, the next step should be a randomised controlled trial comparing inhaled nebulized racemic epinephrine with placebo. This should be looked at both as a routine treatment post-extubation and as specific treatment for post-extubation upper airway obstruction. Study populations should include the group of infants at highest risk for upper airway obstruction from mucosal swelling because of their small glottic and sub-glottic diameters (ie those infants with birthweights less than 1000 grams).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence either supporting or refuting the use of inhaled nebulized racemic epinephrine in newborn infants.

Implications for research

Randomised controlled trials are needed comparing inhaled nebulized racemic epinephrine with placebo in neonates post-extubation. This should be looked at both as a routine treatment post-extubation and as specific treatment for post-extubation upper airway obstruction. Study populations should include the group of

infants at highest risk for upper airway obstruction from mucosal swelling because of their small glottic and sub-glottic diameters (ie those infants with birthweights less than 1000 grams).

POTENTIAL CONFLICT OF INTEREST

None

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- No sources of support supplied

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- Dept of Paediatrics and Child Health, University of Queensland, Brisbane AUSTRALIA
- Cochrane Perinatal Team, Brisbane AUSTRALIA

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TABLES**Characteristics of excluded studies**

Study	Reason for exclusion
Courtney 1987	No clinically important outcomes (the need for additional respiratory support, an increase in oxygen requirement/respiratory distress, the occurrence of stridor or side effects of epinephrine post-extubation) are given.
Echevarria-Ybar 1986	Reporting of clinically relevant outcomes is incomplete.
Koren 1986	Not a RCT.
Marshall 1984	Not a RCT.

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS**Medical Subject Headings (MeSH)**

Administration, Inhalation; Epinephrine [*administration & dosage]; Infant, Newborn; *Intubation, Intratracheal; Nebulizers and Vaporizers; *Respiration, Artificial; Respiratory Insufficiency [therapy]; Vasoconstrictor Agents [*administration & dosage]; *Ventilator Weaning

MeSH check words

Humans

COVER SHEET

Title Nebulized racemic epinephrine for extubation of newborn infants

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Contribution of author(s)	Information not supplied by author
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What's New	This review updates the existing review of "Nebulized racemic epinephrine for extubation of newborn infants" which was published in the Cochrane Library, Issue 1, 2001 (Davies 2001). A new search for studies was performed on 30/09/2001 and no new studies were found to include in this review.
Date new studies sought but none found	30 September 2001
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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