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Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation (Review)

Henderson-Smart DJ, Davis PG

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Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation (Review)

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[Intervention Review]

Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation

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ABSTRACT

Background

When preterm infants have been given intermittent positive pressure ventilation (IPPV) for respiratory failure, weaning from support and tracheal extubation may be difficult. A significant contributing factor is thought to be the relatively poor respiratory effort and tendency to develop hypoventilation and apnea, particularly in very preterm infants. Doxapram stimulates breathing and appears to act via stimulation of both the peripheral chemoreceptors and the central nervous system. This effect might increase the chance of successful tracheal extubation.

Objectives

To determine the effect of doxapram on the use of intubation and IPPV and morbidity in preterm infants being weaned from IPPV and in whom endotracheal extubation is planned. In this regard, how does doxapram compare with standard treatment or with an alternative treatment such as methylxanthine or CPAP? Subgroup analyses were prespecified according to birth weight and/or gestational age, use of co-interventions (methylxanthines or nasal CPAP), and route of administration (intravenous or oral).

Search methods

The standard search strategy of the Neonatal Review Group as outlined in The Cochrane Library was used. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), Oxford Database of Perinatal Trials, MEDLINE, EMBASE and CINAHL up to May 2009.

Selection criteria

Eligible studies included published trials utilising random or quasi-random patient allocation in which preterm or low birth weight infants being weaned from IPPV were given doxapram compared with standard care or other treatments, to facilitate weaning from IPPV and endotracheal extubation. Trials were independently assessed by the review authors before inclusion.

Data collection and analysis

The standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. Each review author extracted data separately. The results were compared and any differences resolved. The data were synthesized using the standard method of Neonatal Review Group with use of relative risk and risk difference.

Main results

Two trials involving a total of 85 infants compared doxapram and placebo. In both the individual trials and the meta-analyses there were no significant differences between the doxapram and placebo groups in any of the outcomes (failed extubation, death before discharge, respiratory failure, duration of IPPV, side effects, oxygen at 28 days or oxygen at discharge). There was a trend towards an increase in side effects (hypertension or irritability leading to cessation of treatment) in the doxapram group [summary RR 3.21 (0.53, 19.43)]. In one of these two trials (Huon 1998) an 'alarming rise in blood pressure' occurred in five infants in the doxapram group and none of the controls, although in only one was treatment withdrawn. One additional trial involving only eight infants compared doxapram with aminophylline, but there were insufficient data for meaningful analysis.

Authors' conclusions

The evidence does not support the routine use of doxapram to assist endotracheal extubation in preterm infants who are eligible for methylxanthine and/or CPAP. The results should be interpreted with caution because the small number of infants studied does not allow reliable assessment of the benefits and harms of doxapram. Further trials are required to evaluate the benefits and harms of doxapram compared with no treatment or with other treatments, such as methylxanthines or CPAP, to evaluate whether it is more effective in infants not responding to these other treatments, and to assess whether the drug is effective when given orally.

PLAIN LANGUAGE SUMMARY

Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation

Doxapram has not been shown to improve outcomes for babies being weaned off mechanical breathing support. When preterm babies have been on mechanical breathing support in neonatal intensive care, it can be hard to wean them off the machine (tracheal extubation). Using drugs called methylxanthines, or breathing support via the nose (nasal CPAP - continuous positive airways pressure) can help. Doxapram stimulates breathing, and is another drug that is sometimes used around extubation. However, the review of trials found no evidence that doxapram can reduce problems for babies around extubation, and it may cause some adverse effects. Further research is needed.

BACKGROUND

Description of the condition

When preterm infants have been given intermittent positive pressure ventilation (IPPV) for respiratory failure, weaning from support and tracheal extubation may be difficult. A significant contributing factor is thought to be the relatively poor respiratory effort and tendency to develop hypoventilation and apnea, particularly in very preterm infants (reviewed by [Bancalari 1992](#); [Henderson-Smart 1995](#)).

Weaning from support may be prolonged or, if extubation is achieved, frequent episodes of apnea may occur in association with respiratory failure (hypercarbia, hypoxaemia and acidosis) of sufficient severity as to lead to re-intubation and the use of IPPV. As a consequence, the use of IPPV is prolonged with associated costs for higher dependency care and a potential for morbidity from the intervention. Systematic reviews have suggested that methylxanthines ([Henderson-Smart 2003](#)) and nasal continuous positive airways pressure (CPAP) ([Davis 2003](#)) may assist weaning from IPPV and endotracheal extubation.

Description of the intervention

Doxapram hydrochloride is a respiratory stimulant (an analeptic agent). It can be administered either intravenously (IV) or orally, although in intubated infants, IV would be most likely.

How the intervention might work

Doxapram stimulates breathing and appears to act via stimulation of both the peripheral chemoreceptors and the central nervous system ([Blanchard 1992](#); [Barrington 1986](#)). This effect might increase the chance of successful tracheal extubation on its own or in combination with other treatments, such as methylxanthines or CPAP. Short term side effects (reviewed by [Blanchard 1992](#)) such as hypertension, excessive central nervous system stimulation, gastrointestinal disturbances with oral use ([Tay-Uyboco 1991](#)) and heart block ([De Villiers 1998](#)) have been reported.

Why it is important to do this review

This updates the review "Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation" published in The Cochrane Library, Issue 2, 2006 ([Henderson-Smart 2006](#)).

OBJECTIVES

To determine the effect of doxapram on the use of intubation and IPPV and morbidity in preterm infants being weaned from IPPV and in whom endotracheal extubation is planned. In this regard, how does doxapram compare with standard treatment or with an alternative treatment such as methylxanthine or CPAP?

Prespecified subgroup analyses:

1. Birth weight (greater or less than about 1 kg) and/or gestational age (greater or less than about 28 weeks) subgroups, as the baseline failure rate is likely to be higher in infants born at lower weights and gestational ages
2. Routine use, or not, of co-interventions (methylxanthines or nasal CPAP) as this would lower the baseline rate of failure

3. Administration route (intravenous or oral) as drug levels achieved and side effects may be different

METHODS

Criteria for considering studies for this review

Types of studies

All published trials utilising random or quasi-random patient allocation.

Types of participants

Preterm or low birth weight infants being weaned from IPPV and in whom endotracheal extubation is planned.

Types of interventions

Doxapram compared with control (placebo or no treatment), and doxapram compared with an alternative treatment.

Types of outcome measures

Primary outcomes

Failed extubation (unable to wean from IPPV and extubate, or re-intubation for IPPV) within about one week.

Secondary outcomes

1. Death before discharge
2. Duration of IPPV
3. Side effects leading to cessation of therapy (tachycardia, agitation, seizures, hypertension or feed intolerance)
4. Chronic lung disease (oxygen requirement at about 28 days and at about 36 weeks postmenstrual age)
5. Reduced somatic growth (weight, length and head circumference) and delayed neurodevelopment (more than 2 SDs below the mean on a standard developmental assessment, or abnormal neurological signs) during infancy and childhood

Search methods for identification of studies

Electronic searches

The standard search strategy of the Neonatal Review Group as outlined in The Cochrane Library was used. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2009), MEDLINE (1966 - May 2009), CINAHL (1982 - May 2009) and EMBASE (1988 - May 2009). The text term 'doxapram' and MeSH term 'infant, premature' were used in these searches.

Searching other resources

Also searched were previous reviews including cross references, and abstracts published in the program issues of the Society for Pediatric Research 1996 - 2009 and the European Society for Pediatric Research, 1995 - 2005. Expert informants were also consulted.

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

Data collection and analysis

The standard method of the Cochrane Neonatal Review Group were employed.

Selection of studies

The title and abstract of each retrieved report was examined to assess eligibility. If there was uncertainty, the full paper was examined. All randomised and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section were included.

Data extraction and management

Each review author extracted data separately. The results were compared and any differences resolved.

Assessment of risk of bias in included studies

The methodological quality of the studies were assessed using the following key criteria: allocation concealment (blinding of randomizations), blinding of intervention, completeness of follow-up, and blinding of outcome measurement/assessment. For each criteria, assessment was yes, no, can't tell. All three review authors separately assessed each study. Any disagreement was resolved by discussion.

In addition, the Risk of Bias table was completed.

Measures of treatment effect

Statistical analyses was performed using Review Manager software. Categorical data was analyzed using relative risk (RR), risk difference (RD) and the number needed to treat (NNT). Continuous data was analyzed using weighted mean difference (WMD). The 95% Confidence interval (CI) was reported on all estimates.

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using *post hoc* sub group analyses.

Data synthesis

The data were synthesized using the standard method of Neonatal Review Group using Review Manager software (RevMan 5), supplied by the Cochrane Collaboration. This included estimates of typical relative risk and risk difference using the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. All meta-analyses were to be done using the fixed effect model.

Subgroup analysis and investigation of heterogeneity

Prespecified subgroup analyses:

1. Birth weight (greater or less than about 1kg) and/or gestational age (greater or less than about 28 weeks) subgroups, as the baseline failure rate is likely to be higher in infants born at lower weights and gestational ages
2. Routine use, or not, of co-interventions (methylxanthines or nasal CPAP) as this would lower the baseline rate of failure

3. Administration route (intravenous or oral) as drug levels achieved and side effects may be different

RESULTS

Description of studies

Doxapram vs standard treatment

Two eligible trials were found. [Barrington 1998](#) enrolled 56 preterm infants less than three weeks of age with birth weights less than 1251 g and gestational age less than 30 (mean 25 - 26) weeks, while [Huon 1998](#) enrolled 29 preterm infants less than six days of age with birth weights less than 1250 g and gestational age less than 34 (mean 29 - 30) weeks. Treatment groups were well matched at entry in the [Barrington 1998](#) trial. In [Huon 1998](#) the doxapram group had a significantly lower birth weight and more male infants, and showed clinically important trends to higher gestational age and more small for gestational age infants.

[Barrington 1998](#) used a loading dose of 3.5 mg/kg followed by 1 mg/kg/hr, whereas [Huon 1998](#) had no loading dose of doxapram and the initial infusion rate was lower at 0.5 mg/kg/hr, with option of doubling if there was failure to respond. Both trials enrolled infants being weaned from IPPV although the amount of ventilatory support in [Barrington 1998](#) was greater (FiO₂ < 0.4, rate < 30, peak inspiratory pressure < 26 cms H₂O) than in [Huon 1998](#) (FiO₂ < 0.26, rate < 16, peak inspiratory pressure < 10 cms H₂O).

[Barrington 1998](#) loaded infants with IV aminophylline during weaning of IPPV; then, one and a half days later on average, each infant was extubated to nasal CPAP for 72 hours. [Huon 1998](#) loaded infants with caffeine eight hours prior to attempted extubation, after which CPAP was allowed if there was deterioration in respiratory function.

Doxapram vs. an alternative treatment

One small pilot study of doxapram vs. aminophylline in eight infants was found ([Eyal 1985](#)).

One study comparing doxapram vs. theophylline was found in abstract form ([Carrizales 1990](#)) and is awaiting further assessment pending more information from an author.

Risk of bias in included studies

Both trials evaluating doxapram vs. control are of high quality in terms of blinding of randomization, intervention and outcome assessment, as well as completeness of follow-up. The one small trial comparing doxapram with aminophylline is of insufficient size for meaningful analysis.

Effects of interventions

Doxapram vs. standard care (Comparison 1):

In both the individual trials and the meta-analyses there were no significant differences between the doxapram and placebo groups in any of the outcomes [failed extubation, death before discharge, side effects, oxygen at 28 days or oxygen at discharge (Outcomes 1.1, 1.2, 1.4, 1.5, 1.6)]. The data on 'failed extubation' (unable to extubate or reintubated within about one week) from [Barrington 1998](#) were confounded by the use of open label doxapram in four control infants with severe apnea after extubation and so could not

be used. There was no difference in the duration of IPPV between the doxapram and placebo groups in either trial or in the meta-analysis (Outcome 1.3).

There was a trend towards an increase in side effects (hypertension or irritability leading to cessation of treatment) in the doxapram group [summary RR 3.21 (0.53, 19.43)] (Outcome 1.4). In [Huon 1998](#) an 'alarming rise in blood pressure' occurred in five infants in the doxapram group and none of the controls, although in only one was treatment withdrawn.

Respiratory failure without the use of reintubation was not a prespecified outcome. [Barrington 1998](#) reported that apnea was a cause of failure in fewer of the doxapram (4/12) compared with the placebo group (12/14). [Huon 1998](#) also noted more apnea in the placebo group but this was only so for moderate apnea (> 10 sec. with bradycardia < 80 bpm for < 30 secs) and not for severe apnea (bradycardia > 30 sec).

There were no trial data as to the effect of doxapram without use of methylxanthine and/or CPAP, so the prespecified subgroup analysis of trials by use, or not, of co-interventions was not possible. Subgroup analyses by birth weight, gestational age or route of administration could not be carried out as the required data were not reported. No study reported later growth or development in the infants.

Doxapram vs. aminophylline (Comparison 2):

In the only trial ([Eyal 1985](#)), six infants were randomised to doxapram and four failed extubation, while two received aminophylline and both failed to be extubated.

DISCUSSION

Doxapram vs. standard care

Both the trials eligible for this review used doxapram as an addition to standard measures [methylxanthines ([Henderson-Smart 2003](#)) and nasal CPAP ([Davis 2003](#))] known to assist endotracheal extubation in preterm infants. In this setting doxapram did not appear to provide additional assistance. Observational studies suggest that doxapram could be useful in preterm infants who cannot be extubated despite standard treatments such as methylxanthines and CPAP ([Barrington 1986](#)). This has not been examined in a randomised controlled trial.

The [Huon 1998](#) trial was stopped because the baseline rate of failed extubation in the control group was much lower than the rate prior to commencing the trials. They attribute this to the introduction of a standard protocol for endotracheal extubation.

The trend towards increased side effects including hypertension is consistent with observational studies ([Blanchard 1992](#)). The [Huon 1998](#) trial emphasized this and reported higher blood levels despite lower dosage when doxapram was given in the first few days of life.

Doxapram vs. aminophylline

There are insufficient data available for any conclusions to be made.

One additional study ([Carrizales 1990](#)), reported in abstract form, is awaiting assessment. It compared doxapram and theophylline and it reported that twelve infants were randomised to doxapram and two failed extubation (undefined), while thirteen infants were randomised to theophylline and five failed extubation. This study requires author clarification which is being sought.

One observational study has suggested an association between the total dose and duration of doxapram treatment and isolated mental developmental delay in infants weighing less than 1250 grams at birth ([Sreenan 2001](#)). As discussed by the authors, they could not control for the severity of apnea, which has also been associated with poor neurodevelopmental outcome ([Cheung 1999](#)).

Another suggested source of toxicity is benzyl alcohol used in the intravenous preparation of doxapram in the USA. It has been pointed out that the [Sreenan 2001](#) observations were made in Canada where doxapram does not contain benzyl alcohol ([Finer 2002](#)).

This information suggests that new trials need to evaluate neurological development.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence does not support the routine use of doxapram to assist endotracheal extubation in preterm infants who are eligible to receive methylxanthine and/or CPAP. There are no data on the effects of doxapram vs. control in the absence of use of methylxanthine or CPAP. The results should be interpreted with caution because the small number of infants studied does not allow reliable assessment of the benefits and harms of doxapram.

Implications for research

Further trials are required to evaluate the benefits and harms of doxapram compared with no treatment or with other treatments such as methylxanthines or CPAP. Trials could also evaluate whether it is effective in infants not responding to these other treatments. Doxapram would be a more useful drug if it were effective when given orally although no randomised controlled trials have evaluated its use by this route.

Any future trials should include important outcomes including long term growth and development.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Barrington 1998

Methods	Blinding of randomizations - yes; blinding of intervention - yes; complete follow up - yes; blinding of outcome assessment - yes.
Participants	56 infants (27 treatment and 29 control) weight <1251 g and gestation <30 weeks at birth; less than 3 weeks old and in FiO ₂ <0.4 and ventilator rate < 30 and peak insp. pressure < 26 cms H ₂ O. Exclusion criteria not given.
Interventions	IV doxapram 3.5 mg/kg over 20 mins, then infusion of 1 mg/kg/hr. Placebo was saline.
Outcomes	Death before discharge; Failed extubation - not extubated or reintubation within 3 days Respiratory failure; apnoea > 3 in 12 hrs or PaCO ₂ > 60 mm Hg or FiO ₂ >80 to keep PaO ₂ >60; side effects; oxygen therapy at discharge.
Notes	All extubated to nasal prong CPAP (6 cms H ₂ O) for 72 hrs when vent rate 6 for 12 hrs and FiO ₂ < 0.45; all given aminopylline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of randomizations - yes Blinding of intervention - yes Blinding of outcome assessment - yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up - yes
Selective reporting (reporting bias)	High risk	One infant in the control group was accidentally given doxapram and included in the control analysis and publication because it was in the intention group due to randomization. A re-analysis with it in the doxapram group made no difference to the results.
Other bias	Low risk	

Eyal 1985

Methods	Randomization not mentioned - double blind, numerically coded drugs - by pharmacy; blinding of treatment - yes; completeness of follow-up - yes; blinding of outcome assessment - yes.
Participants	8 preterm infants (6 treatment and 2 control) recovering from RDS, unable to wean ventilator rate over 24 hrs. Mean gestational age 30 weeks, birthweight 1215 g.
Interventions	Doxapram 2.5 mg/kg/hr vs aminophylline 6 mg/kg load and 1.5 mg/kg/8hr IV.

Eyal 1985 (Continued)

Each given for 48 hrs.

Outcomes	Failed to wean from ventilation, failed to extubate.
Notes	Infants who failed were given the alternative treatment after 48 hrs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Randomization not mentioned - double blind, numerically coded drugs - by pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated blinding of initial treatment but not of blinding later outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completeness of follow-up - yes.
Other bias	High risk	The trial had very small numbers. Failing in the assigned group led to change over to the alternative treatment. This included one in doxapram group and three in the aminophylline group.

Huon 1998

Methods	Blinding of randomization - yes; blinding of intervention - yes; complete followup - yes; blinding of outcome assessment - yes.
Participants	29 infants who required mechanical ventilation up to 21 days (14 treatment and 15 control) weight < 1250 grams and gestational age < 34 weeks at birth; and < 6 days old; and on IPPV but never needed more than FiO2 0.3; at entry FiO2 < 0.25, IMV < 16, PIP < 10, normal chest xray. Excluded - congenital abnormality, severe brain lesion (IVH > grade 2, white matter densities), PDA with L to R shunt, uncontrolled infection or metabolic disorder.
Interventions	Doxapram IV 0.5 mg/kg/hr, dose could be doubled if no response. Placebo was normal saline.
Outcomes	Death before discharge; failed extubation (could not be extubated or reintubated within 5 days); side effects; oxygen therapy at 28 days; apnea; IVH or PVL; infection; NEC; ROP;
Notes	All infants given caffeine citrate (20 mg/kg load and 5 mg/kg/ day). Nasal CPAP could be used (number not given). Extubation was carried out 8 hrs after starting doxapram / placebo if possible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Randomization mentioned but details not given.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of randomization, treatment and outcome assessment.

Huon 1998 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up - yes.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

CPAP = continuous positive airways pressure; IPPV = intermittent positive pressure ventilation; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia; NEC = necrotizing enterocolitis; ROP = retinopathy of prematurity.

Characteristics of studies awaiting assessment [ordered by study ID]

Carrizales 1990

Methods	Randomized - method unknown. Blinding of treatment - unknown. Completeness of follow up - unknown. Blinding of outcome assessment - unknown.
Participants	25 very low birth weight infants (700 - 1500 grams), mean age 61 +/- 58 hrs. Ready to wean from mechanical ventilation (inspired oxygen < or equal to 30%, mean airway pressure 10 -15 cms H ₂ O, positive inspiratory pressure < or equal to 18 cms H ₂ O). 12 infants in the doxapram group and 13 in the theophylline group.
Interventions	Doxapram incremental doses of 0.5 to 2.5 mg/kg/hr IV Theophylline loading dose of 6 mg/kg and maintenance dose of 2 mg/kg/8 hrs IV.
Outcomes	Failed extubation during 7 day trial period. Side effects - hypertension, seizures, tachycardia or intracranial hemorrhage.
Notes	Only published as abstract.

DATA AND ANALYSES
Comparison 1. Doxapram vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed extubation	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.22, 2.97]
2 Death before discharge	2	85	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.34, 6.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Days of IPPV	2	85	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-2.85, 2.13]
4 Side effects causing cessation of therapy	2	85	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.53, 19.43]
5 Oxygen at 28 days	1	29	Risk Ratio (M-H, Fixed, 95% CI)	3.2 [0.14, 72.62]
6 Oxygen at discharge in survivors	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.39, 1.99]

Analysis 1.1. Comparison 1 Doxapram vs control, Outcome 1 Failed extubation.

Analysis 1.2. Comparison 1 Doxapram vs control, Outcome 2 Death before discharge.

Analysis 1.3. Comparison 1 Doxapram vs control, Outcome 3 Days of IPPV.

Analysis 1.4. Comparison 1 Doxapram vs control, Outcome 4 Side effects causing cessation of therapy.

Analysis 1.5. Comparison 1 Doxapram vs control, Outcome 5 Oxygen at 28 days.

Analysis 1.6. Comparison 1 Doxapram vs control, Outcome 6 Oxygen at discharge in survivors.

WHAT'S NEW

Date	Event	Description
25 February 2013	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 3, 2000

Date	Event	Description
18 April 2012	Amended	Contact person changed.
7 December 2010	Amended	Contact details updated.
8 June 2009	New search has been performed	<p>This updates the review "Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation" published in the Cochrane Database of Systematic Reviews, Issue 2, 2006 (Henderson-Smart 2006).</p> <p>The search was updated in May 2009.</p> <p>No new trials were identified for inclusion.</p> <p>Updated information has been added to Carrizales 1990, Studies awaiting classification.</p>
27 April 2009	New search has been performed	Converted to new review format.
16 January 2006	New search has been performed	<p>This review updates the existing review 'Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation', published in The Cochrane Library, Disk Issue 3, 2000. The search strategy has been updated to include the CINAHL database.</p> <p>One abstract was found and has been added to the studies awaiting assessment.</p> <p>The conclusions of this review are unchanged.</p>
23 May 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Each review author independently evaluated the trials for quality and extracted the data.

DHS double entered the data and wrote the text of the review.

DHS has updated the review with assistance from co-author Peter Davis.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.
- Royal Prince Alfred Hospital, Sydney, Australia.
- Royal Women's Hospital, Melbourne, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Premature; Doxapram [adverse effects] [*therapeutic use]; Intermittent Positive-Pressure Ventilation; Intubation, Intratracheal; Randomized Controlled Trials as Topic; Respiratory System Agents [adverse effects] [*therapeutic use]; Ventilator Weaning [*methods] [mortality]

MeSH check words

Humans; Infant, Newborn