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Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants (Review)

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Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants.
Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD002061.
DOI: 10.1002/14651858.CD002061.

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[Intervention Review]

Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants

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Editorial group: Cochrane Neonatal Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Woodgate PG, Davies MW. Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD002061. DOI: 10.1002/14651858.CD002061.

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ABSTRACT

Background

Experimental animal data and uncontrolled, observational studies in human infants have suggested that hyperventilation and hypocapnia may be associated with increased pulmonary and neurodevelopmental morbidity. Protective ventilatory strategies allowing higher levels of arterial CO2 (permissive hypercapnia) are now widely used in adult critical care. The aggressive pursuit of normocapnia in ventilated newborn infants may contribute to the already present burden of lung disease. However, the safe or ideal range for PCO2 in this vulnerable population has not been established.

Objectives

To assess whether, in mechanically ventilated neonates, a strategy of permissive hypercapnia improves short and long term outcomes (esp. mortality, duration of respiratory support, incidence of chronic lung disease and neurodevelopmental outcome).

Search methods

Standard strategies of the Cochrane Neonatal Review Group were used. Searches were made of the Oxford Database of Perinatal Trials, MEDLINE, CINAHL, and Current Contents. Searches were also made of previous reviews including cross-referencing, abstracts, and conference and symposia proceedings published in Pediatric Research.

Selection criteria

All randomised controlled trials in which a strategy of permissive hypercapnia was compared with conventional strategies aimed at achieving normocapnia (or lower levels of hypercapnia) in newborn infants who are mechanically ventilated were eligible.

Data collection and analysis

Standard methods of the Cochrane Neonatal Review Group were used. Trials identified by the search strategy were independently reviewed by each author and assessed for eligibility and trial quality. Data were extracted separately. Differences were compared and resolved. Additional information was requested from trial authors. Only published data were available for review. Results are expressed as relative risk and risk difference for dichotomous outcomes, and weighted mean difference for continuous variables.

Main results

Two trials involving 269 newborn infants were included. Meta-analysis of combined data was possible for three outcomes. There was no evidence that permissive hypercapnia reduced the incidence of death or chronic lung disease at 36 weeks (RR 0.94, 95% CI 0.78, 1.15), intraventricular haemorrhage grade 3 or 4 (RR 0.84, 95% CI 0.54, 1.31) or periventricular leukomalacia (RR 1.02, 95% CI 0.49, 2.12). There

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were no differences in any other reported outcomes when the strategy of permissive hypercapnia/minimal ventilation was compared to routine ventilation in newborn infants. Long term neurodevelopmental outcomes were not reported. One trial reported that permissive hypercapnia reduced the incidence of chronic lung disease in the 501 to 750 gram subgroup.

Authors' conclusions

This review does not demonstrate any significant overall benefit of a permissive hypercapnia/minimal ventilation strategy compared to a routine ventilation strategy. At present, therefore, these ventilation strategies cannot be recommended to reduce mortality, or pulmonary and neurodevelopmental morbidity. Ventilatory strategies which target high levels of PCO2 (> 55 mmHg) should only be undertaken in the context of well-designed controlled clinical trials. These trials should aim to establish the safe, or ideal, range for CO2 in ventilated newborns, and examine the role of protective ventilatory techniques in achieving this target.

PLAIN LANGUAGE SUMMARY

Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants

Not enough evidence to show the effect of permissive hypercapnia compared to routine ventilation for preterm babies needing mechanical ventilation. Sometimes preterm babies need help from a machine to breathe (mechanical ventilation). Very low carbon dioxide levels, produced by mechanical ventilation of the lungs are thought to cause lung damage and developmental problems. Hypercapnia (increasing the levels of carbon dioxide in the blood) is used for adults in critical care. It may also help newborn babies, especially those with lung damage on mechanical ventilation. The review of trials found there was not enough evidence to show the effect of permissive hypercania compared to routine ventilation for preterm babies. More research is needed.

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BACKGROUND

More than thirty years have passed since Northway et al reported the severe chronic lung disease of preterm infants they described as bronchopulmonary dysplasia (BPD) (Northway 1967). They considered the inspiration of high concentrations of oxygen (O2) to be the most likely cause. The aetiologic contribution of positive pressure ventilation producing barotrauma has also been recognised for more than twenty years (Moylan 1978). Other factors such as air leak, pulmonary oedema and patent ductus arteriosus, in addition to immaturity, are also thought to play a role in the pathogenesis of BPD (Yu 1983). It has recently been suggested that excessive variation in lung volume, described as volutrauma, during mechanical ventilation, is the cause of the acute lung injury which predisposes to BPD (Dreyfuss 1993).

Following a report by Avery et al (Avery 1987) which highlighted the variance in rates of BPD among neonatal centres, attention was refocussed upon differences in methods of treating acute respiratory disorders in the preterm infant. They postulated that the risk of BPD may be lowered if barotrauma is reduced by the early use of nasal continuous positive airway pressure (CPAP), and by accepting an arterial carbon dioxide level (PaCO2) above the physiologic range. This was the first suggestion that the incidence of BPD might be associated with low PaCO2 levels during the acute management of neonatal respiratory disease. To test this hypothesis, a multicentre historical-cohort analysis of 235 infants with birth weights of 751 to 1000 grams was undertaken by Kraybill et al (Kraybill 1989). In this study population, a PaCO2 of less than 40 mm Hg at 48 or 96 hours of life was the best predictor of BPD. Furthermore, among the 10 participating neonatal centres, the mean PaCO2 in those infants receiving mechanical ventilation at 48 and 96 hours strongly correlated with BPD rates. Garland et al (Garland 1995) performed a retrospective cohort study to determine to what extent the risk of BPD is affected by ventilatory management before the first dose of surfactant. They also found a significant association between low PaCO2 levels prior to the first dose of surfactant and the subsequent development of BPD. In those infants whose lowest PaCO2 level was 29 mm Hg or less, the odds for BPD were 5.6 times those of infants whose lowest PaCO2 level was 40 mm Hg or more. The association of early hypocapnia and BPD was also present in those infants believed to have less severe lung disease. They concluded that the ventilatory strategies used to achieve lower PaCO2 levels produced the volutrauma which contributed to the development of BPD.

The association between hypocapnia in preterm infants and neurodevelopmental status has also been examined. Graziani et al (Graziani 1992) used logistic regression analysis to examine the relationships of perinatal factors, such as mechanical ventilation and hypocapnia, to the subsequent occurrence of neurodevelopmental and neurosonographic abnormalities. This analysis revealed that in the mechanically ventilated infants, extremely low PaCO2 levels (less than 17 mm Hg) during the first three days of life were associated with a significantly increased risk of moderate to severe periventricular echodensity, large periventricular cysts, grade III/IV intracranial haemorrhage, and cerebral palsy. A lowest PaCO2 of greater than 20 mm Hg was not associated with an increased risk of adverse outcomes. All blood gas measurements beyond the third day of life were unrelated to any neurosonographic or neurodevelopmental abnormalities. Further analysis comparing the infants with and without severe hypocapnia did not reveal any clinical factors related to the mechanical ventilation or severity of the respiratory distress that could further define the relationship between lowest PaCO2 and outcome. A similar relationship was described by Fujimoto et al (Fujimoto 1994) who prospectively studied very low birth weight infants whose gestational age was less than 35 weeks. In this population, perinatal complications such as antepartum haemorrhage or severe perinatal asphyxia accounted for less than half of the infants with cystic periventricular leukomalacia (PVL). In the absence of such perinatal complications, there was a strong correlation between severe hypocapnia (PaCO2 less than 20 mm Hg) and cystic PVL. The duration as well as the severity of hypocapnia has also been associated with adverse neurodevelopmental outcome. Calvert et al (Calvert 1987) retrospectively compared preterm infants with cystic PVL with matched controls. They found that infants with cystic PVL had both lower mean PaCO2 levels and longer periods with PaCO2 levels less than 25 mm Hg.

The relationship between neurodevelopmental risk and hypocapnia resulting from treatment with high frequency jet ventilation (HFJV) has recently been reported by Wiswell et al (Wiswell 1996a). They prospectively evaluated premature infants undergoing HFJV with serial neurosonograms, and assessed the cumulative effects of hypotension, acidosis, hypoxaemia and hypocarbia. Using logistic regression analysis, they found that infants with cystic PVL were more likely to have cumulative hypocapnia below a threshold level of 25 mm Hg during the first day of life. However, in a prospective, randomised, controlled trial performed by the same investigators in which HFJV was compared to conventional ventilation in preterm infants with respiratory distress syndrome (Wiswell 1996b), hypocapnia was not found to independently predict an adverse outcome. In this study, treatment with HFJV significantly increased the risk of developing cystic PVL.

In response to the growing concern regarding the association between hypocapnia and increased pulmonary and neurodevelopmental morbidity, the practice of allowing higher PaCO2 levels has developed. The intentional hypoventilation which allows, or specifically targets, high PaCO2 levels is known as permissive hypercapnia (Dries 1995). In this approach, the sometimes aggressive pursuit of normal arterial blood gases, with the subsequent increase in lung injury and possible other neurological morbidities, is avoided, but balanced against the less well known effects of hypercapnia and acidosis. The use of permissive hypercapnic ventilation is becoming widespread in adult critical care (Dries 1995). The effects of hypercapnia on physiological systems, particularly in animal models, have been well summarised (Feihl 1994), and most undesired physiologic effects of moderate respiratory acidosis (PaCO2 <= 80 mm Hg, arterial pH >= 7.15) are thought to be reversible. Two detailed reviews of permissive hypercapnia in acute respiratory failure in adults concluded that experimental and uncontrolled clinical evidence suggests an overall benefit, but there was disagreement as to whether the evidence is convincing enough to warrant its introduction into clinical practice (Tuxen 1994, Bidani 1994). Both did, however, highlight the requirement for randomised, controlled trials.

In early 1998, two randomised trials in adults were simultaneously reported. Amato et al (Amato 1998) compared a strategy of protective ventilation, which involved limitations on both

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positive end-expiratory pressure and tidal volumes, permissive hypercapnia and the preferential use of pressure-limited ventilatory modes, to conventional ventilation. In the group randomised to the protective strategy, there was improved survival at 28 days and a lower rate of barotrauma. However, protective ventilation was not associated with a higher rate of survival to hospital discharge. A similar but smaller trial by Stewart et al (Stewart 1998) reported that there was no difference in mortality, incidence of barotrauma or multiple organ dysfunction and organ failure in patients randomised to either pressure- and volume limited ventilation with permissive hypercapnia or conventional ventilation. More recently, a large randomised, multicentre trial comparing ventilation with lower tidal volumes compared to traditional tidal volumes for acute lung injury and acute respiratory distress syndrome (ARDS) in adults was reported (ARDS Network 2000). In this trial which targeted specific tidal volumes rather than PaCO2 or pH ranges, there were significant reductions in mortality and number of days without ventilator use in the group treated with lower tidal volumes. The results of this well-conducted study suggest that a ventilation strategy designed to protect the lungs from excessive stretch improve important clinical outcomes in patients with acute lung injury and ARDS.

In the management of persistent pulmonary hypertension of the newborn (PPHN), a condition complicating sepsis or meconium aspiration syndrome or occurring in an idiopathic form in term and near-term infants, hyperventilation may be employed to decrease pulmonary arterial pressure. To achieve a significant effect with a resultant increase in oxygenation, it may be necessary to lower the PaCO2 to levels below 20 mm Hg and to increase the pH to above 7.60 (Drummond 1981), although the response may be more directly related to the increase in pH rather than the decrease in PaCO2. However, hypocapnia resulting from the hyperventilation in PPHN management has been shown to be associated with an increased risk for sensorineural hearing loss (Hendricks-Munoz 1988) and low psychomotor developmental test scores (Ferrara 1984). In order to avoid hyperventilation, Wung et al (Wung 1985) described a technique of "gentle ventilation" in infants with PPHN, aiming for PaCO2 levels up to 60 mm Hg. Although they claimed success in all 15 patients, this study is uncontrolled and long term neurodevelopmental outcome was not reported.

At present, experimental animal and uncontrolled clinical evidence suggests that hyperventilation and hypocapnia may be associated with increased pulmonary and neurodevelopmental morbidity. However, a causal relationship has not been established. On the other hand, the safety of hypercapnic ventilatory strategies in the newborn has also not been established. It remains unknown whether it is better to avoid hyperventilation and hypocapnia, aim for normal PaCO2 levels, or to specifically target higher PaCO2 levels. The "safe" or ideal range for PaCO2 is yet to be determined. If such a range does exist, it may not be the same for all neonates but may vary according to birthweight and/or gestational age. Furthermore, there may be variation in effect dependent upon the ventilatory strategy, eg HFOV versus CMV. This can only be established by large randomised controlled clinical trials which examine clinically important short term benefits as well as long term neurodevelopmental outcomes.

OBJECTIVES

The primary objective is to assess whether, in mechanically ventilated neonates, a strategy of permissive hypercapnia improves short and long term outcomes (esp. mortality, duration of respiratory support, incidence of chronic lung disease and neurodevelopmental outcome).

A secondary objective is to assess whether a strategy of permissive hypercapnia is associated with significant side effects.

Sub-group analyses are planned to determine whether the results differ by:

Population:
i. gestational age
ii. birthweight

Intervention:
i. type of ventilation - intermittent positive pressure ventilation (IPPV) volume or pressure controlled or high frequency ventilation (HFV)
ii. target PaCO2 or pH for permissive hypercapnia - eg. 45-55 mmHg, 55-65 mmHg, >65 mmHg

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials in which a strategy of permissive hypercapnia (target PaCO2 > 45 mm Hg) was compared with conventional strategies aimed at achieving normocarbia (or lower levels of hypercapnia) in newborn infants who are mechanically ventilated.

Types of participants

Newborn infants who are mechanically ventilated.

Types of interventions

A mechanical ventilation strategy which allows for a target arterial carbon dioxide tension (PaCO2) greater than the normal range (PaCO2 of 35 to 45 mmHg) or greater than a specified lower range of PaCO2.

A mechanical ventilation strategy which allows for a target arterial pH less than the normal range (pH 7.35 to 7.45) or less than a specified higher range of pH.

Types of outcome measures

- Mortality (neonatal, before discharge)
- Air leak
- Intraventricular haemorrhage (any, grade 3-4)
- Periventricular leukomalacia
- Duration of mechanical ventilation (IPPV)
- Duration of respiratory support (IPPV or CDAP)
- Duration of oxygen therapy
- Duration of hospital stay
- Retinopathy of prematurity (any, stage 2 or greater)

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- Bronchopulmonary dysplasia/Chronic lung disease (28 days, 36 weeks PMA)
- Neurodevelopmental outcome

Immediate adverse effects such as altered haemodynamics or cerebral blood flow, and oxygenation.

Search methods for identification of studies

Using MeSH search terms 'hypercapnia' and 'exp infant, newborn' searches were made of MEDLINE back to 1966, CINAHL back to 1982, Current Contents back to 1998, the Oxford Database of Perinatal Trials. Also searched were previous reviews including cross references, abstracts, and conference and symposia proceedings published in Pediatric Research.

Data collection and analysis

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. The two reviewers worked independently to search for and assess trials for inclusion and methodological quality. Studies were assessed using the following key criteria: blindness of randomisation, blindness of intervention, completeness of follow up and blinding of outcome measurement. Data were extracted independently by the reviewers. Differences were resolved by discussion and consensus of the reviewers. Where necessary, investigators were contacted for additional information or data.

Weighted mean differences (WMD) are reported for continuous variables such as duration of oxygen therapy. For categorical outcomes such as mortality, the relative risks (RR) are reported. For significant findings, the risk difference (RD) and number need to treat (NNT) are also reported. The fixed effects model has been used for this review.

RESULTS

Description of studies

The search strategy for identification of studies identified two studies (Carlo 1999, Mariani 1999) which met the inclusion criteria. Details of the participants, interventions and outcomes in each trial are provided in the table Characteristics of included studies. One study (Carlo 1999) has been published in abstract from only. Further data has been requested from authors of both studies but at present only published data is available for review.

Ventilatory Strategy
The definition of permissive hypercapnia, and therefore the ventilatory strategy employed to achieve the targets, differed slightly between the two studies. One study (Mariani 1999) aimed to maintain PaCO2 between 45 and 55 mmHg, and pH > 7.20 in the intervention (permissive hypercapnia) group, whilst the goal in the control (normocapnia) group was to maintain PaCO2 between 35 and 45 mmHg and PaCO2 > 7.25. These goals were used for the first 96 hours following randomisation, after which time higher levels of PaCO2 were also allowed in the control group with the ventilatory changes directed at the pH criteria. Changes in the ventilator settings were made according to a modified clinical algorithm. The data from 49 randomised infants are available for analysis.

The other included study (Carlo 1999) aimed for a target PaCO2 > 52 mmHg in the intervention group (minimal ventilation) and PaCO2 < 48 mmHg in the control group (routine ventilation). These ventilatory strategies were maintained for 10 days, using a mechanical ventilation protocol. This study was a component of a 2 X 2 factorial design, multicentre, randomised controlled trial of the two ventilatory strategies and early postnatal steroids versus placebo in the first 10 days of life. This trial was terminated early due to unanticipated side effects of steroids. The data from 220 randomised infants are available for analysis.

Outcomes
Both studies reported respiratory and non-respiratory outcomes. One study (Carlo 1999) reported chronic lung disease (CLD) using the definition of O2 dependency at 36 weeks postmenstrual age, and reported pulmonary interstitial emphysema (PIE) and pneumothorax separately. The other study (Mariani 1999) reported bronchopulmonary dysplasia (BPD) using the definition of oxygen requirement and abnormal chest radiograph on day 28, and pneumothorax and/or PIE were combined and reported as air leak. Both studies reported intraventricular haemorrhage (IVH) grade 3-4, and periventricular leukomalacia (PVL). Neither study reported neurodevelopmental outcomes.

Additional data
Contact has been made with authors of both included studies and additional data has been requested but not yet received. Thus, this review includes published data only.

Risk of bias in included studies

In both studies, allocation to treatment group was randomly assigned. One study (Mariani 1999) used a block randomisation procedure with group assignments sealed within opaque envelopes. The method of randomisation was not described in the abstract which reported the other study (Carlo 1999). Due to the nature of the intervention, blinding of the investigators and clinicians to the intervention group was not possible. However, in both studies, the ventilatory management of all infants was based upon an algorithm or protocol in an effort to reduce bias. Follow-up was complete in both studies. Although objective criteria were used to define outcomes, it is not stated whether those assessing these outcomes were blinded to the allocation group.

Effects of interventions

Ventilation Parameters and PaCO2

In one study (Mariani 1999), the PaCO2 was significantly higher and ventilatory pressures and rates were significantly lower at most 12 hour intervals in the intervention group during the first 96 hours following randomisation. The other study (Carlo 1999) reported that during the 10 day period following randomisation, the PaCO2 in the minimal ventilation group was 4 mmHg higher than in the routine ventilation group.

Mortality

One trial (Mariani 1999) reported this outcome. There was no evidence of effect on mortality. (RR 1.04, 95% CI 0.23, 4.66)

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Bronchopulmonary Dysplasia and Chronic Lung Disease (in survivors)

One trial (Mariani 1999) reported these outcomes. There was no evidence of effect on either bronchopulmonary dysplasia defined as oxygen requirement and abnormal chest radiograph at 28 days of postnatal age (RR 0.64, 95% CI 0.36, 1.15) or chronic lung disease defined as oxygen requirement at 36 weeks (RR 1.05, 95% CI 0.16, 6.77).

Death or Chronic Lung Disease at 36 weeks

Both trials (Carlo 1999; Mariani 1999) reported the combined outcome of death or CLD. There was no evidence of effect in either of the individual trials or in the meta-analysis (RR 0.94, 95% CI 0.78, 1.15).

Intraventricular Haemorrhage and Periventricular Leukomalacia

Intraventricular haemorrhage of all grades was reported in one trial (Mariani 1999), while both trials reported IVH grades 3 and 4 (Carlo 1999; Mariani 1999). There was no evidence of effect on IVH all grades (RR 0.82, 95% CI 0.47, 1.43) or IVH grades 3 and 4 (RR 0.84, 95% CI 0.54, 1.31). Both trials reported PVL (Carlo 1999; Mariani 1999). Neither found evidence of effect, and the meta-analysis did not support an effect on PVL (RR 1.02, 95% CI 0.49, 2.12).

Air Leak

In the one trial (Mariani 1999) which reported airleak as a single outcome, there was no evidence of effect (RR 0.52, 95% CI 0.10, 2.59). One trial (Carlo 1999) reported pulmonary interstitial emphysema and pneumothorax as separate outcomes. This trial found no evidence of effect on either PIE (RR 1.14, 95% CI 0.63, 2.07) or pneumothorax (RR 2.29, 95% CI 0.73, 7.22).

Retinopathy of Prematurity

One trial (Mariani 1999) reported ROP stage 2 or above. There was no evidence of effect on ROP (RR 1.04, 95% CI 0.07, 15.73).

Duration of Hospital Stay

The duration of hospital stay (days) was reported in one trial (Mariani 1999). There was no evidence of effect on duration of hospital stay (WMD -2.00, 95% CI -14.87, 10.87).

Subgroup analysis

Due to the limited availability of data, subgroup analyses according to either population or type of intervention were not possible. However, one study (Carlo 1999) reported a reduction in CLD or death in the subgroup of 501 to 750 gram infants (minimal ventilation strategy 68% vs routine ventilation 86%, $p < 0.05$) due to a reduction in CLD in this group. This outcome does not appear in the table of comparisons as the number of infants in each subgroup was not reported.

DISCUSSION

Analysis of the data available from the two studies included in this review does not provide evidence to support the use of permissive hypercapnia to prevent morbidity or mortality in ventilated newborn infants. The only significant difference reported was a reduction in the incidence of CLD defined as oxygen dependency at 36 weeks post-menstrual age in the subgroup of newborn infants of birthweight 501 to 750 grams reported in one study. There were no other differences in any reported pulmonary or nonpulmonary outcomes, and there was no reported neurodevelopmental follow-up. Data used to assess most outcomes in this review are mostly derived from one trial (Carlo 1999) which has been published in abstract form only at this stage. The full report, which is expected in the near future, may provide further evidence for or against the strategy of permissive hypercapnia/minimal ventilation.

The ventilatory targets used in each trial were similar, although the study periods were different. It should be noted that the trial which reported the reduction in CLD in the 501 to 750 gram subgroup (Carlo 1999) maintained the minimal ventilation strategy for a period of 10 days. During this time, the mean PCO2 was 4 mmHg higher than in the intervention group. It is not clear, however, how quickly these targets were achieved. In the trial which maintained the target PCO2 for 96 hours (Mariani 1999), the difference in PCO2 levels did not become significant until 12 hours after randomisation. If permissive hypercapnia/minimal ventilation techniques were to reduce pulmonary morbidity and be neuroprotective, the benefits of these strategies may only be realised if they are instituted immediately following birth, and maintained throughout the duration of the ventilatory support.

Experimental animal data and observational data from human infants (Garland 1995, Graziani 1992, Calvert 1987) suggest that the levels of PCO2 which may be either harmful or protective to the lungs and immature brain are more extreme than those which were targeted in the two included studies. A higher PCO2 and lower pH in the intervention group may be required in order to demonstrate the beneficial effects suggested by the experimental and observational data.

There were no adverse effects due to the permissive hypercapnia/minimal ventilation strategies reported in the included studies. It can be concluded that hypercapnia at least in the range targeted in these two trials is not harmful in the short term. However, long term neurodevelopmental evaluation has not been reported. The safety of prolonged exposure to higher levels of CO2 remains to be shown in controlled studies.

AUTHORS' CONCLUSIONS

Implications for practice

This review which includes data from two trials does not demonstrate any significant overall benefit of a permissive hypercapnia/minimal ventilation strategy which targeted hypercapnia compared to a routine ventilation strategy aiming for normocapnia. At present, therefore, these ventilation strategies cannot be recommended to reduce mortality, or pulmonary and neurodevelopmental morbidity. Although there was a reduction in CLD in the 501 to 750 gram group in one study, the adoption of this "protective" ventilation strategy should not precede a more detailed analysis including thorough neurodevelopmental assessment. Until more evidence which supports the safety and benefits of this strategy is available, it would seem wise to avoid the exposure of ventilated newborns to either severe hypocapnia or hypercapnia. Ventilatory strategies which target higher levels of PCO2 (> 55 mmHg) should only be undertaken in the context of well designed controlled clinical trials.

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Implications for research

Further clinical trials evaluating the effects of permissive hypercapnia/minimal ventilation strategies should be undertaken. They should evaluate short term outcomes such as death and pulmonary morbidity as well as clinically significant long term outcomes such as neurodevelopmental status and CLD. Where possible, the differential effects of both degree and duration of hypercapnia should be investigated. The combination of permissive hypercapnia with new ventilatory techniques such as high frequency ventilation and tracheal gas insufflation should also be studied. The economic implications of any change in practice should be measured. Randomised clinical trials should have sufficient power to detect clinically significant differences in important subgroups, and should employ strategies which achieve the ventilatory targets as soon as possible and maintain them throughout the period of ventilatory support.

ACKNOWLEDGEMENTS

Nil

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REFERENCES

References to studies included in this review

Carlo 1999 *{published data only}*

Carlo WA, Stark AR, Bauer C, Donovan E, Oh W, Papile L-A, Shankaran S, Tyson JE, Wright LL, Temprosa, Poole K. Effects of minimal ventilation in a multicenter randomized controlled trial of ventilator support and early corticosteroid therapy in extremely low birthweight infants. *Pediatrics* 1999;**104**(3, Suppl):738-39.

Mariani 1999 *{published data only}*

Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics* 1999;**104**:1082-8.

References to studies awaiting assessment

Carlo 1999 (full) *{published data only}*

Full report of Carlo 1999 expected in 2001.

Additional references

Amato 1998

Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *New England Journal of Medicine* 1998;**338**:347-54.

ARDS Network 2000

The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine* 2000;**342**:1301-8.

Avery 1987

Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable?: A survey of eight centers. *Pediatrics* 1987;**79**:26-30.

Bidani 1994

Bidani A, Tzouanakis AE, Cardenas VJ, et al. Permissive hypercapnia in acute respiratory failure. *JAMA* 1994;**272**:957-62.

Calvert 1987

Calvert SA, Hoskins EM, Fong KW, et al. Etiologic factors associated with the development of periventricular leukomalacia. *Acta Paediatrica Scandinavica* 1987;**76**:254-9.

Dreyfuss 1993

Dreyfuss D, Sauman G. Role of tidal volume, FRC, and end-expiratory volume in the development of pulmonary oedema following mechanical ventilation. *American Review of Respiratory Disease* 1993;**148**:1194-203.

Dries 1995

Dries DJ. Permissive hypercapnia. *Journal of Trauma* 1995;**39**:984-9.

Drummond 1981

Drummond WH, Gregory GA, Heyman MA, et al. The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. *The Journal of Pediatrics* 1981;**98**:603-11.

Feihl 1994

Feihl F, Perret C. Permissive hypercapnia. How permissive should we be?. *American Journal of Respiratory and Critical Care Medicine* 1994;**150**:1722-37.

Ferrara 1984

Ferrara B, Johnson DE, Change P-N, et al. Efficacy and neurologic outcome of profound hypocapneic alkalosis for the treatment of persistent pulmonary hypertension in infancy. *The Journal of Pediatrics* 1984;**105**:457-61.

Fujimoto 1994

Fujimoto S, Togari H, Yamagichi N, et al. Hypocarbia and cystic periventricular leukomalacia in premature infants. *Archives of Disease in Childhood* 1994;**71**:F107-10.

Garland 1995

Garland JS, Buck RK, Allred EN, et al. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. *Archives of Pediatrics and Adolescent Medicine* 1995;**149**:617-22.

Graziani 1992

Graziani LJ, Spitzer AR, Mitchell DG, et al. Mechanical ventilation in preterm infants: Neurosonographic and developmental studies. *Pediatrics* 1992;**90**:515-22.

Hendricks-Munoz 1988

Hendricks-Munoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics* 1988;**81**:650-6.

Kraybill 1989

Kraybill EN, Runyan DK, Bose CL, et al. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. *The Journal of Pediatrics* 1989;**115**:115-20.

Moylan 1978

Moylan FM, Walker AM, Kramer SS, et al. Relationship of bronchopulmonary dysplasia to the occurrence of alveolar rupture during positive pressure ventilation. *Critical Care Medicine* 1978;**6**:140-2.

Northway 1967

Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline membrane disease: BPD. *New England Journal of Medicine* 1967;**276**:357-68.

Stewart 1998

Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *New England Journal of Medicine* 1998;**338**:355-61.

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Tuxen 1994

Tuxen DV. Permissive hypercapnic ventilation. *American Journal of Respiratory and Critical Care Medicine* 1994;**150**:870-4.

Wiswell 1996a

Wiswell TE, Graziani LJ, Kornhauser MS, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics* 1996;**98**:918-24.

Wiswell 1996b

Wiswell TE, Graziani LJ, Kornhauser MS, et al. High frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics* 1996;**98**:1035-43.

Wung 1985

Wung J-T, James LS, Kilchevsky E, et al. Management of infants with severe respiratory failure and persistence of the fetal circulation without hyperventilation. *Pediatrics* 1985;**76**:488-94.

Yu 1983

Yu VY, Orgill AA, Lim SB, et al. Bronchopulmonary dysplasia in very low birthweight infants. *Australian Paediatric Journal* 1983;**19**:233-6.

CHARACTERISTICS OF STUDIES

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

Carlo 1999

Methods	RCT 2x2 factorial design (with early postnatal steroids) Blinding of randomisation: Can't tell from abstract Blinding of intervention: No Complete followup: Yes Blinding of outcome: Can't tell from abstract
Participants	220 newborn infants. 501-1000 grams birthweight. Mechanically ventilated at <12 hours old. If 751-1000 grams birthweight then FiO2 >= 0.3 and received surfactant.
Interventions	Intervention group - Minimal ventilation with PaCO2 goal of >52 mmHg for 10 days. (n = 109) Control group - PaCO2 goal of <48 mmHg for 10 days. (n = 111)
Outcomes	CLD or death. PIE. Pneumothorax. IVH grade 3 or 4. PVL. Reintubation.
Notes	The other arms of the factorial design compared early steroids with placebo. The entire study was terminated early because of "unanticipated adverse effects of steroids".

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mariani 1999

Methods	RCT Blinding of randomisation: Yes

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Mariani 1999 *(Continued)*

	Blinding of intervention: No Complete followup: Yes Blinding of outcome: Can't tell
Participants	49 newborn infants. 601-1250 grams birthweight. Had RDS and ventilated <24 hours old. Received surfactant.
Interventions	Intervention group - Permissive hypercapnia - PaCO2 45-55 mmHg and pH >= 7.2. (n = 24) Control group - PaCO2 35-45 mmHg and pH >= 7.25. (n = 25) These goals maintained for the first 96 hours following randomisation. After 96 hours the changes in the ventilator settings were directed at the pH criteria allowing high levels of PaCO2 also in the control group.
Outcomes	Primary - Duration assisted ventilation. Secondary - Duration supplemental O2. Postnatal steroid use. Air leaks. IVH. PVL. ROP. PDA. NEC. Duration of hospital stay.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

DATA AND ANALYSES

Comparison 1. Permissive hypercapnia versus normocapnia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death before discharge	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.23, 4.66]
2 Bronchopulmonary dysplasia in survivors at 28 days	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.37, 1.21]

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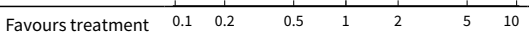
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Chronic lung disease in survivors at 36 weeks post menstrual age	1	43	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.16, 6.77]
4 Death or chronic lung disease (36 weeks)	2	269	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.15]
5 Intraventricular haemorrhage (all IVH)	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.47, 1.43]
6 Intraventricular haemorrhage (grade 3 or 4)	2	269	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
7 Periventricular leukomalacia	2	269	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.49, 2.12]
8 Air leak	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.59]
9 Pneumothorax	1	220	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [0.73, 7.22]
10 Pulmonary interstitial emphysema	1	220	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.63, 2.07]
11 Retinopathy of prematurity (grade 2 or above)	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 15.73]
12 Duration of hospital stay (days) in survivors	1	43	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-14.87, 10.87]

Analysis 1.1. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 1 Death before discharge.

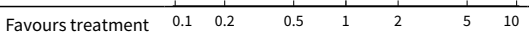
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mariani 1999	3/24	3/25		100%	1.04[0.23,4.66]
Total (95% CI)	**24**	**25**		**100%**	**1.04[0.23,4.66]**
Total events: 3 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					



Favours treatment — Favours control

Analysis 1.2. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 2 Bronchopulmonary dysplasia in survivors at 28 days.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mariani 1999	9/21	14/22		100%	0.67[0.37,1.21]



Favours treatment — Favours control

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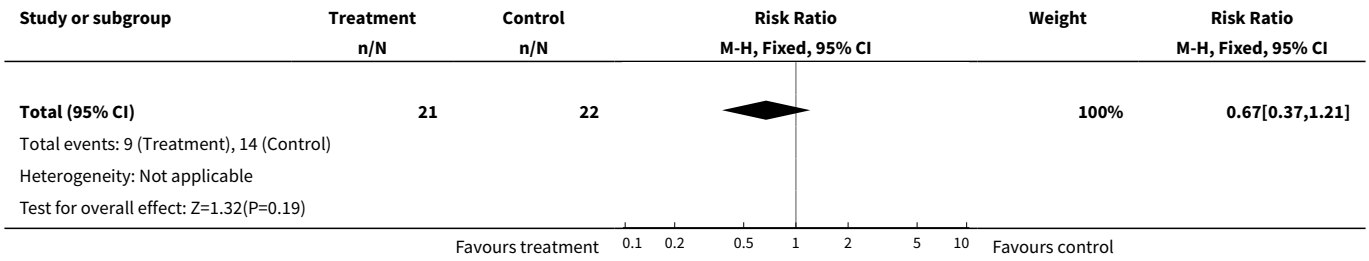
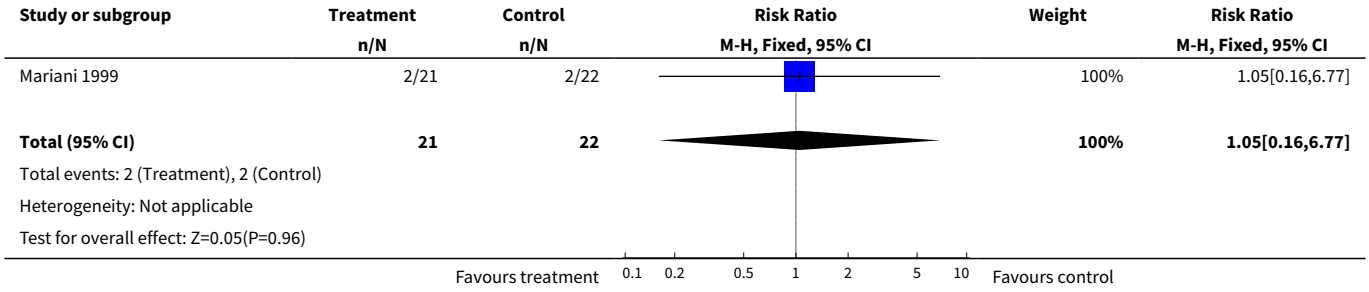
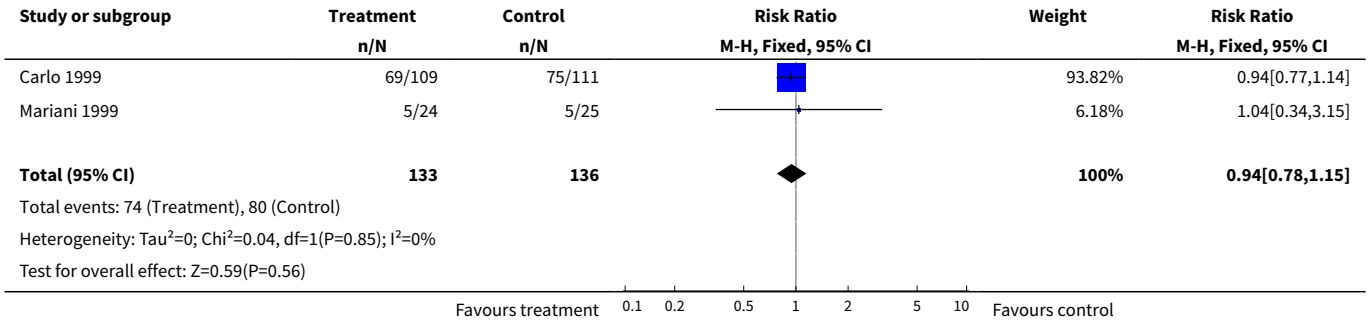


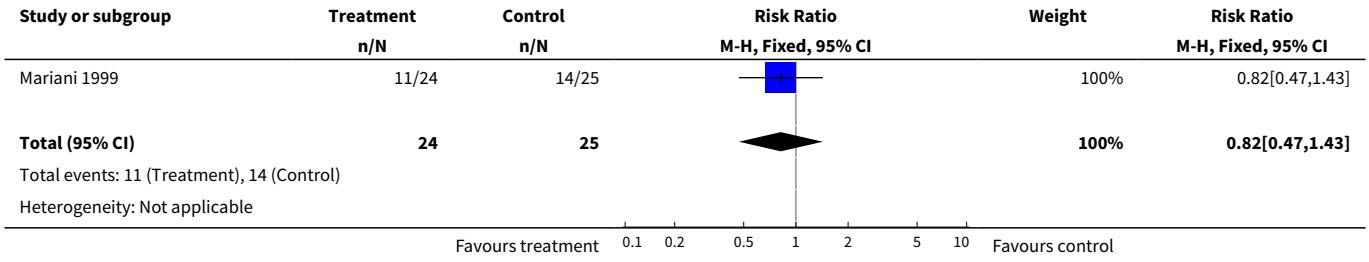
Analysis 1.3. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 3 Chronic lung disease in survivors at 36 weeks post menstrual age.



Analysis 1.4. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 4 Death or chronic lung disease (36 weeks).



Analysis 1.5. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 5 Intraventricular haemorrhage (all IVH).



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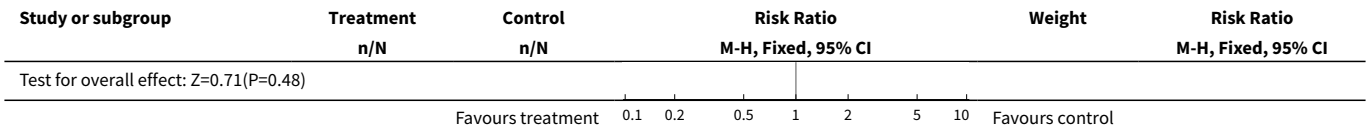
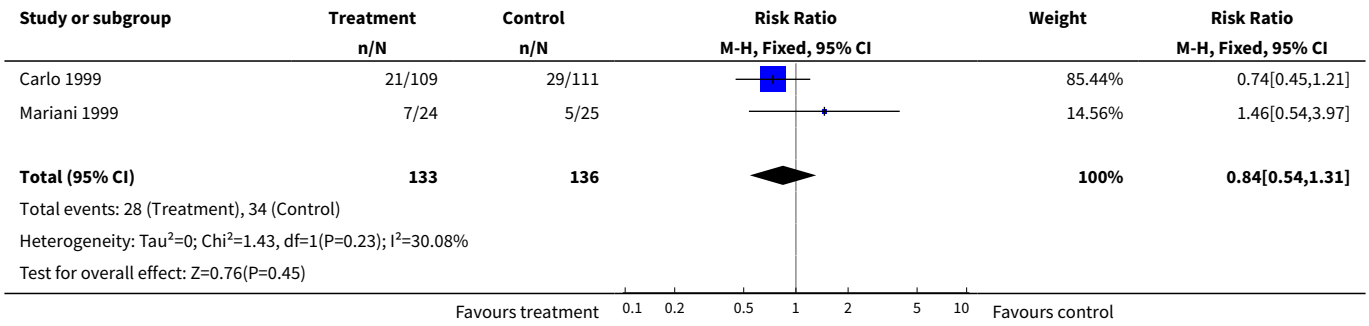
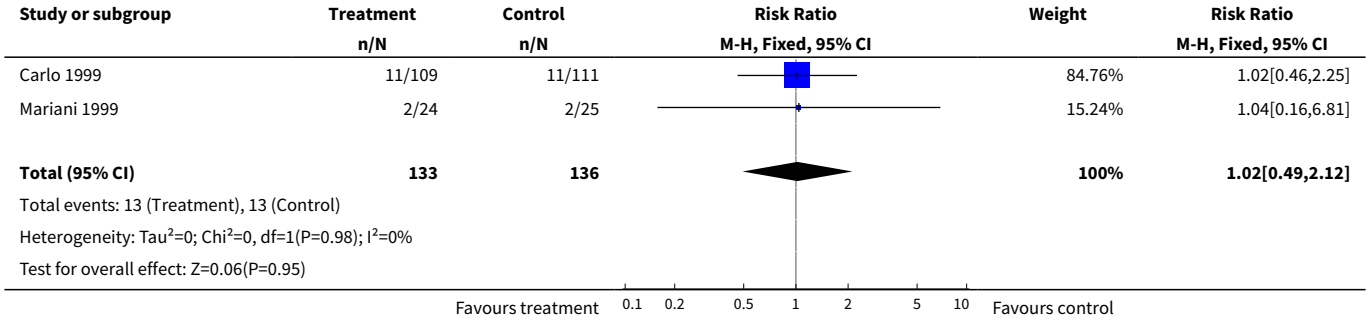


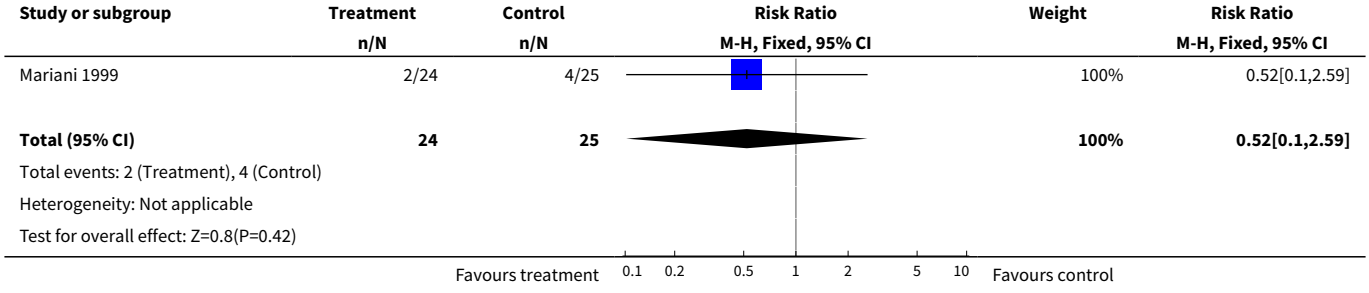
Analysis 1.6. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 6 Intraventricular haemorrhage (grade 3 or 4).



Analysis 1.7. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 7 Periventricular leukomalacia.



Analysis 1.8. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 8 Air leak.



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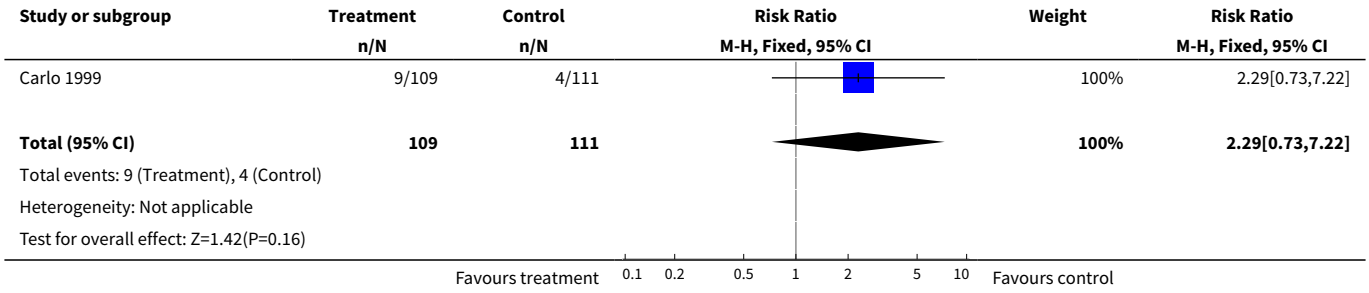
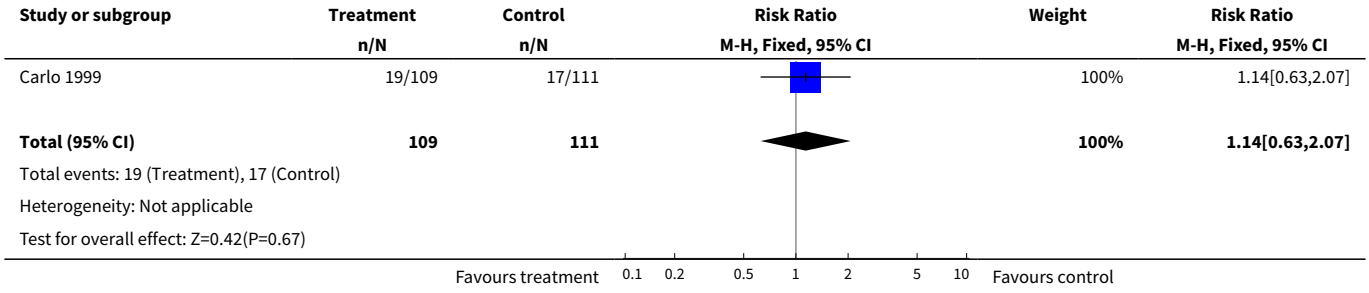
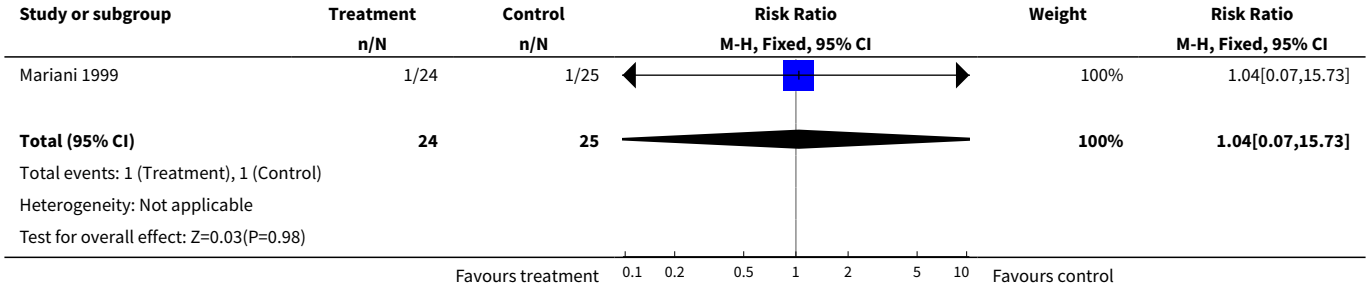
Analysis 1.9. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 9 Pneumothorax.



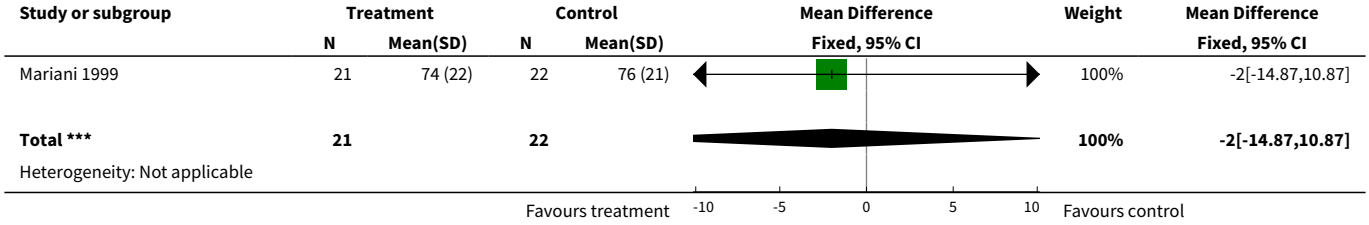
Analysis 1.10. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 10 Pulmonary interstitial emphysema.



Analysis 1.11. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 11 Retinopathy of prematurity (grade 2 or above).



Analysis 1.12. Comparison 1 Permissive hypercapnia versus normocapnia, Outcome 12 Duration of hospital stay (days) in survivors.



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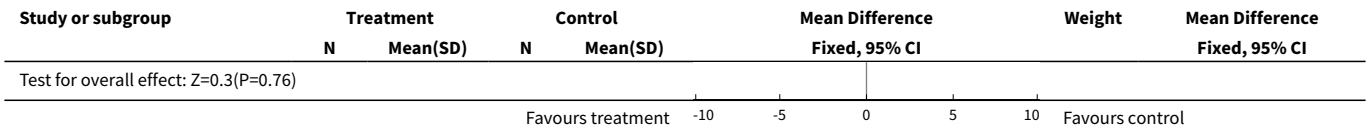

WHAT'S NEW

Date	Event	Description
5 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2001

Date	Event	Description
10 February 2001	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

Nil

SOURCES OF SUPPORT

Internal sources

- Dept of Neonatology, Mater Mother's Hospital, Brisbane, Australia.
- Perinatal Research Centre, Royal Women's Hospital, Brisbane, Australia.
- Royal Children's Hospital Foundation, Brisbane, Australia.
- Grantley Stable Neonatal Unit, Royal Women's Hospital, Brisbane, Australia.
- Mater Perinatal Epidemiology Unit, Mater Hospital, South Brisbane., Australia.
- Dept of Paediatrics and Child Health, University of Queensland, Brisbane, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Respiration, Artificial; Bronchopulmonary Dysplasia [prevention & control]; Carbon Dioxide [*blood]; Cerebral Hemorrhage [prevention & control]; Chronic Disease; Infant Mortality; Leukomalacia, Periventricular [prevention & control]; Lung Diseases [prevention & control]; Randomized Controlled Trials as Topic; Respiration; Retinopathy of Prematurity [prevention & control]

MeSH check words

Humans; Infant, Newborn

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