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Neuromuscular paralysis for newborn infants receiving mechanical ventilation (Review)

Cools F, Offringa M

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[Intervention Review]

Neuromuscular paralysis for newborn infants receiving mechanical ventilation

Filip Cools[1], Martin Offringa[2]

[1]Neonatology, Universitair Ziekenhuis Brussel, Brussels, Belgium. [2]Pediatrics, H3-144, Academic Medical Center, Amsterdam, Netherlands

Contact address: Filip Cools, Neonatology, Universitair Ziekenhuis Brussel, Laarbeekaan 101, Brussels, 1090, Belgium. Filip.Cools@uzbrussel.be.

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ABSTRACT

Background

Ventilated newborn infants breathing in asynchrony with the ventilator are potentially exposed to more severe barotrauma and are at risk for complications such as pneumothorax or intraventricular haemorrhage. Neuromuscular paralysis, which eliminates the spontaneous breathing efforts of the infant, creates complete synchronization with the ventilator and may minimize these risks. However, complications have been reported with prolonged neuromuscular paralysis in newborn infants.

Objectives

To determine whether routine neuromuscular paralysis compared with no routine paralysis results in clinically important benefits or harms in newborn infants receiving mechanical ventilation.

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2009), MEDLINE (from 1966 to January 2009), EMBASE (from 1988 to January 2009) and Cinahl (from 2005 - January 2009) were searched. References of review articles were hand searched.

Selection criteria

All trials using random or quasi-random patient allocation in which the use of neuromuscular blocking agents during mechanical ventilation were compared to no paralysis or selective paralysis in newborn infants.

Data collection and analysis

Data were abstracted using standard methods of the Cochrane Collaboration and its Neonatal Review Group, with independent evaluation of trial quality and abstraction and synthesis of data by both review authors. Treatment effect was analysed using relative risk, risk difference and weighted mean difference.

Main results

Ten possibly eligible trials were identified, of which six were included in the review. All the included trials studied preterm infants ventilated for respiratory distress syndrome and used pancuronium as the neuromuscular blocking agent. In the analysis of the results of all trials, no significant difference was found in mortality, air leak or chronic lung disease. There was a significant reduction in intraventricular haemorrhage and a trend towards less severe intraventricular haemorrhages. In the subgroup analysis of trials studying a selected population of ventilated infants with evidence of asynchronous respiratory effort, a significant reduction in intraventricular haemorrhage

(any grade and severe IVH) was found, and a trend towards less air leak. In the subgroup analysis of trials studying an unselected population of ventilated infants, no significant differences were found for any of the outcomes.

Authors' conclusions

For ventilated preterm infants with evidence of asynchronous respiratory effort, neuromuscular paralysis with pancuronium seems to have a favourable effect on intraventricular haemorrhage and possibly on pneumothorax. However, uncertainty remains regarding the long-term pulmonary and neurologic effects and the safety of prolonged use of pancuronium in ventilated newborn infants. There is no evidence from randomised trials on the effects of neuromuscular blocking agents other than pancuronium. The routine use of pancuronium or any other neuromuscular blocking agent in ventilated newborn infants cannot be recommended based on current evidence.

PLAIN LANGUAGE SUMMARY

Neuromuscular paralysis for newborn infants receiving mechanical ventilation

Long-term effects of muscle paralysing drugs on newborns needing mechanical ventilation are as yet unclear.

When newborn infants develop breathing difficulties, they need mechanical ventilation to help them breathe. Sometimes they do not breathe in rhythm with the ventilator but 'fight' the ventilator, causing bleeding in the brain or serious lung injuries. Treating distress or pain caused by the ventilator and adjusting the ventilator to the infant's own breathing pattern can help. Paralysing newborn infants with muscle relaxing drugs such as pancuronium also stops them fighting the ventilator. However, the review of trials found that, although there seems to be some advantage regarding bleeding in the brain, long term effects of this method are not clear. More research is needed.

BACKGROUND

Description of the condition

Asynchronous respiratory efforts in newborn infants receiving mechanical ventilation is a common problem. These infants, "fighting" the ventilator, are at risk for complications during mechanical ventilation which, as a consequence, could impair their clinical outcome. In 1983 Greenough showed that asynchronous spontaneous breathing during mechanical ventilation was associated with a high risk for pneumothorax (Greenough 1983). In a prospective study of preterm infants, Perlman showed that fluctuating cerebral blood-flow velocity during the first day of life was associated with an increased risk for intraventricular haemorrhage (Perlman 1985); this pattern of cerebral blood-flow is likely to be present in struggling infants. Spontaneous breathing during mechanical ventilation is also associated with higher peak transpulmonary pressures (Stark 1979), which may put the infant at higher risk for chronic lung disease due to barotrauma.

Description of the intervention

Non-depolarizing neuromuscular-blocking agents block neuromuscular transmission at the neuromuscular junction causing paralysis of the affected skeletal muscles. Specifically, non-depolarizing neuromuscular-blocking agents block the binding of acetylcholine to its receptors. Commonly used non-depolarizing neuromuscular-blocking agents include Vecuronium (Norcuron), Rocuronium (Zemuron), and Pancuronium (Pavulon).

How the intervention might work

Neuromuscular blocking agents eliminate the spontaneous breathing efforts of the infant during mechanical ventilation. Potentially, this could reduce the risk for acute complications such as pneumothorax (Greenough 1984), thereby improving short-term outcome and mortality, and could lead to a more efficient ventilation and a shorter duration of mechanical ventilation, thereby reducing the risk for lung injury (Pollitzer 1981).

However, a number of complications have been reported with neuromuscular paralysis in infants such as hypotension (McIntosh 1985), hypoxaemia (Philips 1979), prolonged muscle weakness (Torres 1985), joint contractures (Sinha 1984; Fanconi 1995) and, recently, sensorineural hearing loss (Cheung 1999). Some clinical studies show benefit, whereas other studies show no difference or marked adverse effects of paralysis.

Why it is important to do this review

This review updates the previous systematic review of "Neuromuscular paralysis for newborn infants receiving mechanical ventilation" published in The Cochrane Library (Cools 2005).

OBJECTIVES

To determine whether routinely paralysing newborn infants receiving mechanical ventilation compared with not routinely paralysing such infants (i.e. either no paralysis at all, or selective paralysis if the infant fails to improve on standard treatment) results in a clinically important reduction in acute pulmonary and neurologic complications during mechanical ventilation and in improvement in long term pulmonary and neurologic outcome. Further, we planned to determine whether routine neuromuscular paralysis in ventilated newborn infants has circulatory or pulmonary adverse effects.

We planned to do the following subgroup analyses:

1. In order to test the hypothesis that neuromuscular paralysis is more effective in the subgroup of newborn infants who are fighting the ventilator, we planned to analyse the subgroup of trials where the study patients were selected at study entry on some evidence of asynchrony with the ventilator, in contrast to the subgroup of trials including all mechanically ventilated newborn infants.

2. To investigate whether routine neuromuscular blockade is more effective in premature infants, who are at risk for chronic lung disease or intracranial haemorrhage or, on the contrary, is more effective in term infants, who are often ventilated for severe diseases such as meconium aspiration or persistent pulmonary hypertension, we planned to analyse the subgroup of trials with study infants with a gestational age of 34 weeks or less, and the subgroup of trials with study infants of more than 34 weeks gestation.

METHODS

Criteria for considering studies for this review

Types of studies

Trials using random or quasi-random patient allocation.

Types of participants

Mechanically ventilated newborn infants.

Types of interventions

Routine neuromuscular paralysis in newborn infants during mechanical ventilation, versus no routine paralysis. Control intervention could be either no use at all of neuromuscular blockade during mechanical ventilation, or the selective use of neuromuscular blockade, meaning that control subjects were only allowed to receive neuromuscular blocking agents if predefined criteria, indicating a high risk of complications, were met.

Types of outcome measures

Primary outcomes

Primary clinical outcome measures:
1. Mortality before discharge
2. Mortality at 28 days postnatal age
3. Air leak syndrome, i.e. pneumothorax and/or pulmonary interstitial emphysema
4. Intraventricular haemorrhage, any grade, according to classification of Papile et al (Papile 1978)
5. Severe intraventricular haemorrhage, grade 3 or 4, according to classification of Papile et al (Papile 1978)
6. Chronic lung disease at 28 days postnatal age, i.e. oxygen dependency at that age
7. Chronic lung disease at 36 weeks of postmenstrual age, i.e. oxygen dependency at that age

Secondary outcomes

Secondary outcome measures will include potential adverse effects of neuromuscular paralysis and aspects of pulmonary morbidity:

1. Cardiocirculatory instability, i.e. systolic blood pressure above 95 mm Hg or below 50 mm Hg for infants more than 34 weeks gestation, and systolic blood pressure above 95 mm Hg or below 35 mm Hg for infants of 34 weeks gestation or less, during the first week of life
2. Periventricular leukomalacia, defined as periventricular cysts on brain ultrasound
3. Duration of mechanical ventilation
4. Duration of oxygen need
5. Total duration of hospitalisation

Search methods for identification of studies

Electronic searches

The initial literature search was done in May 2000 according to the Cochrane Neonatal Review Group search strategy. The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2000) was searched. MEDLINE (from 1966 to May 2000) and EMBASE (from 1988 to May 2000) were searched using the MeSH headings: infant, newborn; neuromuscular blocking agent; neuromuscular blockade; pancuronium; curare; paralysis. References of review articles were hand searched. Language restrictions were not imposed.

The search was repeated in the same databases with the same search terms in April 2004. Issue 1, 2004 of The Cochrane Library, Central Register of Controlled Trials, was also searched.

The search was repeated in the same databases with the same search terms in January 2009. Cinahl from 2005 - January 2009, was also searched. Issue 1, 2009 of The Cochrane Library, Central Register of Controlled Trials, was also searched.

Searching other resources

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

Data collection and analysis

Standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. Authors from trials published only in abstract form were contacted in order to obtain more information on the trial. The decision to include or exclude a specific study was made independently by the two review authors. In case of discrepancies a decision was made by consensus of the two review authors.

Selection of studies

Standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. Authors from trials published only in abstract form were contacted in order to obtain more information on the trial. The decision to include or exclude a specific study was made independently by the two review authors. In case of discrepancies a decision was made by consensus of the two review authors.

Data extraction and management

A data collection form was created and the following data were abstracted from the included studies: inclusion and exclusion criteria, treatment and control group regimens, sample size, baseline characteristics of the participants, age at enrolment into study, co interventions and outcomes. Data were abstracted by the two review authors independently and differences resolved by consensus.

Assessment of risk of bias in included studies

The standard method of the Cochrane Neonatal Review Group were employed. The methodological quality of each trial was reviewed independently by the two review authors (FC and MO). Each identified trial was assessed for methodological quality with respect to a) masking of allocation b) masking of intervention c) completeness of follow-up d) masking of outcome assessment. This information is included in the table 'Characteristics of Included Studies'.

For the update in 2009, the risk of bias table was completed in order to address the following questions:

1. Sequence generation: Was the allocation sequence adequately generated?

2. Allocation concealment: Was allocation adequately concealed?

3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

4. Incomplete outcome data: Were incomplete outcome data adequately addressed?

5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?

6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Measures of treatment effect

Treatment effects were described using relative risk (RR) and risk difference (RD) for categorical outcomes, and weighted mean difference (WMD) for outcomes measured on a continuous scale.

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examine 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 explored the possible causes using subgroup analyses.

Data synthesis

When there were at least two randomised controlled trials that evaluated the effectiveness of neuromuscular paralysis using the same outcome measures, the results were pooled to obtain an overall estimate of treatment effect using a fixed effects model with RevMan.

Subgroup analysis and investigation of heterogeneity

We planned to do the following subgroup analyses:

1. In order to test the hypothesis that neuromuscular paralysis is more effective in the subgroup of newborn infants who are fighting the ventilator, we planned to analyse the subgroup of trials where the study patients were selected at study entry on some evidence of

asynchrony with the ventilator, in contrast to the subgroup of trials including all mechanically ventilated newborn infants.

2. To investigate whether routine neuromuscular blockade is more effective in premature infants, who are at risk for chronic lung disease or intracranial haemorrhage or, on the contrary, is more effective in term infants, who are often ventilated for severe diseases such as meconium aspiration or persistent pulmonary hypertension, we planned to analyse the subgroup of trials with study infants with a gestational age of 34 weeks or less, and the subgroup of trials with study infants of more than 34 weeks gestation.

RESULTS

Description of studies

Ten possibly eligible trials on the use of neuromuscular blockade in newborn infants were identified. One trial was excluded because no randomisation was used (Miall-Allen 1987). A second trial was excluded because the randomised intervention was the administration of fentanyl versus morphine, whereas neuromuscular blockade was not randomised (Ionides 1994). In a third excluded trial (Finer 1981) the investigators studied the infants during two periods of 12 hours, one with and one without muscle relaxation, randomising the order of the two periods in each patient; no clinically relevant or long term outcome measures were studied. Two trials were only published in abstract form (Bancalari 1980; Bonta 1992). The trial by Bancalari including 139 infants was never published in full, but the author provided an unpublished manuscript of the results. The trial used a two by three factorial design testing the effect of both neuromuscular paralysis (paralysis or no paralysis) and mechanical ventilation strategy (three levels of peak inspiratory pressure and inspiratory time). For the purpose of this review, data were extracted pertaining to the main effect of neuromuscular paralysis. Eligibility was assessed and the trial was included in the review. In the study by Bonta 25 infants < 1500 g ventilated for RDS were randomised to either early paralysis or standard paralysis. Until present we have been unable to find more information on this small trial, so it is categorized in this review as "awaiting assessment".

Six randomised, controlled trials, including a total of 486 infants, reported on the effectiveness of neuromuscular paralysis in ventilated newborn infants, and were included in the review (Bancalari 1980; Greenough 1984; Perlman 1985; Pollitzer 1981; Quinn 1992; Shaw 1993). Except for the trial by Shaw with 193 infants, the trials have a rather small sample size.

There were two possible objectives in those trials: either to compare routine paralysis in the intervention group with no paralysis in the control group (Bancalari 1980; Greenough 1984; Perlman 1985; Pollitzer 1981), or to compare routine paralysis in the intervention group with selective paralysis in the control group (Quinn 1992; Shaw 1993). In the second design control infants were allowed to receive neuromuscular blockade only if they met certain criteria. Those criteria reflected a failure to respond to an alternative intervention in the control group. In the study by Quinn the alternative intervention was analgesia with a continuous infusion of morphine. In the study by Shaw mechanical ventilation in the control group was adjusted according to the infant's spontaneous respiration rate by using a higher ventilation rate. In both studies control infants only received pancuronium if they continued to be asynchronous with the ventilator despite the alternative intervention.

Both objectives could be studied either in an unselected population of ventilated newborn infants (Bancalari 1980; Pollitzer 1981; Shaw 1993), or in a selected population of ventilated newborn infants with some evidence of asynchrony with the ventilator (Greenough 1984; Perlman 1985; Quinn 1992). In the first group of trials all mechanically ventilated infants fulfilling the entry criteria were eligible. In the second group of trials ventilated infants were only eligible if they met certain criteria reflecting asynchrony with the ventilator. The method used to assess asynchrony differed from trial to trial. Greenough considered an infant to be actively expiring against artificial ventilation by combining measurements of oesophageal pressure with gas flow measurements into the infant's chest. Perlman assessed cerebral blood flow velocity in the anterior cerebral artery by Doppler flow, considering the infant asynchronous if the pattern of blood flow velocity was fluctuating (coefficient of variation of more than 10%). In the study by Quinn, finally, asynchrony was assessed by clinical evaluation. Ventilated infants who gave the impression of "fighting the ventilator" were considered to be eligible.

Pancuronium was the only drug used as the neuromuscular blocking agent in a dose ranging from 0.03 mg/kg to 0.1 mg/kg, repeated in order to maintain paralysis. Neuromuscular blockade was usually continued until mechanical ventilation could be weaned sufficiently (peak pressure < 20 cmH2O or fractional inspired oxygen concentration < 0.40 - 0.45). In one study (Perlman 1985) infants were paralyzed until they were 72 hours old.

The number of control infants receiving pancuronium varied between studies. In the trials comparing routine paralysis with no paralysis the rate of neuromuscular blockade in the control group ranged from 0% (Bancalari 1980; Perlman 1985; Pollitzer 1981) to 54% (Greenough 1984). In the study by Greenough all the control infants (11) developed a pneumothorax, whereafter six of them were paralyzed. In the trials comparing routine paralysis with selective paralysis 24% and 26% of the control infants received pancuronium in the studies by Quinn and Shaw respectively.

None of the trials evaluated long-term outcome measures such as neurodevelopment or pulmonary function.

Risk of bias in included studies

The risk of bias is addressed in the table Characteristics of Included Studies and the Risk of Bias table.

Except for one trial (Bancalari 1980), the quality of the trials was generally good.

All trials used randomisation to assign treatment. In four trials allocation was considered to be adequately concealed with the use of sealed envelopes. In one trial the method of randomisation was not described (Shaw 1993), and in another trial a list of random numbers was used (Bancalari 1980). In the Bancalari trial, the number of infants initially randomised to the paralysis and no paralysis group was unequal (61 for the paralysis group versus 78 for the no paralysis group). The reason for this is not explained in the report, but it might be related to the factorial design of the trial.

Due to the nature of the intervention, blinding of the caregiver was not possible. In this case, blinding of the outcome assessment,

such as interpreting a chest X-ray for interstitial emphysema or ultrasound images for intraventricular haemorrhage, is even more important. In most trials this was unclear. Only in one study it was explicitly stated that interpretation of brain ultrasound was done without knowledge of the patient's treatment status (Perlman 1985), and in another trial (Bancalari 1980) chest X-ray was interpreted by a pediatric radiologist who was unaware of the patient's group assignment.

Completeness of follow-up for the primary outcomes was excellent in all but one trial, ranging from 96% to 100%. In the trial by Bancalari 1980 study patients could be excluded within the first 24 hours after randomisation according to two criteria (weaning of mechanical ventilation or sepsis/pneumonia). As a result, 20% of the study patients (28 out of the 139 randomised infants) were excluded. Since no information is available on the outcome of those infants, analysis based on an intent-to-treat principle is not possible. As a result, there is a substantially higher risk for bias in the results of the trial by Bancalari 1980.

Effects of interventions

ROUTINE PARALYSIS VERSUS NO OR SELECTIVE PARALYSIS (ALL TRIALS) (COMPARISON 1)

MORTALITY (Outcomes 1.1 and 1.2):
Five studies reported on mortality before discharge. None of the studies found a significant difference. Meta-analysis of these five trials (264 infants) showed no significant effect of paralysis on mortality before discharge (typical relative risk (RR) 1.24, 95% CI 0.88, 1.74; typical risk difference (RD) 0.06, 95% CI -0.04, 0.17).
Only one study (Shaw 1993) reported on mortality before 28 days of life. No significant difference was found (RR 0.84, 95% CI 0.45, 1.57; RD -0.03, 95% CI -0.14, 0.08).

PNEUMOTHORAX and AIR LEAK (Outcomes 1.3 and 1.4):
All the studies reported on the incidence of pneumothorax with or without pulmonary interstitial emphysema (PIE). One study (Greenough 1984) found a significant decrease in risk of pneumothorax (RR 0.13, 95% CI 0.03, 0.59; RD -0.91, 95% CI -1.13, -0.69). In the other studies, the incidence of pneumothorax was similar in both groups. Meta-analysis of five trials (400 infants) showed no significant difference in risk for pneumothorax (with or without PIE) (typical RR 0.84, 95% CI 0.58, 1.21; typical RD -0.04, 95% CI -0.11, 0.04) (Outcome 1.3). When the infant that was excluded from the analysis in the study by Greenough 1984 was included in the meta-analysis for this outcome, the result did not change significantly (typical RR 0.85, 95% CI 0.59, 1.22). In the meta-analysis of all trials, there is substantial heterogeneity for pneumothorax (I^2 = 94%, p < 0.00001 for RD), that appears to be attributable to the study by Greenough 1984. In the subgroup analysis of trials not selecting for asynchrony at study entry where the Greenough study is not included, no heterogeneity is noted.

Only one study reported on the combined "any air leak", defined as pneumothorax or pulmonary interstitial emphysema. Quinn noted no difference in the risk of any air leak (RR 1.86, 95% CI 0.71, 4.88; RD 0.15, 95% CI -0.07, 0.37) (Outcome 1.4)(Quinn 1992).

INTRAVENTRICULAR haemorrhage **(IVH) (Outcomes 1.5 and 1.6):**
Three studies reported on the incidence of intraventricular haemorrhage, and one additional study reported only on severe IVH. One study (Perlman 1985) found a significant decrease in risk for IVH (any grade) (RR 0.38, 95% CI 0.20, 0.76; RD -0.64, 95% CI -0.92, -0.37). Another study (Greenough 1984) found a trend towards less IVH (any grade) in paralysed infants, but it was not statistically significant. In the third study (Quinn 1992) no difference was noted. Meta-analysis of these three trials shows a significant decrease in risk of any grade IVH in paralysed infants, with a relative risk reduction of 46% (typical RR 0.55, 95% CI 0.34, 0.89), and an absolute risk reduction of 24% (typical RD -0.24, 95% CI -0.41, -0.07).

Two studies reported on the risk for severe IVH. In one study (Perlman 1985) a marked decrease was found (RR 0.05, 95% CI 0.00, 0.77; RD -0.70, 95% CI -0.99, -0.41). In the other study (Shaw 1993) no difference was noted. Meta-analysis of these two trials showed a reduction of severe IVH in paralysed infants, of borderline statistical significance: typical RR 0.51, 95% CI 0.25, 1.06; typical RD -0.08, 95% CI -0.17, -0.00. Statistical heterogeneity is noted for the effect of paralysis on severe IVH (I^2 = 95% for RD).

CHRONIC LUNG DISEASE (CLD) IN SURVIVORS (Outcome 1.7 and 1.8):
Two studies (Bancalari 1980; Shaw 1993) reported on chronic lung disease. In the study by Bancalari 1980 a trend towards less chronic lung disease at 28 days postnatal age, defined as the need for supplemental oxygen with the presence of opacifications on chest radiograph, was found in the group of paralysed infants (RR 0.46, 95% CI 0.19, 1.09; RD -0.24, 95% CI -0.46, -0.01). However, in the meta-analysis of both trials (224 infants) no significant difference was found for this outcome (typical RR 0.83, 95% CI 0.61, 1.12; typical RD -0.08, 95% CI -0.21, 0.04).

Only Shaw reported on the risk for chronic lung disease at 36 weeks postmenstrual age. No significant difference was found (RR 1.23, 95% CI 0.80, 1.88; RD 0.07, 95% CI -0.08, 0.22).

CYSTIC PERIVENTRICULAR LEUKOMALACIA (PVL) (Outcome 1.9):
Shaw 1993 reported on the incidence of PVL. No difference was noted (RR 1.26, 95% CI 0.35, 4.56; RD 0.01, 95% CI -0.05, 0.07).

DURATION OF MECHANICAL VENTILATION
This outcome measure was reported in three studies (Bancalari 1980; Pollitzer 1981; Quinn 1992). In the study by Bancalari the duration of ventilation is reported for the 64 infants who survived after 28 days. No significant difference was found between the paralysed and non-paralysed infants: median 3.2 days (range 1.0 - 111.2) versus 5.1 days (range 1.0 - 82.3). In the studies by Pollitzer and Quinn it was unclear whether the outcome was reported for all randomised infants or just for the surviving infants. In the study by Pollitzer 1981 infants in the paralysis group were ventilated for a mean duration of 114 hours (range 32 - 264) compared to 105 hours (range 36 - 240) for the infants in the control group, which was not significantly different. Also, no difference was found in the study by Quinn 1992 in the median number of days of mechanical ventilation: 5.0 days (range 1 - 63) for the paralysed infants (group P) versus 5.0 days (range 1 - 32) for the selectively paralysed infants (group M). Because the outcome was expressed differently in the two studies (mean versus median) and the standard deviations were not available, we did not pool the results for meta-analysis. In the study by Greenough 1984 a retrospective comparison was made for this outcome. Paralysed infants from the trial (Greenough 1984), who had little or no pneumothorax, were compared with a historical group of matched ventilated infants, from the six months preceding the randomised study, who had pneumothorax but

who had not been paralysed after the pneumothorax developed. The paralysed infants did require more prolonged mechanical ventilation [median 129 hours (range 55 - 2302) versus 55 hours (range 13 - 181), p < 0.01].

DURATION OF OXYGEN DEPENDENCY

Bancalari 1980 and Shaw 1993 reported on the duration of oxygen dependency. In both studies no statistically significant difference was found. In the study by Bancalari 1980 (data reported for the 64 infants surviving after 28 days) the paralysed infants were weaned from the oxygen more quickly, but there was a wide individual variation in oxygen requirement: median of 9.4 days (range 3.8 - 162.7) for the paralysed infants versus a median of 17.2 days (range 2.1 - 154.5) for the non-paralysed infants. Greenough 1984 retrospectively compared the paralysed infants with the matched control infants. No significant difference was found in the median hours of oxygen use: 196 hours (range 88 - 4300) for the paralysed versus 221 hours (range 84 - 2208) for the nonparalysed infants.

DURATION OF HOSPITALISATION

None of the studies reported on this outcome.

CARDIOCIRCULATORY INSTABILITY

In the study by Quinn 1992 blood pressure, which was not further defined, increased by a median of 2 mm Hg (range -12 to +17) in the paralysed infants, compared with a median increase of 3 mm Hg (range -7 to +18) in the control infants, which was not significantly different. Greenough 1984 reported three out of 22 study infants having hypotension, defined as a diastolic blood pressure of less than 20 mm Hg, of which two were from the control group. Pollitzer 1981 just stated that no differences were found in blood pressure between paralysed and nonparalysed infants, if data were pooled. Again, blood pressure was not defined.

SENSITIVITY ANALYSES

Because of the higher risk for bias in the study by Bancalari 1980 sensitivity analyses were performed in order to evaluate the importance of the results of the trial in the calculation of the pooled estimates of effect on mortality, pneumothorax and CLD. No clinically relevant changes of the pooled estimates of effect occurred when the meta-analyses were done with or without the study by Bancalari 1980 (see Table 1).

ROUTINE PARALYSIS VERSUS NO OR SELECTIVE PARALYSIS (TRIALS SELECTING FOR ASYNCHRONY AT ENTRY) (COMPARISON 2)

In three trials, ventilated infants were selected before entering the trial on some evidence of asynchrony with the ventilator indicating a higher risk of complications. Two trials based their selection on the respiratory pattern of the infant (Greenough 1984, Quinn 1992). In a third study, selection was based on cerebral blood flow velocity pattern (Perlman 1985). Meta-analysis of these three trials showed no significant difference in mortality before discharge (typical RR 0.95 95% CI 0.49, 1.84; typical RD -0.01, 95% CI -0.18, 0.15) (Outcome 2.1). There was a significant decrease in risk of pneumothorax (typical RR 0.29, 95% CI 0.11, 0.77; typical RD -0.43, 95% CI -0.64, -0.23) (Outcome 2.2) and a significant reduction in intraventricular haemorrhage (typical RR 0.55, 95% CI 0.34, 0.89; typical RD -0.24, 95% CI -0.41, -0.07) (Outcome 2.4). Severe IVH was reported in only one trial (Perlman 1985), showing a reduction (RR 0.05, 95% CI 0.00, 0.77; RD -0.70, 95% CI -0.99, -0.41) (Outcome 2.5). If the excluded infant from the study by Greenough 1984 was included in the meta-analysis for the outcome of pneumothorax, no significant change for this outcome was seen.

ROUTINE PARALYSIS VERSUS NO OR SELECTIVE PARALYSIS (TRIALS NOT SELECTING FOR ASYNCHRONY AT ENTRY) (COMPARISON 3)

In the studies by Bancalari 1980; Pollitzer 1981 and Shaw 1993 all preterm infants ventilated for respiratory distress syndrome were included, irrespective of their own respiratory pattern. No significant differences were found in the meta-analyses for the various outcomes (mortality before discharge, pneumothorax with/without PIE and chronic lung disease at 28 days postnatal age in survivors).

ROUTINE PARALYSIS VERSUS NO OR SELECTIVE PARALYSIS IN PRETERM INFANTS (< 34 WEEKS GA) VERSUS TERM INFANTS (> 34 WEEKS GA)

All the included randomised trials studied preterm infants ventilated for respiratory distress syndrome, so that this subgroup analysis could not be performed.

DISCUSSION

The methodologic quality of the included trials was generally good as regards control of selection bias and attrition bias. In one trial (Bancalari 1980), however, a substantial proportion of randomised infants were excluded during the first 24 hours of the trial and lost for further analyses. Sensitivity analysis, however, showed that the pooled estimates of effect did not change substantially by adding or subtracting the Bancalari trial in the meta-analysis. Nevertheless, results of meta-analysis for the outcomes where the Bancalari trial adds data should be interpreted with more caution. Because of the nature of the intervention, blinding of care givers was not possible. Knowledge of the intervention (paralysis or no paralysis) could have led to biased use of co-interventions (additional therapeutic, diagnostic or screening interventions), although we have no direct evidence that this was the case. In all but one trial, it was unclear if outcome assessment was blinded, and thus it is unclear whether there was biased ascertainment of outcomes including grade of IVH.

The relatively small sample size of most of the eligible trials for this review, leaving 224 infants in the treatment arm and 234 infants in the control arm for the meta-analyses, results in imprecision in estimating the effect sizes. This is evident from the wide confidence intervals around the point estimate for some of the outcomes. Thus, the power of the meta-analyses may be insufficient to detect an existing effect from neuromuscular paralysis for some of the outcomes.

All the included trials studied preterm infants ventilated for respiratory distress syndrome; thus, the conclusions are only applicable to this specific population of newborn infants. Since no randomised trial of neuromuscular paralysis of term ventilated infants was found, no conclusions can be drawn about the efficacy of neuromuscular paralysis in term newborn infants.

All trials used pancuronium as the neuromuscular blocking agent, with a dosage varying between 0.03 mg/kg and 0.1 mg/kg per dose. Pancuronium was the first steroidal nondepolarizing muscle relaxant. It has vagolytic effects, is long acting and is metabolized in the liver and excreted in the urine (Alexander 1998).

Other and newer nondepolarizing neuromuscular blocking agents, such as cis-atracurium, could have advantages over pancuronium because of their shorter elimination half-life and a non-enzymatic degradation pathway, making them independent of either hepatic or renal function (Atherton 1999). There is no evidence on the benefits and adverse effects of these newer neuromuscular blocking agents in newborn infants.

From the results of the individual trials and the meta-analysis, there seems to be some benefit of routine neuromuscular paralysis with pancuronium on acute pulmonary and neurologic complications, if restricted to ventilated infants showing evidence of asynchrony with the ventilator, but not if routinely administered to all ventilated infants. In the subgroup analysis of trials selecting the ventilated infants before they enter the study on the basis of a higher risk of pneumothorax or intraventricular haemorrhage, neuromuscular paralysis reduces the incidence of IVH and possibly air leak syndrome. In the subgroup of trials where no selection of the ventilated infants was done, no benefit is seen for any of the outcomes. Whether muscle relaxation also improves long term pulmonary and neurologic outcome is not clear from this review. The two trials reporting on chronic lung disease (Bancalari 1980 and Shaw 1993), in which ventilated infants were not selected on the basis of asynchrony with the ventilator, found no benefit of neuromuscular paralysis. For the effect of paralysis on the duration of mechanical ventilation and oxygen dependency, no conclusions can be drawn from the analyses of the included randomised trials because of lack of suitable data. None of the studies measured neurologic development as an outcome measure. Thus, although there seems to be some benefit of neuromuscular paralysis with pancuronium on the risk of air leak and intraventricular haemorrhage in ventilated infants "fighting" the ventilator, uncertainty remains regarding the long term pulmonary and neurologic effects.

Adverse effects from neuromuscular paralysis are mainly reported in case reports, case control studies and other observational studies. In 1979 Philips already warned about hypoxaemia after pancuronium paralysis (Philips 1979). In a prospective study of 49 infants Runkle observed a decrease of PaO2 in infants with hyaline membrane disease following muscle relaxation (Runkle 1984). Miller demonstrated that functional residual capacity of the lungs and oxygenation decreased after muscle relaxation in preterm infants (Miller 1994). Other adverse effects reported are tachycardia and increased blood pressure (Cabal 1985), and an increased risk for intraventricular haemorrhage (Bancalari 1980). Following prolonged paralysis, muscle weakness and atrophy (Torres 1985) and joint contractures (Sinha 1984; Fanconi 1995) have been described. Recently, sensorineural hearing loss has been mentioned to be associated with prolonged use of neuromuscular blocking agents (Cheung 1999). Data concerning those adverse events from the randomised trials included in this review are insufficient to allow for a conclusion about the safety of neuromuscular paralysis. Thus, uncertainty remains regarding the short term and longer term risks of the routine use of muscle relaxation in ventilated newborn infants.

The question remains how to select in daily practice those infants who are in asynchrony with the ventilator and, thus, are at risk for pulmonary or neurologic complications during or following mechanical ventilation. The methods used by Greenough 1984 and Perlman 1985, as previously described, are very detailed and reproducible, but not practical in a busy neonatal unit. A selection based on a clinical impression of the infant "fighting" the ventilator, as is used in the study by Quinn 1992, is easy to apply, but may be more subjective and, thus, less reproducible. Levene and Quinn (Levene 1992) suggest combining clinical assessment of asynchrony with the ventilator with variability of the arterial blood pressure trace, which should be less than 10%. According to Alexander and Todres (Alexander 1998) assessment of ventilator wave form could help determine whether an infant is breathing in synchrony or not. Finally, they suggest that a short therapeutic trial is an easy way to determine whether an infant would benefit from neuromuscular paralysis. At present, it is unknown which is the best method. In daily practice neonatologists most often rely on their clinical impression of the infant "fighting" the ventilator.

An important issue in the discussion of neuromuscular paralysis is the question whether paralysis is the best and safest strategy to obtain a more efficient mechanical ventilation in the newborn infant who is "fighting" the ventilator. The clinician should be aware that this phenomenon could be a sign of pain or stress caused by mechanical ventilation and, thus, should provide for adequate analgesia and sedation, given an adequate ventilation with normoxia and normocapnia and an adequate circulation. Another approach to synchronize the infant with the ventilator and improve mechanical ventilation could be to tune the mechanical ventilation in to the infant's own respiratory pattern. A review by Greenough 1998 showed that high frequency positive pressure ventilation, mimicking the preterm infant's respiratory rate, reduces the risk for air leak compared with conventional ventilation. Furthermore, patient triggered ventilation or synchronized intermittent mandatory ventilation were associated with a shorter duration of ventilation compared with conventional ventilation. Thus, it is reasonable to consider neuromuscular paralysis as a treatment only if the infant is still "fighting" the ventilator, despite adequate analgesia and/or sedation and optimised synchronized mechanical ventilation.

A limitation of this review concerns the external validity of the included trials. In only one trial (Shaw 1993) was exogenous surfactant used for the treatment of respiratory distress syndrome. It is known that the use of surfactant changed neonatal outcome dramatically, including a significant reduction in the incidence of pneumothorax (Soll 1998). Moreover, in current practice preterm infants often exhibit less severe respiratory distress syndrome because of antenatal lung maturation, and they are treated with new ventilation techniques such as high-frequency ventilation, which may cause less lung injury. Moreover, the increasing use of analgesics and sedatives certainly has had an effect on the behaviour of the newborn infant during mechanical ventilation. Only in the study by Quinn 1992 were control infants systematically treated with morphine. Thus, it is uncertain whether the conclusions of this review are applicable to the present population of preterm infants.

AUTHORS' CONCLUSIONS

Implications for practice

The routine use neuromuscular blockade with pancuronium in a selected population of ventilated preterm infants breathing in asynchrony with the ventilator results in a reduction of intraventricular haemorrhage and possibly of pneumothorax. No definite conclusions can be drawn regarding the effect on

long term pulmonary and neurologic outcome or regarding the safety of prolonged use of pancuronium in ventilated preterm infants. Because of the lack of data from randomised trials and because of limited external validity of the trials, the routine use of pancuronium in ventilated preterm infants cannot be recommended based on current evidence. No data are available from randomised controlled trials about the efficacy or adverse effects of neuromuscular paralysis in term ventilated newborn infants, or about the effects of neuromuscular blocking agents other than pancuronium.

Implications for research

Since there is no evidence of effect regarding some major outcome measures and because of the limited external validity of the existing trials, new trials are needed. Future research should address the effects of routine neuromuscular paralysis on long term pulmonary and neurologic outcome, and on long term adverse effects, such as joint contractures and hearing loss. This could initially be achieved by assessing the infants from the cohorts of the included randomised trials. New studies are needed to identify which ventilated newborn infants might possibly benefit from neuromuscular paralysis. Therefore, methods should be developed and tested to identify in an easy and practical way the ventilated infants who are still asynchronous with the ventilator, after optimisation of ventilation technique and adequate analgesia and sedation. Also, trials are needed to study the short and long term effects of newer neuromuscular blocking agents in ventilated newborn infants.

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REFERENCES

References to studies included in this review

Bancalari 1980 *{published data only}*

Bancalari E, Gerhardt T, Feller R, Gannon J, Melnick G, Abdenour G. Muscle relaxation during IPPV in premature infants with RDS. *Pediatric Research* 1980;**14**:590.

* Bancalari E, Scherf RF, Gerhardt T, Cassady J, Abdenour GE, Goldberg RN, Bauer CR. Influence of ventilator settings and muscle relaxation on outcome of neonates requiring mechanical ventilation for RDS: a prospective evaluation. Unpublished.

Greenough 1984 *{published data only}*

Greenough A, Wood S, Morley CJ, Davis JA. Pancuronium prevents pneumothoraces in ventilated premature babies who actively expire against positive pressure inflation. *Lancet* 1984;**1**:1-3.

Perlman 1985 *{published data only}*

Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *New England Journal of Medicine* 1985;**312**:1353-7.

Pollitzer 1981 *{published data only}*

Pollitzer MJ, Reynolds EOR, Shaw DG, Thomas RM. Pancuronium during mechanical ventilation speeds recovery of lungs of infants with hyaline membrane disease. *Lancet* 1981;**1**:346-8.

Quinn 1992 *{published data only}*

Quinn MW, Otoo F, Rushforth JA, Dean HG, Puntis JW, Wild J, Levene ML. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. *Early Human Development* 1992;**30**:241-8.

Shaw 1993 *{published data only}*

Shaw NJ, Cooke, RWI, Gill AB, Saeed M. Randomised trial of routine versus selective paralysis during ventilation for neonatal respiratory distress syndrome. *Archives of Disease in Childhood* 1993;**69**:479-82.

References to studies excluded from this review

Finer 1981 *{published data only}*

Finer NN, Tomney PM. Controlled evaluation of muscle relaxation in the ventilated neonate. *Pediatrics* 1981;**67**:641-6.

Ionides 1994 *{published data only}*

Ionides SP, Weiss MW, Angelopoulos M, Myers TF, Handa RJ. Plasma beta-endorphin concentrations and analgesia-muscle relaxation in the newborn infant supported by mechanical ventilation. *Journal of Pediatrics* 1994;**125**:113-6.

Miall-Allen 1987 *{published data only}*

Miall-Allen VM, Whitelaw AG. Effect of pancuronium and pethidine on heart rate and blood pressure in ventilated infants. *Archives of Disease in Childhood* 1987;**62**:1179-80.

References to studies awaiting assessment

Bonta 1992 *{published data only}*

Bonta BW. Early intervention with muscle relaxation among VLBW infants (< 1500 grams) with respiratory distress syndrome (RDS) requiring mechanical ventilation. *Pediatric Research* 1992;**31**:301A.

Additional references

Alexander 1998

Alexander SM, Todres ID. The use of sedation and muscle relaxation in the ventilated infant. *Clinics in Perinatology* 1998;**25**:63-78.

Atherton 1999

Atherton DP, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clinical Pharmacokinetics* 1999;**36**:169-89.

Cabal 1985

Cabal LA, Siassi B, Artal R, Gonzales F, Hodgman J, Plajstek C. Cardiovascular and catecholamine changes after administration of pancuronium in distressed neonates. *Pediatrics* 1985;**75**:284-7.

Cheung 1999

Cheung PY, Tyebkhan JM, Peliowski A, Ainsworth W, Robertson CM. Prolonged use of pancuronium bromide and sensorineural hearing loss in childhood survivors of congenital diaphragmatic hernia. *Journal of Pediatrics* 1999;**135**:233-9.

Fanconi 1995

Fanconi S, Ensner S, Knecht B. Effects of paralysis with pancuronium bromide on joint mobility in premature infants. *Journal of Pediatrics* 1995;**127**:134-6.

Gemelli 1990

Gemelli M, Manganaro R, Mami C, De Luca F. Longitudinal study of blood pressure during the 1st year of life. *European Journal of Pediatrics* 1990;**149**:318-20.

Greenough 1983

Greenough A, Morley CJ, Davis JA. Interaction of spontaneous respiration with artificial ventilation in preterm babies. *Journal of Pediatrics* 1983;**103**:769-73.

Greenough 1998

Greenough A, Milner AD, Dimitriou G. Synchronized mechanical ventilation in neonates. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000456]

Hegyi 1996

Hegyi T, Anwar M, Carbone MT, Ostfeld B, Hiatt M, Koons A, et al. Blood pressure ranges in premature infants. II. The first week of life. *Pediatrics* 1996;**97**:336-42.

Levene 1992

Levene MI, Quinn MW. Use of sedatives and muscle relaxants in newborn babies receiving mechanical ventilation. *Archives of Disease in Childhood* 1992;**67**:870-3.

McIntosh 1985

McIntosh N. Hypotension associated with pancuronium use in the newborn. *Lancet* 1985;**2**:279.

Miller 1994

Miller J, Law AB, Parker RA, Sundell H, Silberberg AR, Cotton RB. Effects of morphine and pancuronium on lung volume and oxygenation in premature infants with hyaline membrane disease. *Journal of Pediatrics* 1994;**125**:97-103.

Papile 1978

Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemmorrhage: a study of infants with birth weight less than 1,500 gm. *Journal of Pediatrics* 1978;**92**:529-34.

Perlman 1983

Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory distress syndrome. Relation to the development of intraventricualr hemorrhage. *New England Journal of Medicine* 1983;**309**:204-9.

Philips 1979

Philips JB 3rd, Setzer ES, Drummond WH, Nelson RM, Eitzman DV. Hypoxaemia in ventilated neonates after pancuronium paralysis. *Lancet* 1979;**1**:877.

Runkle 1984

Runkle B, Bancalari E. Acute cardiopulmonary effects of pancuronium bromide in mechanically ventilated newborn infants. *Journal of Pediatrics* 1984;**104**:614-7.

Sinha 1984

Sinha SK, Levene MI. Pancuronium bromide induced joint contractures in the newborn. *Archives of Disease in Childhood* 1984;**59**:73-5.

Soll 1998

Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 1998, Issue 2. [DOI: 10.1002/14651858.CD001079]

Stark 1979

Stark AR, Bascom R, Frantz ID 3rd. Muscle relaxation in mechanically ventilated infants. *Journal of Pediatrics* 1979;**94**:439-43.

Torres 1985

Torres CF, Maniscalco WM, Agostinelli T. Muscle weakness and atrophy following prolonged paralysis with pancuronium bromide in neonates. *Annals of Neurology* 1985;**18**:403.

References to other published versions of this review

Cools 2000

Cools F, Offringa M. Neuromuscular paralysis for newborn infants receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002773.pub2]

Cools 2005

Cools F, Offringa M. Neuromuscular paralysis for newborn infants receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD002773.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bancalari 1980

Methods	Randomised allocation, list of random numbers; blinding of randomisation: unclear; complete follow-up: no (20% excluded after randomisation); blinding of outcome assessment: yes for the interpretation of the chest radiographs (pneumothorax, interstitial pulmonary emphysema and chronic lung disease).
Participants	Study population = unselected population of ventilated infants, n=139. Birth weight 750 g or greater, with clinical and radiological findings of RDS and requiring mechanical ventilation during first 3 days of life. Exclusion after randomisation: 1) if weaned from ventilator or ventilated with inspired fraction of oxygen less than 40% in the first 24 hours after the start of the study; and 2) if presence of septicaemia (positive blood culture) or pneumonia (patchy infiltrates on chest X-ray).
Interventions	Randomisation according to two interventions (factorial design):

Bancalari 1980 *(Continued)*

	1) Type of mechanical ventilation. Group A: low peak pressure, long inspiratory time; group B: intermediate peak pressure, normal inspiratory time; group C: high peak pressure, normal inspiratory time. 2) Neuromuscular paralysis. Comparison = routine paralysis versus no paralysis. Treatment (n=61): pancuronium 0.1 mg/kg IV, repeated as needed, until inspired fraction of oxygen below 40%; Control (n=78): no pancuronium.
Outcomes	Mortality, pneumothorax, interstitial pulmonary emphysema, chronic lung disease at 28 days postnatal age
Notes	28 of the 139 randomised infants (17 in the control group and 11 in treatment group) were excluded after randomisation: 18 because of weaning from the ventilator or weaning of inspired fraction of oxygen below 40% in the first 24 hours of the study, and another 10 because of sepsis or pneumonia. No information is available on the outcome of those infants. Chronic lung disease was defined as the need for supplemental oxygen for more than 28 days with the presence of persistent diffuse opacities on chest radiograph. Intracranial haemorrhage was diagnosed in 52 out of 111 infants. In 33 infants it was confirmed with CT-scan or postmortem examination. In the remaining 19 infants the diagnosis was made clinically (sudden deterioration, tense fontanel, seizures, blood in CSF). No ultrasound was used to diagnose intracranial haemorrhage. Therefore this outcome could not be used for the meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomised allocation, list of random numbers.
Allocation concealment?	Unclear risk	Unclear if list with random numbers was concealed to those who performed randomisation.
Blinding? All outcomes	Low risk	Blinding of outcome assessment: yes for the interpretation of the chest radiographs (pneumothorax, interstitial pulmonary emphysema and chronic lung disease).
Incomplete outcome data addressed? All outcomes	High risk	Complete follow-up: no. Twenty percent excluded after randomisation, not included in analyses and no information on outcomes).

Greenough 1984

Methods	Randomised allocation, sealed envelopes; blinding of randomisation: yes; complete follow-up: 96%; blinding of outcome assessment: unclear
Participants	Study population = selected population of ventilated infants in asynchrony with ventilator. 23 infants < 33 weeks' gestation, ventilated for RDS and with evidence of asynchronous respiratory efforts. Asynchrony was defined as active expiration against artificial ventilation on two separate occasions, and assessed by measuring oesophageal pressure and flow entry into infant's chest.
Interventions	Comparison = routine paralysis versus no paralysis. Treatment (n=12) Pancuronium 0.1 mg/kg IV every 2 hours until ventilator settings reduced to peak pressure < 20 cmH20 and rate < 20/min Control (n=11): no pancuronium unless attending physician considered it desirable.

Greenough 1984 *(Continued)*

Outcomes	pneumothorax, intraventricular haemorrhage, mortality, blood pressure, lung function.
Notes	One infant from the paralyzed group was excluded from the analysis because a pneumothorax had developed before pancuronium was given. Six of the 11 control infants were paralyzed after pneumothoraces developed, and all were analyzed in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomised allocation, but method of random sequence generation not described.
Allocation concealment?	Low risk	Sealed envelopes.
Blinding? All outcomes	Unclear risk	Blinding of outcome assessment: unclear.
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: 96%
Free of other bias?	Unclear risk	One infant from the paralyzed group was excluded from the analysis because a pneumothorax had developed before pancuronium was given. Six of the 11 control infants were paralyzed after pneumothoraces developed, and all were analyzed in the control group.

Perlman 1985

Methods	Randomised allocation, sealed envelopes; blinding of randomisation: yes; complete follow-up: yes; blinding of outcome assessment: yes for some outcomes (brain ultrasound)
Participants	Study population = selected population of ventilated infants in asynchrony with ventilator. 24 infants with birth weight between 700 and 1500 g, ventilated for RDS, and without intraventricular haemorrhage at study entry. Asynchrony defined as evidence of fluctuating cerebral blood flow velocity and assessed by measuring blood flow velocity in the anterior cerebral artery. The infant was eligible if the coefficient of variation exceeded 10%.
Interventions	Comparison = routine paralysis versus no paralysis. Treatment (n=14) Pancuronium 0.1 mg/kg IV, repeated to maintain paralysis until the age of 72 hours. Control (n=10) No pancuronium
Outcomes	Cerebral blood flow velocity, intraventricular haemorrhage, mortality.
Notes	None of the control infants received pancuronium. Outcomes were reported on all infants.

Perlman 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomised allocation, but method of random sequence generation not described.
Allocation concealment?	Low risk	Sealed envelopes.
Blinding? All outcomes	Low risk	Blinding of outcome assessment: yes for some outcomes (brain ultrasound).
Incomplete outcome data addressed? All outcomes	Unclear risk	Complete follow-up: yes.

Pollitzer 1981

Methods	Randomised allocation, sealed envelopes; blinding of randomisation: yes; complete follow-up: yes; blinding of outcome assessment: unclear.
Participants	Study population = unselected population of ventilated infants. 50 infants with gestational age of 28 weeks or more, ventilated for RDS. Infants with pneumothorax or interstitial emphysema on initial X-ray were excluded.
Interventions	Comparison = routine paralysis versus no paralysis. Treatment (n=24) Pancuronium 0.03 mg/kg IV or intra-arterially, repeated to maintain paralysis until inspired oxygen concentration < 0.40 to maintain arterial oxygen tension > 50 mmHg. Control infants (n=26) could receive sedation with phenobarbitone, if necessary.
Outcomes	Mortality, pneumothorax, pulmonary interstitial emphysema, duration of mechanical ventilation.
Notes	Bronchopulmonary dysplasia was reported as an outcome, but was not defined. Outcomes were reported on all infants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomised allocation, but method of random sequence generation not described.
Allocation concealment?	Low risk	Sealed envelopes.
Blinding? All outcomes	Unclear risk	Blinding of outcome assessment: unclear.
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes.

Quinn 1992

Methods	Randomised allocation, sealed envelopes; blinding of randomisation: yes; complete follow-up: yes; blinding of outcome assessment: unclear.
Participants	Study population = selected population of ventilated infants in asynchrony with ventilator. 95 infants with gestational age of 34 weeks or less, ventilated for RDS, between 4 and 48 hours old, and no prior treatment with a narcotic analgesic or neuromuscular blocking agent. Asynchrony was assessed by clinical evaluation. Infants were eligible if they were being considered as "fighting the ventilator".
Interventions	Comparison = routine paralysis versus selective paralysis. Treatment (n=28) Group P: pancuronium 0.1 mg/kg IV, repeated to maintain paralysis until inspired oxygen concentration < 0.45; Control (n=29) Group M: morphine 50 microg/kg/h continuous infusion; could be increased to 100 microg/kg/h after 2 hours; infants received pancuronium if they were still fighting the ventilator after 4 hours of morphine infusion.
Outcomes	Intraventricular haemorrhage, air leak (pneumothorax or pulmonary interstitial emphysema), patent ductus arteriosus, duration of mechanical ventilation, mortality.
Notes	Group P is used as intervention group, and group M as control group for this review. Group M+P: pancuronium 0.1 mg/kg IV repeatedly + morphine 50 microg/kg/h. This group was not eligible for inclusion in this review. Clinical outcomes were reported on all infants. Blood pressure, heart rate and ventilator settings were reported on 69 of the 95 infants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomised allocation, but method of random sequence generation not described.
Allocation concealment?	Low risk	Sealed envelopes.
Blinding? All outcomes	Unclear risk	Blinding of outcome assessment: unclear.
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes.

Shaw 1993

Methods	Randomised allocation, method not described; stratification according to birth weight; blinding of randomisation: uncertain; complete follow-up: yes; blinding of outcome assessment: unclear.
Participants	Study population = unselected population of ventilated infants. 193 infants with birth weight < 2000 g, ventilated for RDS within 24 hours after birth.

Shaw 1993 *(Continued)*

Interventions	Comparison = routine paralysis versus selective paralysis. Treatment (n=96) Pancuronium 0.08 mg/kg IV repeatedly to maintain paralysis, provided mean blood pressure is > 10th centile for gestational age; paralysis maintained until ventilator settings reduced to rate of 30/min and peak inspiratory pressure of 20 cm H2O, or earlier in case of excessive fluid retention; Control infants (n=97) were ventilated with a synchronised fast rate ventilation according to the infant's spontaneous respiration rate. They received pancuronium only if they constantly expired during ventilator inflation and there was no improvement in oxygenation.
Outcomes	Mortality before 28 days, pneumothorax, intraventricular haemorrhage, periventricular leukomalacia, chronic lung disease at 28 days and at 36 weeks GA, patent ductus arteriosus, duration of oxygen dependency
Notes	Twenty-five of the 97 control infants (26%) received pancuronium at some stage. Outcomes were reported on all infants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomised allocation, but method of random sequence generation not described.
Allocation concealment?	Unclear risk	Method not described.
Blinding? All outcomes	Unclear risk	Blinding of outcome assessment: unclear.
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes.

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

Study	Reason for exclusion
Finer 1981	Each infant serves as own control, order of 12 hour period of paralysis or no paralysis was randomised; no clinically relevant outcomes
Ionides 1994	No randomisation between paralysis or no paralysis
Miall-Allen 1987	No randomisation

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bonta 1992

Methods	Not known

Bonta 1992 *(Continued)*

Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	Not known

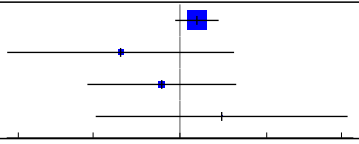
DATA AND ANALYSES

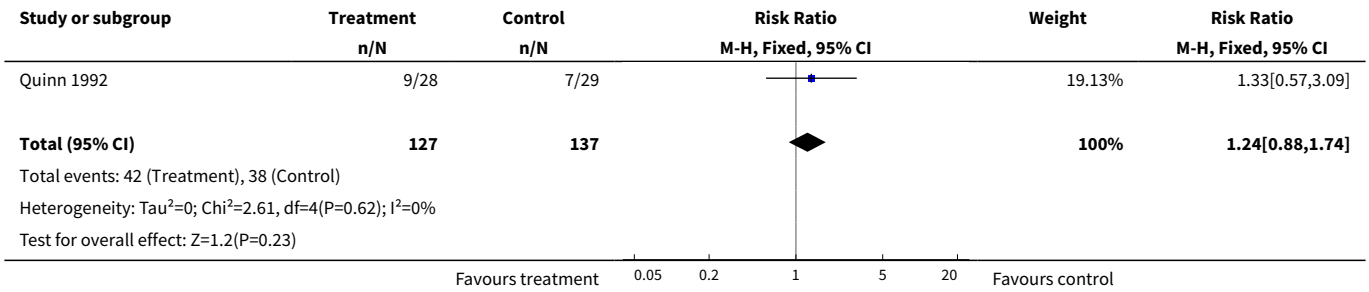
Comparison 1. Routine paralysis versus no/selective paralysis (all trials)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality before discharge	5	264	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.88, 1.74]
2 Mortality at 28 days	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.45, 1.57]
3 Pneumothorax (with or without pulmonary interstitial emphysema)	5	400	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.58, 1.21]
4 Any air leak (pneumothorax or interstitial pulmonary emphysema)	1	57	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.71, 4.88]
5 IVH (any grade)	3	103	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.34, 0.89]
6 Severe IVH (grade 3 or 4)	2	217	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.06]
7 CLD at 28 days postnatal age in survivors	2	224	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.12]
8 CLD at 36 weeks postmenstrual age in survivors	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.80, 1.88]
9 Cystic PVL	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.35, 4.56]

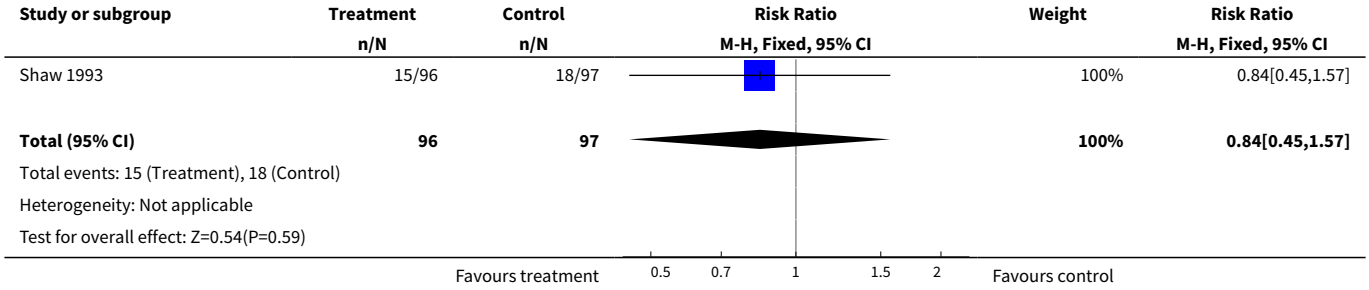
Analysis 1.1. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 1 Mortality before discharge.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bancalari 1980	27/50	24/61		60.13%	1.37[0.92,2.05]
Greenough 1984	1/11	3/11		8.34%	0.33[0.04,2.73]
Perlman 1985	3/14	3/10		9.73%	0.71[0.18,2.84]
Pollitzer 1981	2/24	1/26		2.67%	2.17[0.21,22.39]

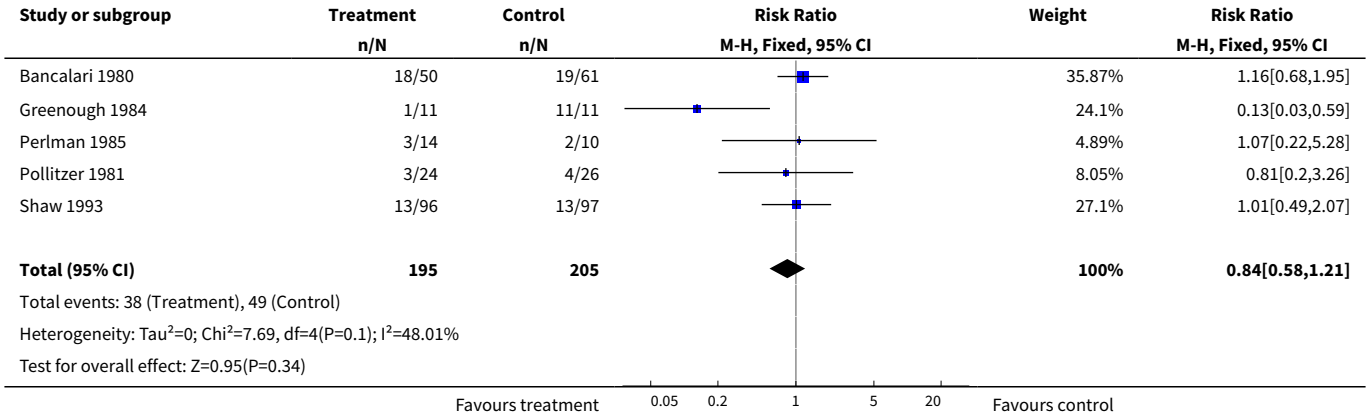




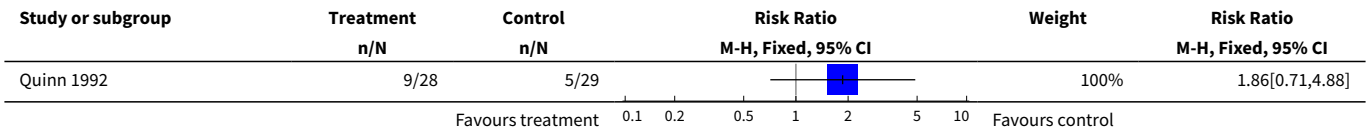
Analysis 1.2. Comparison 1 Routine paralysis versus no/ selective paralysis (all trials), Outcome 2 Mortality at 28 days.

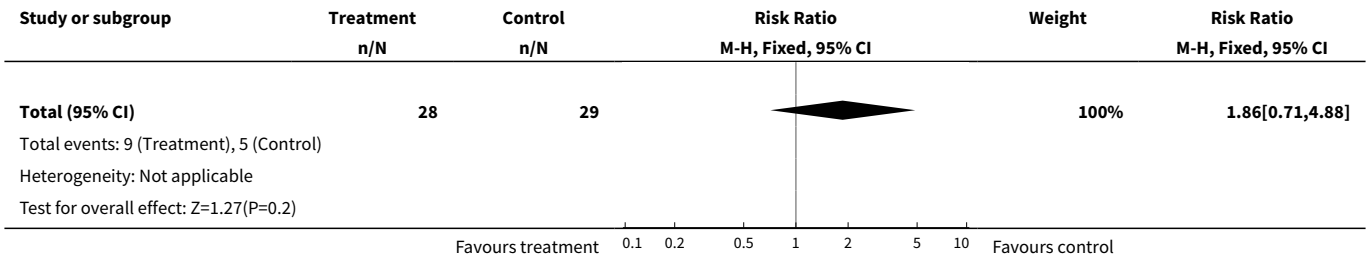


Analysis 1.3. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 3 Pneumothorax (with or without pulmonary interstitial emphysema).

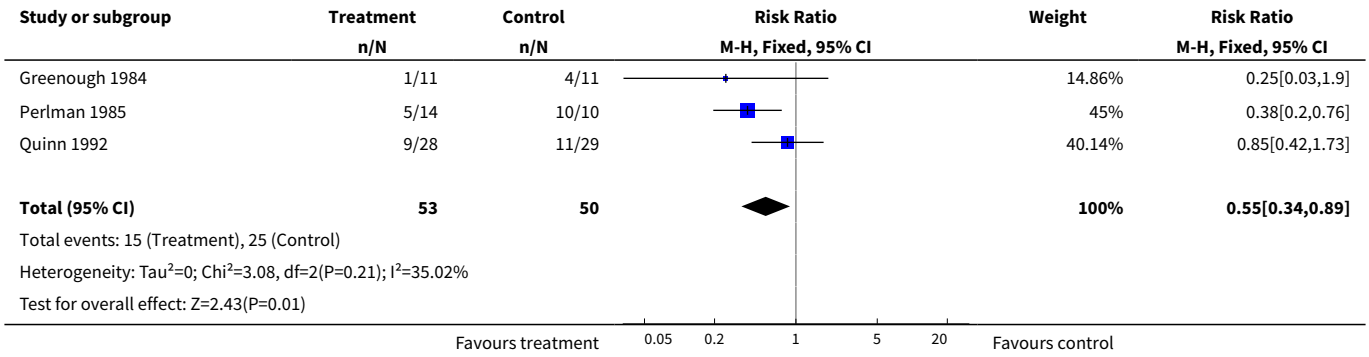


Analysis 1.4. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 4 Any air leak (pneumothorax or interstitial pulmonary emphysema).

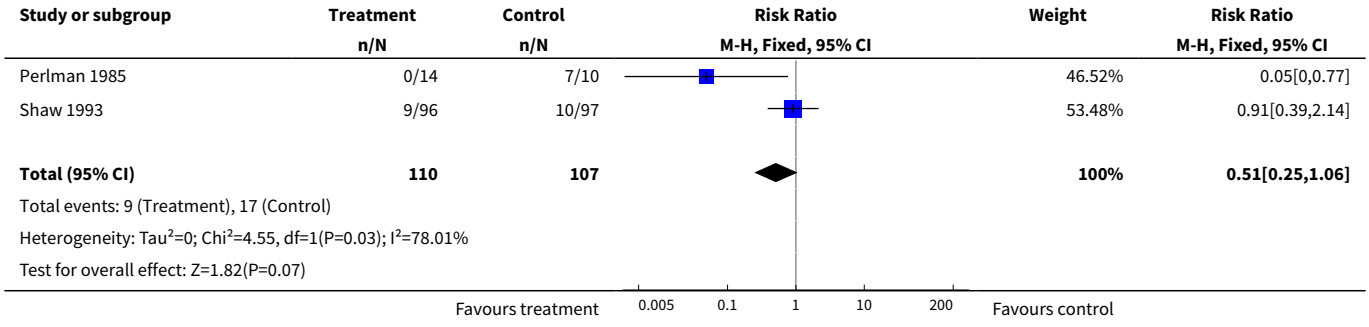




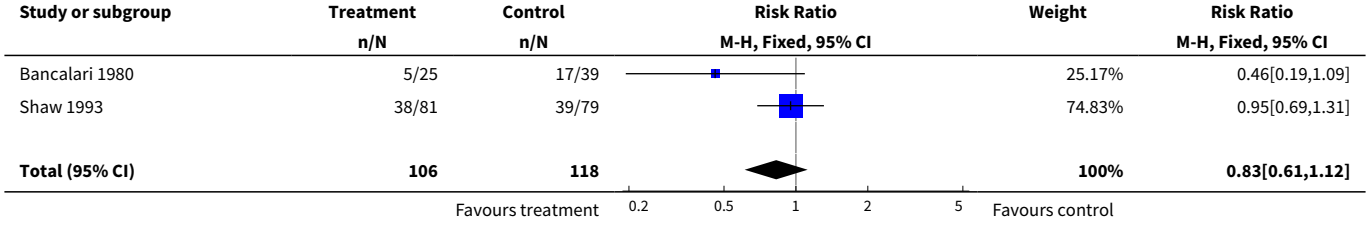
Analysis 1.5. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 5 IVH (any grade).

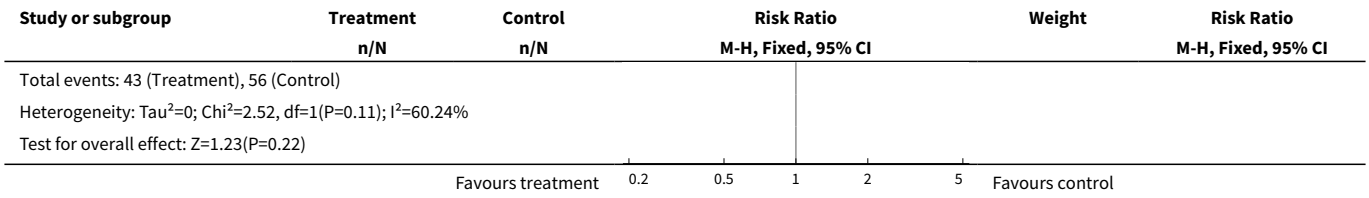


Analysis 1.6. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 6 Severe IVH (grade 3 or 4).

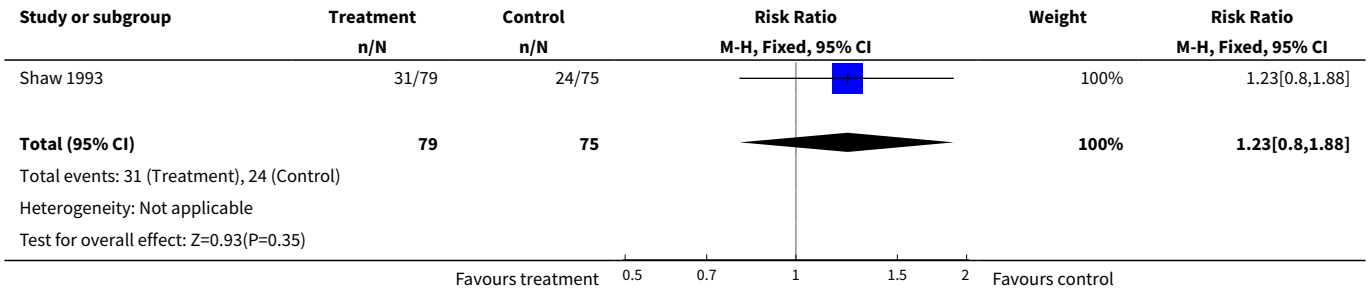


Analysis 1.7. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 7 CLD at 28 days postnatal age in survivors.

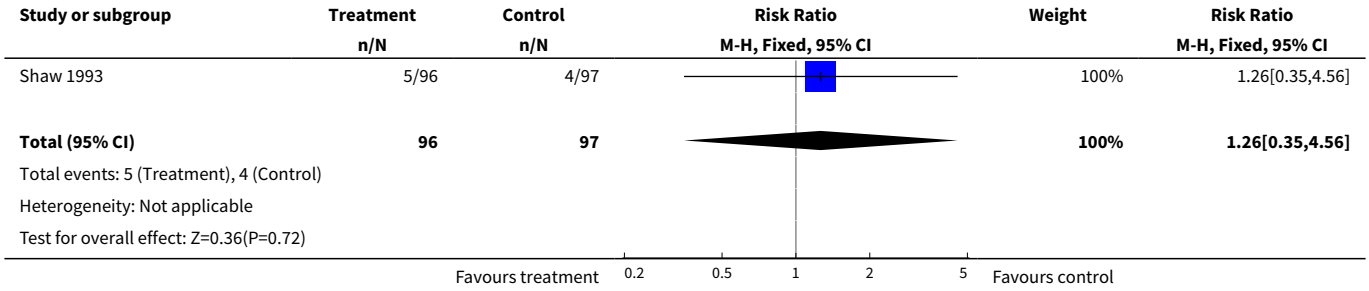




Analysis 1.8. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 8 CLD at 36 weeks postmenstrual age in survivors.



Analysis 1.9. Comparison 1 Routine paralysis versus no/selective paralysis (all trials), Outcome 9 Cystic PVL.



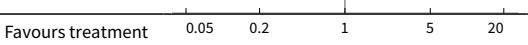
Comparison 2. Routine paralysis versus no/selective paralysis (trials selecting for asynchrony at entry)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality before discharge	3	103	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.49, 1.84]
2 Pneumothorax (with or without pulmonary interstitial emphysema)	2	46	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.77]
3 Any air leak (pneumothorax or interstitial pulmonary emphysema)	1	57	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.71, 4.88]
4 IVH (any grade)	3	103	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.34, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Severe IVH (grade 3 or 4)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.77]

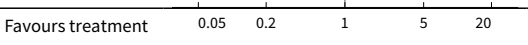
Analysis 2.1. Comparison 2 Routine paralysis versus no/selective paralysis (trials selecting for asynchrony at entry), Outcome 1 Mortality before discharge.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Greenough 1984	1/11	3/11		22.43%	0.33[0.04,2.73]
Perlman 1985	3/14	3/10		26.16%	0.71[0.18,2.84]
Quinn 1992	9/28	7/29		51.41%	1.33[0.57,3.09]
Total (95% CI)	**53**	**50**		**100%**	**0.95[0.49,1.84]**
Total events: 13 (Treatment), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					



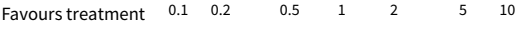
Analysis 2.2. Comparison 2 Routine paralysis versus no/selective paralysis (trials selecting for asynchrony at entry), Outcome 2 Pneumothorax (with or without pulmonary interstitial emphysema).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Greenough 1984	1/11	11/11		83.13%	0.13[0.03,0.59]
Perlman 1985	3/14	2/10		16.87%	1.07[0.22,5.28]
Total (95% CI)	**25**	**21**		**100%**	**0.29[0.11,0.77]**
Total events: 4 (Treatment), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.67, df=1(P=0.06); I^2=72.76%					
Test for overall effect: Z=2.47(P=0.01)					

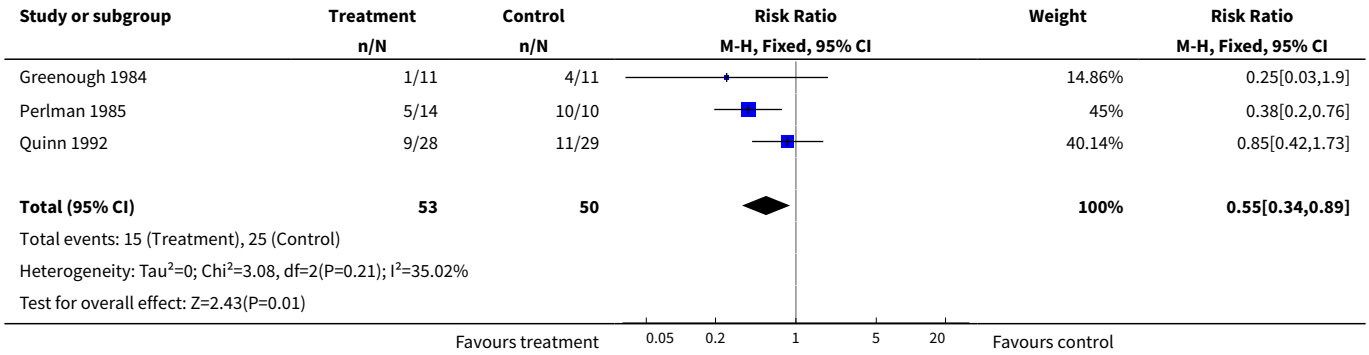


Analysis 2.3. Comparison 2 Routine paralysis versus no/selective paralysis (trials selecting for asynchrony at entry), Outcome 3 Any air leak (pneumothorax or interstitial pulmonary emphysema).

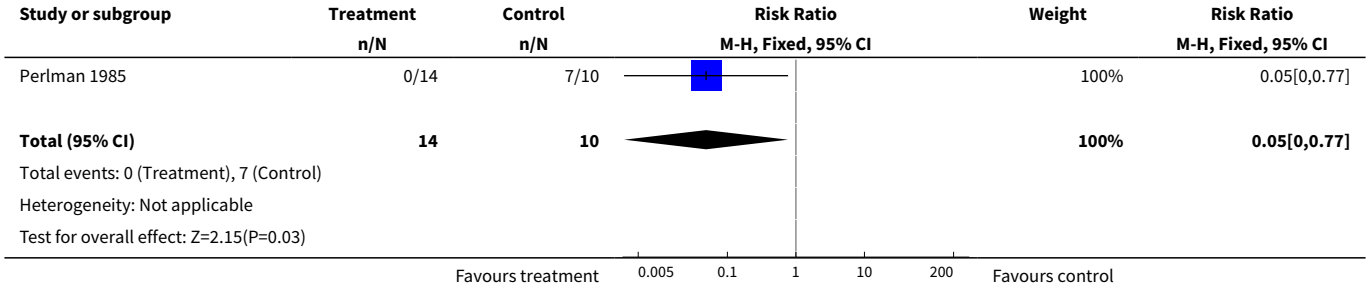
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1992	9/28	5/29		100%	1.86[0.71,4.88]
Total (95% CI)	**28**	**29**		**100%**	**1.86[0.71,4.88]**
Total events: 9 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.27(P=0.2)					



Analysis 2.4. Comparison 2 Routine paralysis versus no/selective paralysis (trials selecting for asynchrony at entry), Outcome 4 IVH (any grade).



Analysis 2.5. Comparison 2 Routine paralysis versus no/selective paralysis (trials selecting for asynchrony at entry), Outcome 5 Severe IVH (grade 3 or 4).

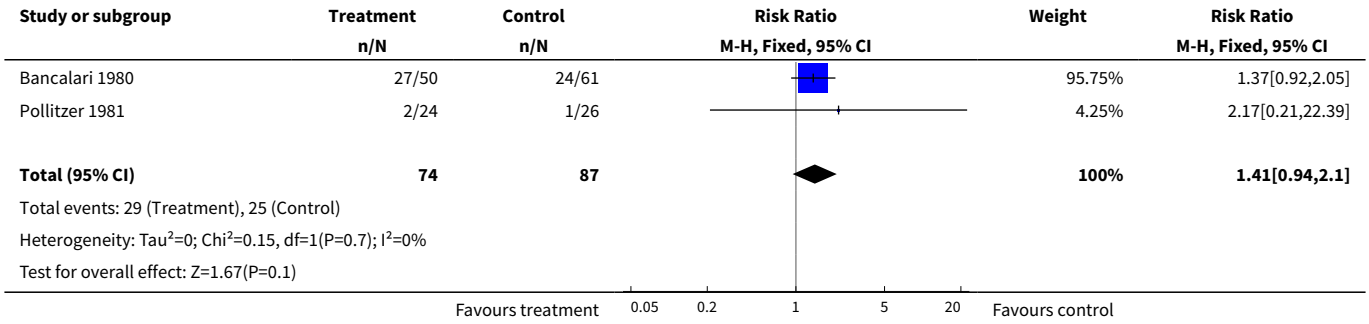


Comparison 3. Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry)

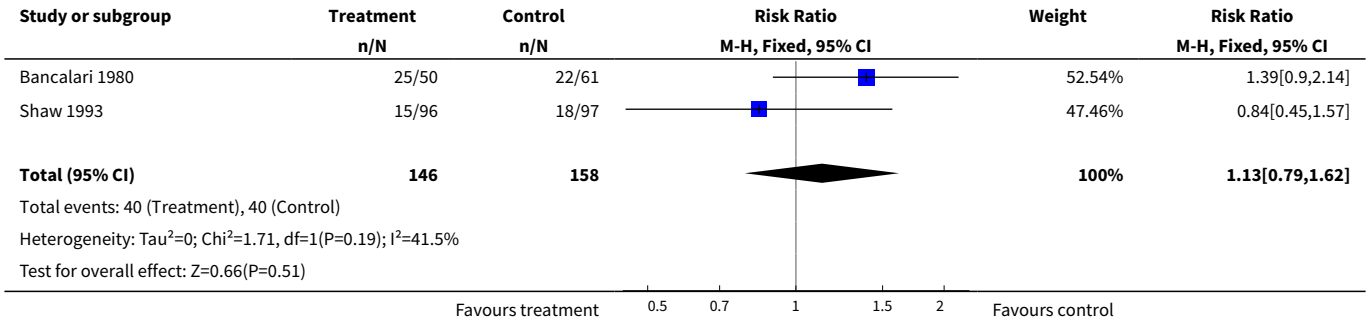
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality before discharge	2	161	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.94, 2.10]
2 Mortality at 28 days	2	304	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.79, 1.62]
3 Pneumothorax (with or without pulmonary interstitial emphysema)	3	354	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.71, 1.60]
4 Severe IVH (grade 3 or 4)	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.14]
5 CLD at 28 days postnatal age in survivors	2	224	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.12]
6 CLD at 36 weeks postmenstrual age in survivors	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.80, 1.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Cystic PVL	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.35, 4.56]

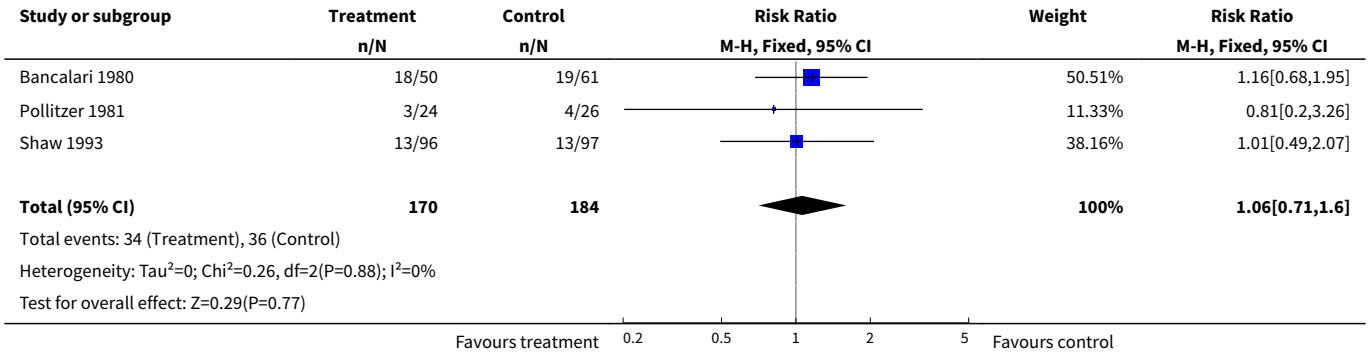
Analysis 3.1. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 1 Mortality before discharge.



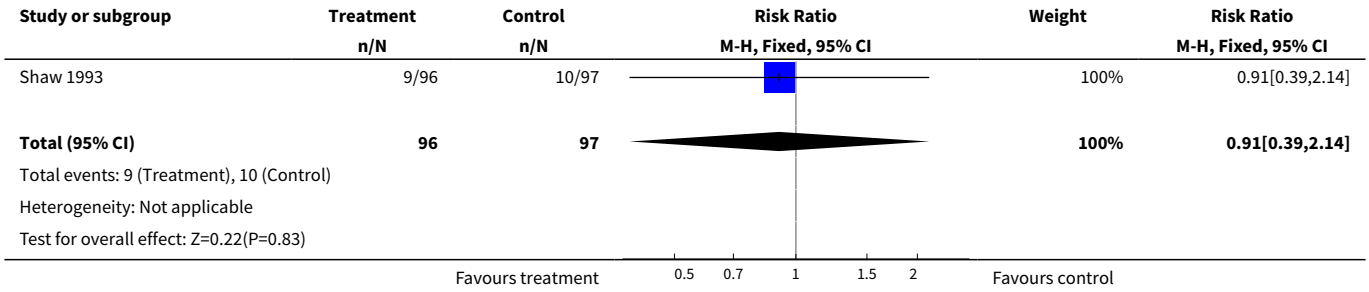
Analysis 3.2. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 2 Mortality at 28 days.



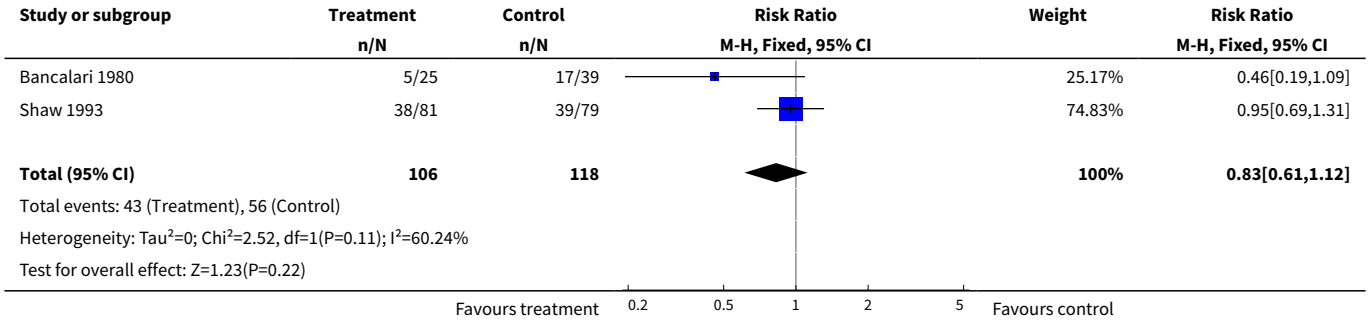
Analysis 3.3. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 3 Pneumothorax (with or without pulmonary interstitial emphysema).



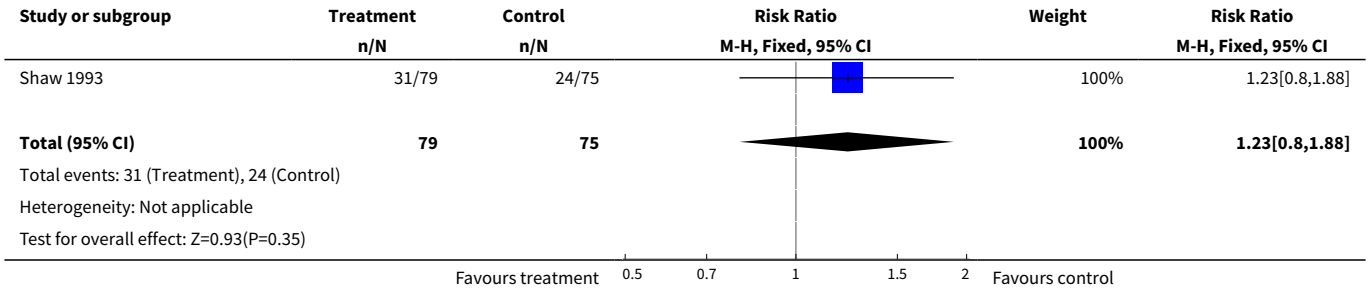
Analysis 3.4. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 4 Severe IVH (grade 3 or 4).



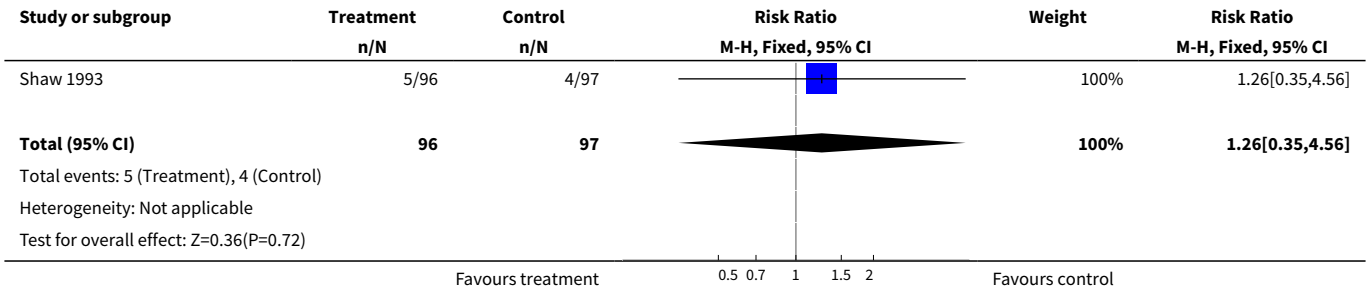
Analysis 3.5. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 5 CLD at 28 days postnatal age in survivors.



Analysis 3.6. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 6 CLD at 36 weeks postmenstrual age in survivors.



Analysis 3.7. Comparison 3 Routine paralysis versus no/selective paralysis (trials not selecting for asynchrony at entry), Outcome 7 Cystic PVL.



ADDITIONAL TABLES

Table 1. Sensivity analysis

	with Bancalari trial	without Bancalari trial	with Bancalari trial	without Bancalari trial
	RR [95% CI]	RR [95% CI]	RD [95% CI]	RD [95% CI]
mortality before discharge	1.24 [0.88; 1.74]	1.03 [0.54; 1.94]	0.06 [-0.04; 0.17]	0.01 [-0.12; 0.13]
pneumothorax with/without PIE	0.85 [0.59; 1.22]	0.67 [0.41; 1.11]	-0.04 [-0.11; 0.04]	-0.07 [-0.15; 0.01]
CLD at 28 days postnatal age in survivors	0.83 [0.61; 1.12]	0.95 [0.69; 1.31]	-0.08 [-0.21; 0.04]	-0.02 [-0.18; 0.13]

WHAT'S NEW

Date	Event	Description
27 July 2009	New search has been performed	This review updates the existing review "Neuromuscular paralysis for newborn infants receiving mechanical ventilation" published in the Cochrane Database of Systematic Reviews (Cools 2005). Updated search found no new trials. No changes to conclusions.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 4, 2000

Date	Event	Description
15 October 2008	Amended	Converted to new review format.
27 January 2005	New citation required but conclusions have not changed	This review updates the existing review "Neuromuscular paralysis for newborn infants receiving mechanical ventilation" published in The Cochrane Library, Issue 4, 2000 (Cools 2000). A search for new trials was done in April 2004. Unpublished data from one trial (Bancalari 1980) were obtained. The trial was assessed and included in the review.

CONTRIBUTIONS OF AUTHORS

The search of the databases was done by F. Cools. The selection of eligible trials, the methodological assessment of the included trials and the data extraction was done by the two reviewers (Cools and Offringa) independently, and discrepancies were solved with discussion. Cools entered the data and wrote the text, and Offringa contributed to data checking and editing. For the 2009 update, the review was updated centrally by the Cochrane Neonatal Review Group staff and reviewed and approved by both review authors.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Dutch Cochrane Centre, Amsterdam, Netherlands.
- Academic Hospital, Free University of Brussels, Brussels, Belgium.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cerebral Hemorrhage [etiology] [prevention & control]; Infant, Premature; Neuromuscular Blockade [*adverse effects]; Neuromuscular Nondepolarizing Agents [therapeutic use]; Outcome Assessment, Health Care; Pancuronium [therapeutic use]; Pneumothorax [etiology] [prevention & control]; Randomized Controlled Trials as Topic; Respiration, Artificial [*adverse effects]; Respiratory Distress Syndrome, Newborn [*therapy]

MeSH check words

Humans; Infant, Newborn