Prevention of ventilator induced lung injury in preterm infants with respiratory distress syndrome: PreVILIG
Cools, F.A.A.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 7

NEUROMUSCULAR PARALYSIS FOR NEWBORN INFANTS RECEIVING MECHANICAL VENTILATION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS (update Cochrane review in 2009)

Published as:
Cools F, Offringa M.
Neuromuscular paralysis for newborn infants receiving mechanical ventilation.
DOI: 10.1002/14651858.CD002773.pub2
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.

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.
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

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).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bancalari 1980</td>
<td>27</td>
<td>50</td>
<td>77</td>
<td>60.1%</td>
<td>1.37 [0.92, 2.05]</td>
<td></td>
</tr>
<tr>
<td>Greenough 1984</td>
<td>1</td>
<td>11</td>
<td>12</td>
<td>8.3%</td>
<td>0.33 [0.04, 2.73]</td>
<td></td>
</tr>
<tr>
<td>Perlman 1985</td>
<td>3</td>
<td>14</td>
<td>17</td>
<td>9.7%</td>
<td>0.71 [0.18, 2.84]</td>
<td></td>
</tr>
<tr>
<td>Pollitzer 1981</td>
<td>2</td>
<td>24</td>
<td>26</td>
<td>2.7%</td>
<td>2.17 [0.21, 22.39]</td>
<td></td>
</tr>
<tr>
<td>Quinn 1992</td>
<td>9</td>
<td>28</td>
<td>37</td>
<td>18.1%</td>
<td>1.33 [0.57, 3.09]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>127</td>
<td>137</td>
<td>264</td>
<td>100%</td>
<td>1.24 [0.88, 1.74]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>42</td>
<td>38</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.61, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

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.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Events Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bancalari 1980</td>
<td>18</td>
<td>50</td>
<td>61</td>
<td>35.9%</td>
<td>1.16 [0.68, 1.95]</td>
<td></td>
</tr>
<tr>
<td>Greenough 1984</td>
<td>1</td>
<td>11</td>
<td>12</td>
<td>24.1%</td>
<td>1.13 [0.03, 0.59]</td>
<td></td>
</tr>
<tr>
<td>Perlman 1985</td>
<td>3</td>
<td>14</td>
<td>17</td>
<td>4.9%</td>
<td>1.07 [0.22, 5.28]</td>
<td></td>
</tr>
<tr>
<td>Pollitzer 1981</td>
<td>3</td>
<td>24</td>
<td>27</td>
<td>8.0%</td>
<td>0.81 [0.20, 3.28]</td>
<td></td>
</tr>
<tr>
<td>Shaw 1993</td>
<td>13</td>
<td>96</td>
<td>109</td>
<td>27.1%</td>
<td>1.01 [0.49, 2.07]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>195</td>
<td>205</td>
<td>400</td>
<td>100.0%</td>
<td>0.84 [0.58, 1.21]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 7.69, df = 4 (P = 0.10); $I^2 = 48\%$
Test for overall effect: Z = 0.95 (P = 0.34)

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 HAEOMRHAGE (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).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Events Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenough 1984</td>
<td>1</td>
<td>11</td>
<td>12</td>
<td>14.9%</td>
<td>0.25 [0.03, 1.96]</td>
<td></td>
</tr>
<tr>
<td>Perlman 1985</td>
<td>5</td>
<td>14</td>
<td>19</td>
<td>40.5%</td>
<td>0.38 [0.20, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Quinn 1992</td>
<td>9</td>
<td>28</td>
<td>37</td>
<td>40.1%</td>
<td>0.89 [0.42, 1.73]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>53</td>
<td>50</td>
<td>103</td>
<td>100.0%</td>
<td>0.55 [0.34, 0.89]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.08, df = 2 (P = 0.21); $I^2 = 35\%$
Test for overall effect: Z = 2.43 (P = 0.01)

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 PERVENTRICULAR 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 - 11.1) versus 5.1 days (range 1.0 - 8.2). 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.

**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).
Pneumothorax:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Bancalari 1980</td>
<td>18</td>
<td>50</td>
<td>1.16 [0.68, 1.95]</td>
<td></td>
</tr>
<tr>
<td>Pollitzer 1981</td>
<td>3</td>
<td>24</td>
<td>0.81 [0.20, 3.28]</td>
<td></td>
</tr>
<tr>
<td>Shaw 1993</td>
<td>13</td>
<td>96</td>
<td>1.01 [0.49, 2.07]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>170</td>
<td>184</td>
<td>1.06 [0.71, 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 34

Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%

Test for overall effect: Z = 0.29 (P = 0.77)

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.
# TABLE OF INCLUDED STUDIES:

**Bancalari 1980**

<table>
<thead>
<tr>
<th>Methods</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Randomisation according to two interventions (factorial design): 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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality, pneumothorax, interstitial pulmonary emphysema, chronic lung disease at 28 days postnatal age</td>
</tr>
<tr>
<td>Notes</td>
<td>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</td>
</tr>
</tbody>
</table>
### Greenough 1984

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomised allocation, sealed envelopes; blinding of randomisation: yes; complete follow-up: 96%; blinding of outcome assessment: unclear</th>
</tr>
</thead>
</table>
| **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 cmH2O and rate < 20/min  
Control (n=11) - no pancuronium unless attending physician considered it desirable. |
| **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. |

### Perlman 1985

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomised allocation, sealed envelopes; blinding of randomisation: yes; complete follow-up: yes; blinding of outcome assessment: yes for some outcomes (brain ultrasound)</th>
</tr>
</thead>
</table>
| **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 15%. |
| **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. |
### Pollitzer 1981

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomised allocation, sealed envelopes; binding of randomisation: yes; complete follow-up: yes; binding of outcome assessment: unclear.</th>
</tr>
</thead>
</table>
| **Participants** | Study population = unsellected 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.  
Treatmen (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,  
pleural interstitial emphysema,  
duration of mechanical ventilation. |
| **Notes** | Bronchopulmonary dysplasia was reported as an outcome, but was not defined.  
Outcomes were reported on all infants. |
**Quinn 1992**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised allocation, sealed envelopes; binding of randomisation: yes; complete follow-up: yes; binding of outcome assessment: unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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”.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Comparison = routine paralysis versus selective paralysis. Treatment (n=29) Group P: pancuronium 0.1 mg/kg IV, repeated to maintain paralysis until inspired oxygen concentration &lt; 0.45. Control (n=29) Group M: morphine 50 μg/kg/h continuous infusion; could be increased to 100 μg/kg/h after 2 hours; infants received pancuronium if they were still fighting the ventilator after 4 hours of morphine infusion.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Intraventricular haemorrhage, air leak (pneumothorax or pulmonary interstitial emphysema), patent ductus arteriosus, duration of mechanical ventilation, mortality.</td>
</tr>
<tr>
<td>Notes</td>
<td>Group P is used as intervention group, and group M as control group for this review. Group M+P: pancuronium: 1 mg/kg IV repeatedly + morphine 50 μg/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.</td>
</tr>
<tr>
<td>Shaw 1993</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised allocation, method not described, stratification according to birth weight; blinding of randomisation: uncertain, complete follow-up: yes, blinding of outcome assessment: unclear.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Study population = unselected population of ventilated infants. 193 infants with birth weight &gt; 2000 g, ventilated for RDS within 24 hours after birth.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Comparison = routine paralysis versus selective paralysis. Treatment (n=96) Pancuronium 0.08 mg/kg IV repeatedly to maintain paralysis, provided mean blood pressure is &gt; 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=57) 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.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mortality before 28 days, pneumothorax, intraventricular haemorrhage, periventricular leukomalacia, chronic lung disease at 20 days and at 36 weeks GA, patent ductus arteriosus, duration of oxygen dependency.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Twenty-five of the 97 control infants (26%) received pancuronium at some stage. Outcomes were reported on all infants.</td>
</tr>
</tbody>
</table>
REFERENCES TO STUDIES

Included studies

Bancalari 1980


Greenough 1984

Perlman 1985

Pollitzer 1981

Quinn 1992

Shaw 1993

Excluded studies

Finer 1981

Ionides 1994

Miall-Allen 1987
Studies awaiting classification

Bonta 1992
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

Atherton 1999

Cabal 1985

Cheung 1999

Fanconi 1995

Gemelli 1990

Greenough 1983

Greenough 1998

Hegyi 1996

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

Miller 1994

Papile 1978

Perlman 1983

Philips 1979

Runkle 1984

Sinha 1984

Soll 1998

Stark 1979

Torres 1985