

Long versus short inspiratory times in neonates receiving mechanical ventilation (Review)

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ABSTRACT

Background

When intermittent positive pressure ventilation (IPPV) was introduced in newborn infants with hypoxic respiratory failure from hyaline membrane disease (HMD), mortality was high and air leaks problematic. This barotrauma was caused by the high peak inspiratory pressures (PIP) required to oxygenate stiff lungs. The primary determinants of mean airway pressure (and thus oxygenation) on a conventional ventilator are the inspiratory time (IT), PIP, positive end expiratory pressure and gas flow rates. In the 1970s uncontrolled studies on a small number of infants demonstrated a benefit in reducing barotrauma using a long IT and slow rates. This strategy was subsequently widely adopted. Current neonatal ventilators have been designed to minimise lung injury but rates of bronchopulmonary dysplasia (BPD) remain high. It is therefore important that the inspiratory time causing least harm is used.

Objectives

To determine in mechanically ventilated newborn infants whether the use of a long rather than a short IT reduces the rates of death, air leak and BPD.

Search strategy

The standard search strategy of the Cochrane Neonatal Review Group (CNRG) was used. Searches of electronic and other databases were performed. These included MEDLINE (1966 - April 2004) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2003). In order to detect trials that may not have been published, the abstracts of the Society for Pediatric Research, and the European Society for Pediatric Research were searched from 1998 - 2003.

Selection criteria

All randomised and quasi-randomised controlled trials enrolling mechanically ventilated infants with or without respiratory pathology evaluating the use of long versus short IT (including randomised crossover studies with outcomes restricted to differences in oxygenation).

Data collection and analysis

The standard method of the Cochrane Collaboration and its Neonatal Review Group were used. Two authors independently assessed eligibility, and the methodological quality of each trial, and extracted the data. The data were analysed using relative risk (RR) and risk difference (RD) and their 95% confidence intervals. A fixed effect model was used for meta-analyses.

Main results

In five studies, recruiting a total of 694 infants, a long IT was associated with a significant increase in air leak [typical RR 1.56 (1.25, 1.94), RD 0.13 (0.07, 0.20), NNT 8 (5, 14)]. There was no significant difference in the incidence of BPD. Long IT was associated with an increase in mortality before hospital discharge that reached borderline statistical significance [typical RR 1.26 (1.00, 1.59), RD 0.07 (0.00, 0.13)].

Authors' conclusions

Caution should be exercised in applying these results to modern neonatal intensive care, because the studies included in this review were conducted prior to the introduction of antenatal steroids, post natal surfactant and the use of synchronised modes of ventilatory

support. Most of the participants had single pathology (HMD) and no studies examined the effects of IT on newborns ventilated for other reasons such as meconium aspiration and congenital heart disease (lungs with normal compliance). However, the increased rates of air leaks and deaths using long ITs are clinically important; thus, infants with poorly compliant lungs should be ventilated with a short IT.

PLAIN LANGUAGE SUMMARY

Synopsis pending.

BACKGROUND

The application of techniques of endotracheal intubation and intermittent positive pressure ventilation (IPPV) for newborns with respiratory failure revolutionised neonatal intensive care. Prior to the introduction of IPPV, the mainstay of early management was supportive care, including the delivery of supplemental oxygen, maintenance of normoglycaemia and correction of metabolic acidosis. These measures had been recognised to reduce morbidity compared to controls (Usher 1963). IPPV was introduced as rescue therapy to treat apnea or correct hypoxaemia and respiratory acidosis in infants likely to die, often after bag and mask ventilation had failed. The techniques applied were initially adapted from those used in adult ventilation and met with limited success when first introduced (D-Papadopoulos 1965, Murdock 1970). The short inspiratory times used in adults to avoid impaired venous return and the fast rates to avoid asynchrony in newborns were not as effective in preterm infants with atelectatic and poorly compliant lungs (Adamson 1968). Gregory 1971 observed dramatic improvements over earlier approaches in neonates with respiratory distress syndrome (RDS) when continuous positive airway pressure (CPAP) was applied through an endotracheal tube. Ventilators were introduced in the early 1970s which used circuits with continuous gas flow and a timing device to close the expiratory valve allowing the infant to breathe spontaneously and receive intermittent mandatory ventilation (IMV). Kumarasamy 1973 reported improved survival when IMV was combined with the application of positive end expiratory pressure (PEEP), although early experiences in this era document the use of high peak inspiratory pressures (PIP) to achieve adequate oxygenation. The high PIPs which were used reflected the poor compliance of the lung and were associated with high rates of mortality and bronchopulmonary dysplasia (BPD) (Northway 1967).

Alternative strategies were sought to treat infants with HMD using lower inflating pressures. Reynolds 1971 and Herman 1973 noted that alveolar recruitment and hence oxygenation could be improved by using low rates (30 - 40 breaths per minute) and long inspiratory to expiratory (I:E) ratios. In some infants, improvements in oxygenation were seen when inspiratory times exceeded the expiratory times (inversed I:E ratios). In inverse-ratio ventila-

tion the IT is prolonged, thereby increasing mean airway pressures and allowing the use of lower PIP. As neonatal ventilation became more widely used in nurseries in the late 1970s/early 1980s, this strategy was often adopted even though the evidence of efficacy was based on small numbers (less than ten in both studies) with only improved arterial blood gases and indices of oxygenation reported as the primary outcomes.

In assisted ventilation, the ventilator maintains oxygenation by providing an effective mean airway pressure (MAP) exceeding atmospheric pressure and a suitable inspired oxygen concentration. It removes carbon dioxide by passively removing the delivered tidal volume. The tidal volume is the volume of gas moving in and out of the lung in a respiratory cycle. The minute ventilation is the product of tidal volume and respiratory frequency. The alveolar ventilation (minute ventilation minus dead space ventilation) determines the amount of carbon dioxide removed. Ventilator “cycling” refers to the change from inspiration to expiration and may be initiated by time (a pre-determined duration of inspiration), pressure (when a preset pressure is reached) or volume (expiration starts after a preset tidal volume is delivered).

Early pressure limited time cycled (PLTC) ventilators produced a square wave when pressure (on the y axis) was plotted against time (on the x axis). MAP is equal to the integration of the area under the pressure-time curve during a single respiratory cycle. The square wave is dependent on the pre-set inspiratory time, gas flow rate and ventilator frequency. Reynolds 1971 used square wave analysis to hypothesise that prolonging inspiratory time and using slower rates would improve oxygenation by increasing MAP. The longer the IT, the longer the lungs are held distended at the set PIP. Sustained inspiratory pressures may have their greatest incremental effect on non-functioning lung units, thereby improving distribution of the delivered tidal volume. With high frequency positive pressure ventilation (HFPPV; rates >60) changes in the pressure waveform are seen with a shortening of the inspiratory plateau such that the square wave is replaced by a sine wave. Thus any change in IT that accompanies frequency adjustments will change pressure waveforms, thereby altering MAP and oxygenation. Increasing MAP has been shown to improve oxygenation in RDS (Boros 1979). In contrast to early work by Reynolds 1971,

Stewart 1981 found that increasing PEEP had the greatest effect on MAP. Whilst a high MAP may be useful in acute RDS, excessive airway pressures in the recovering lung may impede venous return and cause overdistension.

The time required for the lungs to inflate and deflate is determined by the compliance and resistance of the respiratory system which includes the ventilator circuit, endotracheal tube and the patient's lung. The product of resistance and compliance, the time constant, is a measure of how long it takes for alveolar and proximal airway pressures to equilibrate. It provides a theoretical basis on how best to divide the respiratory cycle into inspiratory and expiratory times. The inspiratory time constant is typically short (approximately 0.05 seconds) in RDS and relatively long (0.25 seconds) in infants with normal lungs. For practical purposes, an expiratory time equivalent to three time constants must be provided to allow 95% of inspired tidal volume to be expelled (Harris 1996). Thus if the expiratory times are absolutely or relatively short (as seen in inverted I:E ratios) there is the potential for gas trapping to occur and the build up of pressure known as inadvertent PEEP (Weigl 1973). Potential complications of inadvertent PEEP include gas trapping, reduced compliance and air leak. This can lead to reduced pulmonary blood flow and central venous return, a factor implied in spontaneous intraventricular haemorrhage in preterm infants (Rennie 1987). Ahluwalia 1994 measured spontaneous inspiratory and expiratory times in newborns ventilated for RDS at a median of 0.3 (range 0.26- 0.34) and 0.46 (0.34-0.66) seconds respectively. RDS, characterised by markedly reduced compliance with very short time constants, can theoretically be managed by using either rapid rates (>60) or slow rates with long inspiratory times providing there is sufficient time for passive exhalation. With HFPPV, the expiratory time may be insufficient to allow for deflation and lung units can become overdistended and further reduce the compliance of the lung.

Meconium aspiration affects mature infants and is characterised by both parenchymal and airway disease. Inhalation of meconium or congenital pneumonias can present as non homogenous lung disease typified by adjacent areas of atelectasis and hyperinflation. Setting ventilator parameters for non homogenous lung disease with different time constants is challenging with the aim being to provide sufficient alveolar ventilation without the development of inadvertent PEEP. The measurement of compliance and resistance in these circumstances is then dependent on the frequency of ventilation. With the limitations of PLTC ventilators, it has been observed that tidal volumes decrease as inspiratory times are reduced beyond a critical point (less than the time constant of the respiratory system) and that above a certain rate (>75), dead space ventilation increases and minute ventilation is not a linear function of frequency (Boros 1984).

Recent advances in neonatal intensive care may influence the optimal inspiratory time. These include the availability of exogenous surfactant therapy (Soll 2004, Yost 2003) and the advances in ven-

tilator technology that allow synchronisation of ventilator breaths with an infant's spontaneous breathing (Greenough 2004). Surfactant improves oxygenation by increasing functional residual capacity. By stabilising patent airways and with the gradual recruitment of atelectatic regions of the lung, surfactant improves respiratory system compliance and may alter the optimal inspiratory time (Goldsmith 1996). Attempts to achieve synchrony have included the use of muscle relaxation (Greenough 1986) and rapid rates to avoid active expiration against positive pressure inflation (Greenough 2004). Modern neonatal ventilators achieve synchronisation by assisting each spontaneous breath or providing synchronised intermittent mandatory breaths. In addition, new generation neonatal ventilators with the addition of flow sensors allow continuous respiratory function and lung volume measurements. By measuring lung volumes, tidal volumes, resistance, dynamic and static lung compliance, much of the guesswork of setting ventilator parameters has been eliminated. However, despite these advances in ventilator technology, clinicians still need to set an inspiratory time.

The many variables involved in conventional mechanical ventilation (PIP, PEEP, IT, rate, flow rates) are interdependent making it difficult to assess the effects of changing one variable (IT) whilst holding the others constant. By using stated subgroup analyses (see objectives), the aim of this review is to identify the optimal inspiratory time (or range of times) in newborn infants needing respiratory support on conventional mechanical ventilation.

OBJECTIVES

The primary objective was to evaluate whether, in mechanically ventilated neonates, the use of long inspiratory times compared with short inspiratory times improved short and long term outcomes. These include mortality and the rate of acute lung injury (air leak) and/or chronic lung injury (BPD). For the initial analysis, any definitions of short and long used by the authors of studies were used.

Planned sub-group analyses included:

1. A subgroup of studies defining short IT as less than or equal to 0.5 seconds
2. Subgroup analysis based on the overall ventilator strategy i.e.
 - a. Absolute IT set at different (long and short) levels and maintained constant through the infant's treatment
 - b. I:E ratios set at different levels and maintained constant so that when rate was altered the IT and expiratory time were adjusted to maintain the I:E ratio
 - c. Trials where IT or I:E ratio form only part of the ventilator strategy e.g. when absolute IT and I:E ratios were not prescribed. In these trials an acceptable range of ITs and I:E ratios as defined by the authors would have been used in each arm
3. Underlying pathology (RDS vs other causes)
4. Gestational age i.e. term vs preterm

5. Use of muscle relaxants vs none
6. Surfactant vs no surfactant
7. Mode of ventilation (synchronised vs non synchronised)

Long term neurodevelopmental outcomes in childhood (blindness, sensorineural deafness, developmental delay on recognised psychometric testing)

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised and quasi-randomised controlled trials. Randomised crossover studies were eligible, but only for the assessment of acute effects on oxygenation.

Types of participants

Term and preterm infants less than 28 days of age and requiring conventional mechanical ventilation. No restrictions on underlying pathophysiology were applied.

Types of intervention

Short versus long inspiratory times in conventional mechanical ventilators including time cycled pressure limited ventilators (synchronised and non synchronised) and volume cycled ventilation. Trials using high frequency ventilation (> 150 breaths per minute) were excluded.

Types of outcome measures

Primary

Mortality in the first month of life, and before hospital discharge
Incidence of acute lung injury such as rates of all air leaks (pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, pneumoperitoneum)

Incidence of chronic lung injury (rates of BPD)

- The need for supplemental oxygen at 28 days of life
- The need for supplemental oxygen at 36 weeks postmenstrual age

Secondary

Indices of improved oxygenation including

- Oxygenation index (OI)
- Alveolar-arterial oxygen difference (AaDO₂)
- PaO₂/FiO₂ ratio (P/F ratio)

Lung mechanics (compliance and resistance of either the lung or respiratory system)

Duration of positive pressure respiratory support in days

Duration of supplemental oxygen requirement in days

Radiological evidence of neurological injury

- IVH (All grades and severe grades 3 or 4 intraventricular haemorrhage by Papile 1978 classification)
- Periventricular leukomalacia (PVL)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See: Cochrane Neonatal Research Group (CNRG) search strategy

The standard search strategy of the CNRG was used. These included MEDLINE (1966 - April 2004) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2003). The MEDLINE search terms used were newborn, neonate, infant, mechanical ventilation, positive pressure respiration and the text phrase "ventilator rate" and text words "inspiratory" or "expiratory". No language restrictions were applied. The abstracts of the Society for Pediatric Research, and the European Society for Pediatric Research were searched from 1998 - 2003.

METHODS OF THE REVIEW

The standard methods of the Cochrane Collaboration and the CNRG were used. The methodological quality of each trial was reviewed independently by the two authors for blinding of randomisation, blinding of intervention and outcome measurements as well as completeness of follow up.

The two authors independently assessed eligibility of retrieved studies and extracted data; the results were compared and differences resolved by discussion.

The statistical analysis used the fixed effect model. For categorical data the relative risk (RR), risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals were calculated. Continuous data were analysed using weighted mean difference (WMD). Where data for individual outcomes was incomplete (i.e. did not include all randomised babies), numerators and denominators were those presented in the published manuscript.

DESCRIPTION OF STUDIES

For the summary of the included studies see also table of included studies.

Five published trials (Spahr 1980, Heicher 1981, Greenough 1981, OCTAVE 1991, Pohlandt 1992) recruiting a total of 694 infants were identified. All trials were performed in the pre-surfactant era and when antenatal steroids were not widely used. Three (Spahr 1980, Heicher 1981 and Greenough 1989) were single

centre studies whilst OCTAVE 1991 and Pohlandt 1992 involved 6 and 7 centres respectively.

One study (Nilmeier 1995) was excluded. This was a randomised controlled trial in infants with ventilator dependent HMD recruited at two weeks of age, comparing two ITs of 1.0 and 0.4 seconds over a period of seven days. Oxygenation and respiratory mechanics were measured prior to randomisation and compared after a week of the intervention. The results, however were only published in part and were descriptive in nature. Improvements in oxygenation were described as indicated by FiO₂ requirement rather than our prespecified indices (AaDO₂, PF ratios), and these were only presented for infants randomized to a long IT.

Study Population

The inclusion criteria varied slightly between studies. All the studies except Greenough 1989 recruited infants with acute respiratory failure. Greenough 1989 compared different ITs when weaning infants recovering from HMD. Only Pohlandt 1992 had specific gestational age criteria for inclusion, recruiting infants less than or equal to 32 weeks gestation at birth. Heicher 1981 recruited ventilated infants with a birth weight of greater than 750g. In the study of OCTAVE all ventilated infants less than 72 hours of age were eligible whilst Spahr 1980 recruited all ventilated newborns over a 12 month period. The age at recruitment was not stated in the studies of Heicher 1981 and Spahr 1980. The differences in underlying respiratory pathology between the studies were small. Most infants had HMD although some cases of pneumonia were included. Only OCTAVE 1991 and Heicher 1981 specifically excluded infants with meconium aspiration syndrome (MAS) but no data specific to MAS were provided by any of the included studies.

Interventions

The ventilator strategies and types of ventilator used (see table of included studies) varied with each study.

Once randomised to a long IT or short IT, all infants were ventilated to meet therapeutic range of oxygenation and eucapnia as defined by the authors. All studies allowed adjustments in PIP to correct hypoxia. Ventilation was weaned by decreasing PIP. Where the IT was held constant, weaning of the ventilator rate was achieved by lengthening the expiratory time. All studies had *a priori* failure criteria (see table).

Inspiratory times as defined by the authors were as follows;

- Spahr 1980 2.0 vs 1.0 seconds. Both groups were ventilated at a rate of 20 breaths per minute (bpm). This allowed a comparison of I:E ratios (2:1 vs 1:2). IT ratios were held constant throughout whilst rates were allowed to be increased to 40 bpm to correct acidosis and hypercarbia. The range of ITs compared in this study were thus 2.0 - 1.0 (long) vs 1.0 - 0.5 (short) seconds.
- Heicher 1981 1.0 vs 0.5 seconds. The ITs were held constant throughout the study period. The long IT group were ventilated at a rate of 20 - 40bpm and an IT of 1.0 seconds. The rate was

increased to correct hypercarbia by reducing expiratory time. The short IT group were ventilated at a rate of 60 bpm and an IT of 0.33 seconds. Both groups were weaned by decreasing PIP and rate by increasing the expiratory time only. I:E ratios were thus not held constant.

- OCTAVE 1991 1.0 - 0.75 vs 0.33 seconds. For the long IT group, starting rate was 30 (range 20-40) bpm using an I:E of 1:1 and IT of 1.0 seconds. Whilst weaning the IT was reduced to 0.75 seconds. Thus in the long IT group neither IT or I:E ratio were held constant. The short IT group had an IT of 0.33 seconds, starting rate of 60 bpm, fixing the I:E at 1:2. The IT and I:E ratio was constant throughout in this arm in uncomplicated cases. In the presence of severe hypoxia as defined by the authors, IT could have been increased to 0.5 seconds with the rate unchanged giving an I:E of 1:1 in the short IT group.
- Pohlandt 1992 1.0 - 0.66 vs 0.33 seconds. For the long IT group, the starting rate was 30 bpm, an IT of 1 second with I:E of 1:1. The IT was reduced to 0.66 seconds when weaning and rate decreased by increasing expiratory time. Thus in the long IT group neither IT or I:E ratio were held constant. Infants in the short IT group were ventilated with an IT of 0.3 seconds at a rate of 60bpm, fixing the I:E at 1:2. Infants in this group were weaned by reducing PIP and PEEP until the infant was receiving endotracheal continuous positive airway pressure (CPAP).
- Greenough 1989 0.7 -1.0 vs 0.5 seconds. Infants with HMD were recruited if treated with HFPPV and rate had been reduced to 60 bpm. IT for both groups was 0.5 seconds at recruitment. The long IT group were weaned (reduction of respiratory rate) by adjusting both IT and expiratory time and keeping I:E constant at 1:1.2. The IT was increased incrementally to 1.0 seconds. In the short IT group IT was held constant at 0.5 seconds and I:E was variable. Rate was gradually reduced to zero (endotracheal CPAP). A crossover to the other arm was permitted for 30 minutes when rates were weaned to 40 and 20 bpm, allowing a comparison of arterial blood gases at a given rate and I:E ratio using long and short ITs.

Major Outcomes The major and secondary outcomes as stated by the authors were as follows.

Spahr 1980 and Heicher 1981 - mortality and morbidity (air leak and BPD) and the effect of two different ITs on ventilator settings (MAP, PIP, PEEP and rate compared to baseline). OCTAVE 1991 - mortality and morbidity (air leak and BPD). This study also followed up surviving premature infants (<33 weeks) recruited to assess the effect of treatment allocation on long term neurodevelopmental outcomes. Pohlandt 1992- the incidence of air leak following randomisation. Mortality and the incidence of BPD were recorded as secondary outcomes. In the study of Greenough 1989 the primary outcome was duration of weaning. Secondary outcomes included rates of air leak, death and the need for re-ventilation.

METHODOLOGICAL QUALITY

The methodological quality of each trial was assessed using the criteria of the Neonatal Review Group. For each trial the following were assessed: concealment of allocation schedule, inclusion in the analysis of all randomised participants and blinding of intervention and outcome measurement.

1. Concealment of allocation schedule

OCTAVE 1991 was a multi-centre trial in which the randomisation was adequately concealed by the use of sealed opaque envelopes held at the co-coordinating centre. Participating centres made a telephone call to the co-ordinating centre when an infant was enrolled and the next sealed envelope opened. Methods of concealing the allocation schedule were not used in the studies of Heicher 1981 and Spahr 1980. Lists were constructed in the study of Pohlandt 1992 such that the numbers treated with either a long or short IT were equal after every second infant enrolled for a particular gestation. These lists were not concealed. The method used in randomising enrolled infants was not described by Greenough 1989 and thus concealment of allocation was unknown.

Generation of allocation sequence -

This was not stated for OCTAVE 1991. Pohlandt 1992 used randomisation tables divided into blocks of two for each intervention arm for each of the intended target population (under 28 weeks, 28-30 and 31-32 weeks). Spahr 1980 used a coin toss to determine the treatment allocation sequence. Heicher 1981 quasi-randomised enrolled infants using alternate selection for long and short ITs. The generation of allocation sequence was not stated in the study of Greenough 1989.

2. Inclusion in the analysis of all randomised participants

All participants were accounted for in the included studies. Pohlandt 1992 used an unusual recruitment and randomisation procedure. Consent was not obtained and all preterm infants less than 32 weeks needing mechanical ventilation were provisionally enrolled and randomised. Infants not meeting secondary enrolment criteria ($\text{FiO}_2 > 0.4$) were excluded and replaced by the next preterm infant in the same gestational age category (37 of 181 initially randomised). An additional seven infants were excluded after randomisation because they received the alternate form of therapy during transport. Spahr 1980 excluded five (of 74) patients post randomisation either because of air leaks (one before randomisation, two post PDA ligation), one because of sepsis and one because of use of a muscle relaxant. The remaining three studies had no post randomisation exclusions. OCTAVE 1991 followed a subgroup of enrolled patients (<33 weeks gestation at birth) at a median age of 18 months. Of the 183 surviving eligible infants, 175 (96%) were seen.

3. Blinding of intervention

It was not possible to blind the caregivers in any of the studies.

4. Blinding of outcome assessments

All the primary outcome assessments were unblinded in the five included studies with one exception (Pohlandt 1992), where physicians and radiologists blinded to treatment allocation diagnosed air leak and BPD. In the OCTAVE 1991 study 98% of the long term neurodevelopmental assessments were blinded.

RESULTS

Five studies (Spahr 1980, Heicher 1981, Greenough 1989, OCTAVE 1991, Pohlandt 1992) enrolling 694 infants met the entry criteria and were included in the analysis.

Primary Outcomes

Comparison 01: Long versus short IT as defined by investigators (all trials)

Mortality

Mortality before hospital discharge was reported in all included studies (Table 1). OCTAVE 1991 was the only study to report mortality after hospital discharge. In this study mortality at latest follow up was 30/126 (24%) in the long IT group compared to 36/125 (29%) in the short IT group. In a pooled analysis, there was a trend toward an increased rate of mortality before hospital discharge in newborns ventilated with a long IT that reached borderline statistical significance [typical RR 1.26 (1.00, 1.59), typical RD 0.07 (0.00, 0.13)].

Air Leak

The rates of air leak (acute lung injury) were reported in all included studies (table 2). The studies of Heicher 1981 and Pohlandt 1992 demonstrated statistically significant differences in this outcome disfavoring the use of a long IT. There were no significant differences in the studies of Greenough 1989, Spahr 1980. OCTAVE 1991, the largest individual study in this meta-analysis, reported no overall difference in the rates of air leak but when this outcome was compared within a subgroup of infants with HMD, there was a statistically significant difference favouring the use of a short IT ($p = 0.013$). In a pooled analysis, the use of a long IT was associated with a significantly increased rate of air leak [typical RR 1.56 (1.25, 1.94), typical RD 0.13 (0.07, 0.20), NNT 8 (5, 14)].

BPD (Chronic lung injury)

The rates of BPD in all included studies (Table 3) was defined as the need for supplemental oxygen at 28 post natal days. None of the studies reported on this outcome at 36 weeks post conceptual age. No individual study found a significant difference in this outcome and in a pooled analysis, there was no significant difference in the rates of BPD [typical RR 0.91 (0.66, 1.24), RD -0.02 (-0.08, 0.04)]. The trend towards lower rates of BPD using a longer IT in the studies of Spahr 1980, Heicher 1981 and OCTAVE 1991 is offset by their higher rate of death.

For all primary outcomes there was no significant heterogeneity of treatment effect ($I^2 = 0$ for all outcomes)

Secondary Outcomes

Oxygenation

Improvements in oxygenation using our pre-defined criteria (AaDO₂, OI, P/F ratios) were not reported when comparing IT greater than 0.5 seconds with shorter IT. Spahr 1980 provides data for the mean AaDO₂ (SD) after 6 hours following the intervention (Table 4). At this early time point, no statistically significant differences were noted. Analysing survivors only, the AaDO₂ was significantly lower at 24 and 48 hours in infants ventilated using an IT of 2 seconds versus 1 second.

Duration of mechanical ventilation and oxygen therapy

Data on duration of ventilation in the included studies were either incomplete or presented in a format not permitting a pooled analysis. Pohlandt 1992 and Greenough 1989 did not publish sufficient data to allow a comparison between groups with respect to duration of mechanical ventilation and oxygen therapy. Spahr 1980 presented data only from survivors in the first week of life and Heicher 1981 excluded more than 10% of babies from the analysis of these outcomes. OCTAVE 1991 reported no significant difference between groups with respect to median age of extubation and median age at weaning from supplemental oxygen.

Neurological injury

No individual study reported the outcomes of IVH or PVL based on ultrasound findings. Spahr 1980 reported the incidence of IVH through examination at autopsy in those who died and using computed tomography in two survivors. Heicher 1981 described large IVH diagnosed at autopsy but rates of IVH in survivors was not reported. It was the intention of the OCTAVE 1991 group to report on rates of IVH but difficulty was found in retrieving images from all the participating centres and this was replaced by long term neurodevelopmental follow up. In the available data from two trials, no significant effect on this outcome was shown (Table 6).

Patent ductus arteriosus

Symptomatic patent ductus arteriosus (PDA) requiring treatment was reported in the studies of Spahr and Pohlandt. There was a considerable difference in the rates of PDA, with Spahr (conducted in 1978) reporting an incidence of 9% in all recruited infants and Pohlandt (conducted between 1983 and 1985) reporting an incidence of 35% of all recruited infants. This probably reflects the improvements in echocardiography in the intervening period. In a pooled analysis of these two trials, no significant effect on this outcome was shown (Table 6)

Developmental delay

No individual study used formal psychometric testing to assess long term developmental status. The single study reporting long term outcome data (OCTAVE 1991) followed up surviving infants under 33 weeks gestation to a median age of 18 months. The tools used for these assessments were not stated. The outcomes reported were cerebral palsy (Table 7), sensory deficits (impaired

hearing or vision; Tables 8 and 9) or global developmental delay. There was an increased rate of cerebral palsy with small numbers (12 versus 4 cases) in infants treated with long IT but this was of borderline statistical significance [RR 2.90 (0.97, 8.65), RD 0.09 (0.00, 0.17)].

Subgroup Analyses

Comparison 02: Long (>0.5 seconds) vs Short (<0.5 seconds) IT

This subgroup analysis involved all the included studies except for Spahr 1980 and resulted in findings similar to the overall analysis. In a pooled analysis of four trials involving 625 infants, mortality before hospital discharge showed a trend disfavoured a long IT which did not reach statistical significance [typical RR 1.24 (0.96, -1.60), typical RD 0.06 (-0.01, 0.13)]. A long IT was associated with a significant increase in the number of air leaks [typical RR 1.56 (1.24, 1.97), typical RD 0.13 (0.07, 0.20), NNT 8 (5, 14)]. There was no significant difference in rates of BPD [typical RR 0.92 (0.66, 1.28)].

Analysis based on the overall ventilator strategy

a. constant IT - only Heicher 1981 maintained IT at 1.0 vs 0.5 seconds in the acute and weaning period.

b. constant I:E ratios - only Spahr 1980 and OCTAVE 1991 aimed to keep I:E ratios constant. It should be noted that the ITs in these two studies are vastly different with the duration of inspiration set in the "short IT" arm of Spahr 1980 equal to that set in the "long IT" arm of OCTAVE 1991. With the vastly different ITs and ventilator rates and thus very different absolute ratios, a subgroup analysis of these two studies was not performed based on ventilator strategy. These two trials were combined using all enrolled infants in Spahr 1980 and those with HMD in OCTAVE 1991 in a pooled analysis of infants with HMD (see below).

c. where both IT and I:E ratios are varied

In all studies the short IT remained unchanged. In most of the studies adjustments of the long IT were permissible when weaning commenced. Variable I:E ratios were seen in the long IT group when rate was either increased or decreased. The ventilator rate ranged between 20 and 40 for Heicher 1981 and OCTAVE 1991 and 30 to 40 for Pohlandt 1992. Thus a subgroup analysis was not performed.

Comparison 03: Long versus short IT in HMD (subgroup analysis by diagnosis)

Although the primary respiratory diagnosis was HMD in most infants in the included studies, only Spahr 1980 and OCTAVE 1991 provided published data on outcomes by respiratory pathology. In a pooled analysis of patients with HMD, a significant increase in mortality before discharge [typical RR 1.54 (1.06, 2.23), typical RD 0.12 (0.02, 0.21), NNT 8 (5, 50)] and air leak [typical RR 1.73 (1.17, 2.57), typical RD 0.14 (0.04, 0.24), NNT 7 (4, 25)] was seen in the infants randomised to a long IT.

Gestational age

All the trials except for Pohlandt 1992 (infants less than or equal to 32 weeks gestation randomised) had no restrictions on gestational age at recruitment. In this individual study there was a statistically significant increase in air leak in the long IT group. No significant differences were seen in rates of mortality before hospital discharge and BPD.

Comparison 04: Long versus short IT (subgroup analysis of trials allowing use of muscle relaxants)

Muscle relaxants were allowed in the trials of Heicher 1981, Pohlandt 1992 and OCTAVE 1991 but not used in Spahr 1980 and Greenough 1989. Data on the extent of use of muscle relaxants were not presented in the report by Pohlandt 1992, and were incomplete in OCTAVE 1991 (published data was sourced from only one of the participating centres). Similar use of muscle relaxants occurred in each arm of Heicher 1981 (13 versus 14). In an analysis confined to the three trials permitting muscle relaxants usage, there was a significant increase in air leak [typical RR 1.56 (1.25, 1.94), typical RD 0.14 (0.07, 0.21), NNT 7 (5, 14)] and an increase in mortality [typical RR 1.26 (0.97, 1.62), typical RD 0.07 (-0.01, 0.14)] which reached marginal statistical significance, in infants managed with a long IT. In the trials where no muscle relaxants were used (Spahr 1980, Greenough 1989), there were no statistically significant differences in air leak or mortality.

Trials using surfactant

None of the trials used surfactant in the management of HMD.

Ventilator mode

All infants were ventilated using continuous mandatory ventilation. No synchronised modes were used. Ventilator types differed (see table of included studies).

DISCUSSION

The goals of mechanical ventilation are to achieve and maintain oxygenation and remove carbon dioxide whilst minimizing the risk of lung injury. These studies were performed at a time when mortality rates for ventilated infants with hypoxic respiratory failure were considerably higher than current rates (Doyle 1999). Major changes since their publication may reduce the applicability of the results of these meta-analyses. These changes include the routine use of antenatal steroids and postnatal surfactant. The major complications of HMD seen at the time of these studies (namely hypoxia and air leak despite intervening with IPPV) have been significantly reduced by surfactant replacement therapy (Soll 2004). Although both these interventions have significantly altered the treatment of HMD, the risk of mortality has been markedly reduced but has not been removed. Morbidities such as air leak and BPD continue to occur. The classical definition of BPD by Northway 1967 was based on larger and more mature (>30 weeks) newborns and has been replaced by oxygen and/or ventilator dependency at 36 weeks post conceptual age to reflect the present

population of newborn infants with HMD. These extremely low birth weight, extremely premature infants continue to have significantly high rates of BPD. None of the studies in this systematic review looked at ventilatory or oxygen requirements at 36 weeks.

The use of long vs short ITs has not been well studied in subjects with established BPD or evolving BPD. The one study excluded from this meta-analysis (Nilmeier 1995) investigated the effects of a long or short IT on subjects with BPD (more than one month of age and ventilated) and looked at pulmonary mechanics and oxygenation before and after one week of the intervention. Although a long IT improved delivered tidal volumes, no significant differences were seen in duration of ventilation or hospital stay.

The IT set by the attending clinician is a single parameter that can influence oxygenation. Other manipulations include providing sufficient PEEP, so that positive pressure delivered throughout the respiratory cycle is above the critical opening pressure of the lung, thus avoiding repeated inflation deflation cycles which are injurious to the lung. Gas flow rates are usually held constant and the effects of varying gas flow rates on oxygenation and BPD have yet to be investigated. Of all the included studies, only one (Spahr 1980) provided data on the effects of IT on oxygenation in the acute phase of HMD. Whilst the study used ITs in both arms that would be considered "long", this was a study primarily comparing two I:E ratios. The improvements in oxygenation seen in inverse ratio ventilation can be attained (using the same physiological principles of alveolar recruitment and maintenance of lung volumes) if appropriate PEEP is applied throughout the respiratory cycle. The optimum level of PEEP will vary according to the underlying pulmonary pathophysiology and is yet to be evaluated in a formal clinical trial.

The range of ITs used in the long IT groups in this systematic review was 0.66 to 2.0 seconds. In acute HMD, where the median IT is 0.3 seconds (Ahluwalia 1994), these ITs are likely to cause asynchrony and patient discomfort. If these long ITs were used in surfactant treated infants, the combination of improved compliance and greater likelihood of active expiration against a positive pressure inflation may increase the risk of air leak. Thus using a long IT in acute HMD following surfactant replacement may be an unnecessary strategy unless faced with continuing severe hypoxia. In these situations there are current alternative modes of therapy to improve oxygenation if conventional ventilation is failing, including rescue high frequency ventilation and the use of inhaled nitric oxide in mature infants. Perinatal units are now widely using ventilators that synchronise with the infant's breathing and target tidal volumes. With synchronised ventilation, square wave ventilation has been replaced by sinusoidal waves so that mean airway pressures are less influenced by the length of the IT.

This review has shown no advantage in using long IT over short IT in the treatment of acute respiratory failure (mainly HMD). Whilst there is increasing use of non invasive ventilation such as

nasal continuous positive airway pressure to avoid ventilator induced lung injury in the acute management of HMD, mechanical ventilation will continue to have a role in extremely immature infants and those with HMD complicated by apnea. In institutions where surfactant is unavailable, lengthening the IT may improve oxygenation in the acute phase. However, as compliance improves, the IT should be reviewed regularly as this review demonstrates a significant risk of lung injury (airway leak) with a long IT. The use of a long IT where time constants are longer than acute HMD such as premature infants with BPD, meconium aspiration syndrome and newborns in cardiac failure may be appropriate and is yet to be investigated.

Whilst neonatal respiratory failure is not a single disease entity, relatively recent advances in technology have allowed the bedside display of real time inspiratory and expiratory tidal volumes. Clinicians therefore have the ability to adjust the IT as pulmonary mechanics change during the course of an infant's illness. These strategies will need to be evaluated in future clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

Long inspiratory times when used in acute HMD in a population not exposed to antenatal steroids and postnatal surfactant are associated with higher rates of mortality and morbidity. Stiff lungs with HMD have very short time constants. Mechanically ventilated infants with HMD and especially those treated in institu-

tions where these adjunctive therapies are not available should be ventilated using a short IT.

Implications for research

The availability of real time, continuous measurements of pulmonary mechanics may enhance clinicians' ability to detect the optimal IT for infants with different underlying pathologies and at different time points in their illness. Future research should examine whether new monitoring equipment and ventilator strategies, including adjusting ITs to match underlying compliance, can further reduce the harmful effects of neonatal mechanical ventilation.

POTENTIAL CONFLICT OF INTEREST

None

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- Murdoch Children's Research Institute, Melbourne AUSTRALIA

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TABLES

Characteristics of included studies

Study	Greenough 1989
Methods	Concealment of allocation: Can't tell - method of randomisation to either long IT (group A) or short IT (group B) not stated. Blinding of intervention: No Completeness of follow up: Yes for short-term outcomes - all participants accounted for. Blinding of outcome measurement: No Single centre study. Method of randomisation not stated. Intervention not blinded. Follow up complete to stated primary outcome (duration of weaning).
Participants	Single centre study. All infants with RDS (n=40) and ventilated with HFPPV (>60bpm) were recruited when weaning commenced (PIP = 20cm H20 and rate =60bpm).
Interventions	At recruitment all infants were ventilated using an IT of 0.5 seconds. Weaning then commenced using one of two strategies. In Group A (long IT) (n=20), the rate was reduced by increasing both the IT and ET maintaining a fixed I:E ratio at 1:1.2. Maximum IT in this group was 1 second. In group B (short IT) (n= 20), the rate was weaned by keeping the IT fixed at 0.5 secs whilst increasing the expiratory time (ET). Single (Sechrist) type of ventilator.
Outcomes	Air leak Indices of oxygenation (paO2) Duration of weaning Rate of reintubation
Notes	Year of study = 1989. Pre-surfactant. Age at recruitment not specified.
Allocation concealment	B – Unclear
Study	Heicher 1981
Methods	Concealment of allocation: No - quasi-randomised using alternate allocation for long and short ITs Blinding of intervention: No Completeness of follow up: Yes for short-term outcomes (all outcomes complete for hospital stay) Blinding of outcome measurement: No
Participants	All infants >750g and ventilated with abnormal CXR findings (n=102). Infants with gross abnormalities, chromosomal anomalies and meconium aspiration were excluded.
Interventions	Long IT (n=51) compared with short IT (n=51). Long IT= 1.0 seconds; rates used 20-40bpm. Short IT= 0.5 seconds; rate used 60bpm. Single ventilator (Babybird) used in both groups. Criteria for failed treatment and relaxation of allocated ventilator strategy were as follows; 1. Hypoxia - either (i)PaO2 < 50 torr with FiO2 of 1.0 and PEEP of 8 to 10cm H20 or (ii) FiO2 > 0.6 (short IT) or PIP > 30cm H20 (long IT) for 72 hours. 2. Hypercarbia - PaCO2 > 45 torr on maximum PIP and rate permitted for the group.
Outcomes	Mortality Air leak BPD at 30 days by Northway criteria. Combined outcome of death and IVH

Characteristics of included studies (Continued)

Notes Years of study = 1978 - 79. Pre-surfactant. Age at recruitment not specified.

Allocation concealment C – Inadequate

Study OCTAVE 1991

Methods Concealment of allocation: Yes - sealed opaque, serially numbered envelopes stored at co-ordinating centre.
Blinding of intervention: No
Completeness of follow up: Yes for short-term outcomes - 100% follow up for in-hospital outcomes with 97% of infants born less than 33 weeks accounted for in the long term outcome assessment at 18 months. Blinding of outcome measurement: not for primary outcomes. 98% of neurodevelopmental follow up completed by physicians blinded to ventilation strategy

Participants Newborns of any gestation ventilated for any reason (n=346). Infants with meconium aspiration excluded. Infants were enrolled before 72 hours of age.

Interventions Long IT (n=172) compared with short IT (n=174). Long IT= 1.0 seconds; starting rate=20bpm (range=20-40bpm) and I:E ratios not fixed. Short IT=0.33 seconds; rate used =60bpm and I:E ratio fixed at 1:2. Single ventilator (Sechrist IV 100B) used in both groups. Dopamine and tolazoline used at physician's discretion to treat hypotension or reduce right to left shunting. The use of muscle relaxants was permitted for recurrent air leaks and for poor gas exchange despite recruitment manouvres and optimisation of haemodynamics. Criteria for failed treatment and relaxation of allocated ventilator strategy were as follows; 1. Hypoxia - PaO₂ < 50mmHg despite FiO₂ >0.95 and MAP of 17cmH₂O. 2. Recurrent pneumothoraces

Outcomes Death before discharge
Air leak
BPD defined as need for supplemental oxygen at 28 days
A subgroup of infants less than 33 weeks gestation had long term follow up at a median age of 18 months

Notes Years of study = 1983 - 86. Pre-surfactant.

Allocation concealment A – Adequate

Study Pohlandt 1992

Methods Concealment of allocation: No - all ventilated infants provisionally randomised using one of three randomisation tables (stratified by gestational age). If infant subsequently excluded they were replaced by the next preterm infant in the same gestational age category.
Blinding of intervention: No
Completeness of follow up: Yes for primary outcomes - 100% follow up for in-hospital outcomes
Blinding of outcome measurement: Only for diagnosis of air leak and BPD

Participants Preterm infants equal to or less than 32 weeks gestation and mechanically ventilated (n=181) were randomised if FiO₂ >0.4 after 3 hours of birth (no upper age limit given). Infants later excluded if the FiO₂ was < 0.4 to maintain PaO₂ >50mmHg or if there were any violations of allocated ventilation protocol (exclusions post randomisation=44)

Interventions Long IT (n=63) compared with short IT (n=74). Long IT=1.0 seconds; rates of 30 to 40bpm; I:E ratio 1:1 increased to 2:1 in case of hypoxaemia. IT reduced to 0.66 seconds during weaning. Short IT=0.33 seconds; rate=60bpm. I:E ratios kept constant at 1:2; weaned by reducing PIP, PEEP and inspired oxygen. Seven different ventilators were used in this study. No failure criteria described in the report.

Outcomes Mortality
Extra-alveolar air leak
BPD at 28 days by Northway criteria

Notes Years of study = 1983 - 85. Parental consent not sought as ventilator frequencies of 30 -100 widely used in the participating units. Pre-surfactant.

Allocation concealment C – Inadequate

Study	Spahr 1980
Methods	Concealment of allocation: No - randomised by coin toss Blinding of intervention: No Completeness of follow up: Yes for short-term outcomes Blinding of outcome measurement: No
Participants	All infants admitted in a 12 month period and ventilated for HMD (n=74). Five post randomisation exclusions (pre-existing air leaks=3, sepsis=1, use of paralysing agent=1)
Interventions	Long IT (n=36) compared with short IT (n=33). Long IT=2 seconds; rate=20bpm; I:E ratio 2:1. Short IT=1 seconds; rate=20bpm; I:E ratio 1:2. Target PaO ₂ 45 - 60mmHg and pH 7.25 to 7.35. Single ventilator (Babybird). No failure criteria described in the report.
Outcomes	Mortality at 28 days Air leak BPD defined as need for supplemental oxygen at one month with typical radiographic findings Pulmonary haemorrhage, IVH (all grades), PDA.
Notes	Year of study = 1978. Pre-surfactant and pre antenatal steroids.
Allocation concealment	C – Inadequate
HMD = Hyaline Membrane Disease, RDS = Respiratory Distress Syndrome, IT = inspiratory time, IVH = intraventricular haemorrhage, HFPPV = High Frequency Positive Pressure Ventilation	

Characteristics of excluded studies

Study	Reason for exclusion
Nilmeier 1995	Randomised controlled trial of infants recruited at two weeks of age. Oxygenation and respiratory mechanics were compared after a week of intervention at two ITs (1.0 and 0.4 seconds). Published results however were incomplete (data from only one group) and descriptive in nature (not using our prespecified indices of AaDO ₂ and PF ratios).

ANALYSES

Comparison 01. Long vs Short IT as defined by investigators (all trials)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality before discharge	5	694	Relative Risk (Fixed) 95% CI	1.26 [1.00, 1.59]
02 Air leak	5	685	Relative Risk (Fixed) 95% CI	1.56 [1.25, 1.94]
03 BPD (supplemental oxygen at 28 days)	4	654	Relative Risk (Fixed) 95% CI	0.91 [0.66, 1.24]
04 AaDO ₂ (mmHg) values after 6 hours of intervention	1	69	Weighted Mean Difference (Fixed) 95% CI	-18.60 [-93.78, 56.58]
05 IVH (all grades)	2	171	Relative Risk (Fixed) 95% CI	1.11 [0.72, 1.71]
06 Patent ductus arteriosus (PDA)	2	206	Relative Risk (Fixed) 95% CI	0.91 [0.58, 1.43]
07 Cerebral palsy in survivors less than 33 weeks gestation at birth	1	177	Relative Risk (Fixed) 95% CI	2.90 [0.97, 8.65]
08 Visual impairment in survivors less than 33 weeks gestation at birth	1	177	Relative Risk (Fixed) 95% CI	2.09 [0.83, 5.26]

09 Sensorineural hearing loss in survivors less than 33 weeks gestation at birth	1	177	Relative Risk (Fixed) 95% CI	1.93 [0.60, 6.19]
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Comparison 02. Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality before discharge	4	625	Relative Risk (Fixed) 95% CI	1.24 [0.96, 1.60]
02 Air leak	4	616	Relative Risk (Fixed) 95% CI	1.56 [1.24, 1.97]
03 BPD (supplemental oxygenation at 28 days)	3	585	Relative Risk (Fixed) 95% CI	0.92 [0.66, 1.28]
04 IVH (all grades)	1	102	Relative Risk (Fixed) 95% CI	1.08 [0.55, 2.14]

Comparison 03. Long vs Short IT in HMD (subgroup analysis by diagnosis)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality before hospital discharge	2	306	Relative Risk (Fixed) 95% CI	1.54 [1.06, 2.23]
02 Air leak	2	303	Relative Risk (Fixed) 95% CI	1.73 [1.17, 2.57]
03 BPD (supplemental oxygen at 28 days)	2	253	Relative Risk (Fixed) 95% CI	0.88 [0.60, 1.30]

Comparison 04. Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality before discharge	5	694	Relative Risk (Fixed) 95% CI	1.26 [1.00, 1.59]
02 Air leak	5	685	Relative Risk (Fixed) 95% CI	1.56 [1.25, 1.94]
03 BPD (supplemental oxygen at 28 days)	4	654	Relative Risk (Fixed) 95% CI	0.91 [0.66, 1.24]
04 IVH (all grades)	2	171	Relative Risk (Fixed) 95% CI	1.11 [0.72, 1.71]

INDEX TERMS

Medical Subject Headings (MeSH)

Hyaline Membrane Disease [*complications]; Infant, Newborn; Infant, Premature; *Inhalation; Intermittent Positive-Pressure Ventilation [*methods]; Randomized Controlled Trials; Respiratory Insufficiency [etiology; *therapy]; Time Factors

MeSH check words

Humans

COVER SHEET

Title	Long versus short inspiratory times in neonates receiving mechanical ventilation
Authors	Kamlin COF, Davis PG
Contribution of author(s)	Dr Kamlin and Dr Davis performed the literature search, assessed the methodological quality of eligible trials and extracted data independently. Dr Kamlin wrote the review and Dr Davis reviewed the manuscript.
Issue protocol first published	2003/4

Review first published	2004/4
Date of most recent amendment	11 August 2004
Date of most recent SUBSTANTIVE amendment	23 June 2003
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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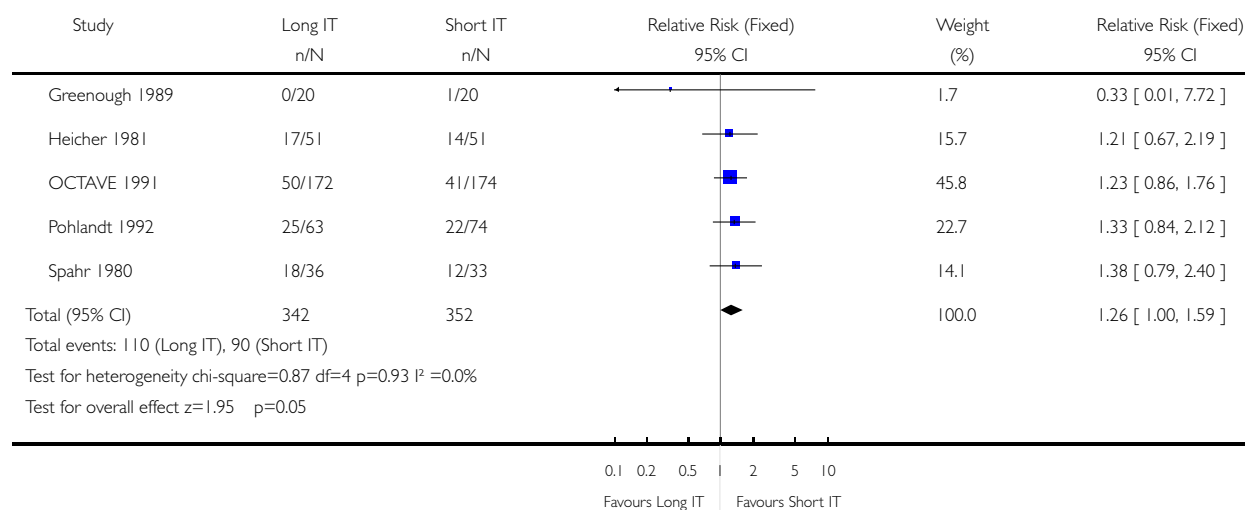
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 01 Mortality before discharge

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 01 Mortality before discharge

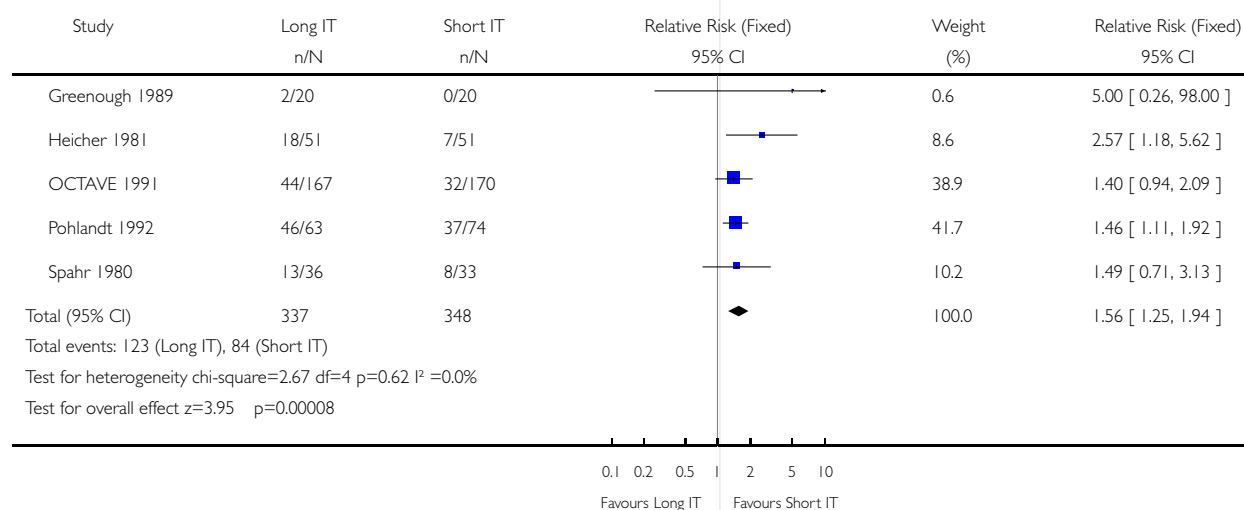


Analysis 01.02. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 02 Air leak

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 02 Air leak

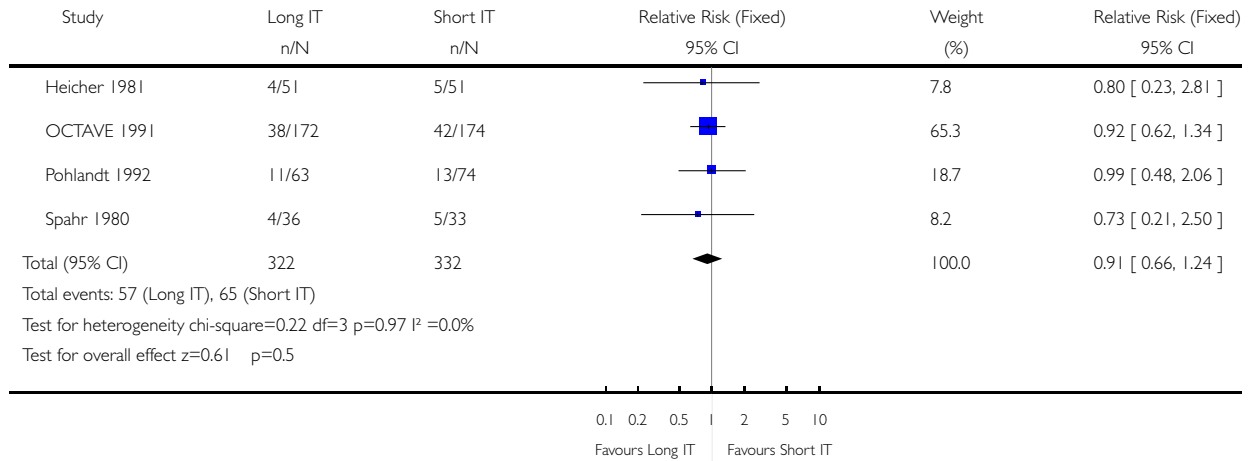


Analysis 01.03. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 03 BPD (supplemental oxygen at 28 days)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 03 BPD (supplemental oxygen at 28 days)

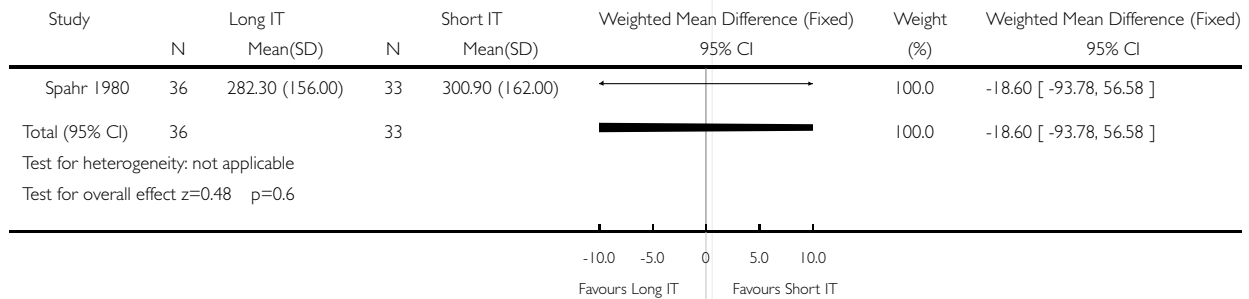


Analysis 01.04. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 04 AaDO₂ (mmHg) values after 6 hours of intervention

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 04 AaDO₂ (mmHg) values after 6 hours of intervention

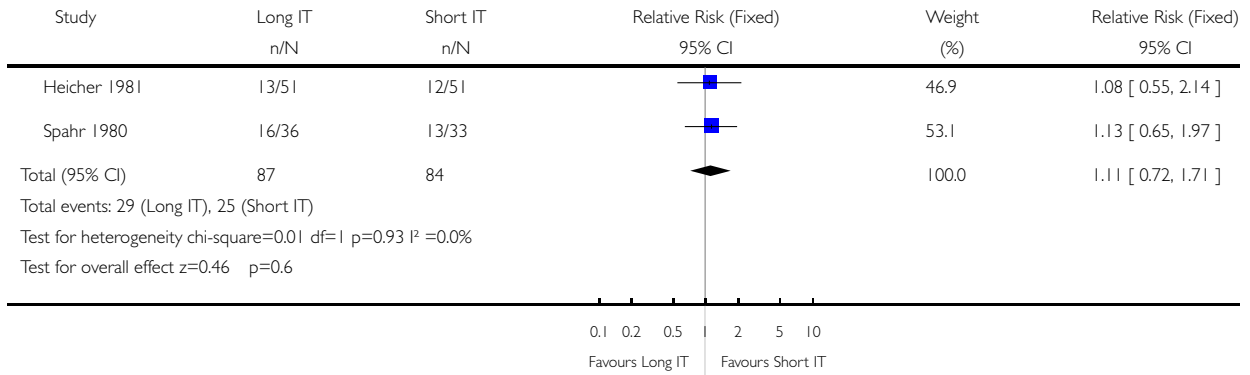


Analysis 01.05. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 05 IVH (all grades)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 05 IVH (all grades)

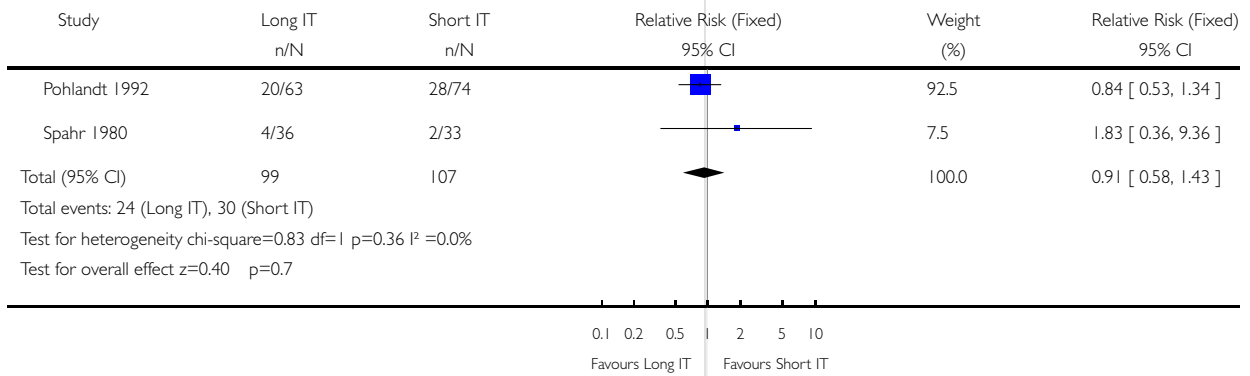


Analysis 01.06. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 06 Patent ductus arteriosus (PDA)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 06 Patent ductus arteriosus (PDA)

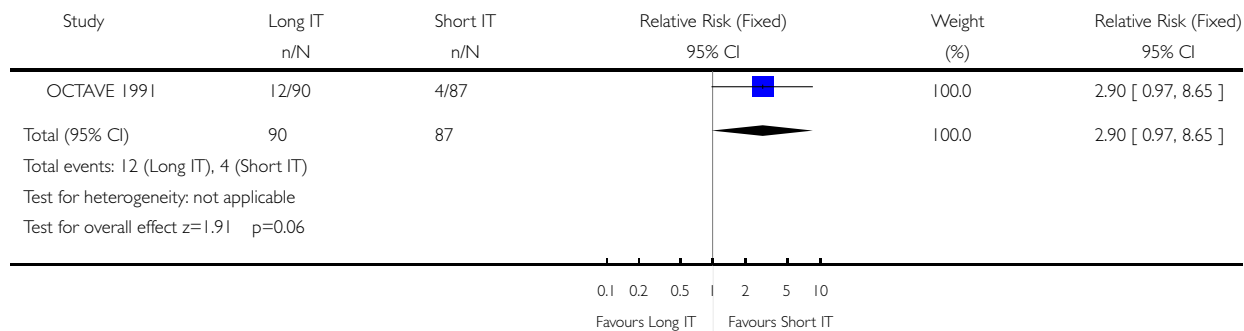


Analysis 01.07. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 07 Cerebral palsy in survivors less than 33 weeks gestation at birth

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 07 Cerebral palsy in survivors less than 33 weeks gestation at birth

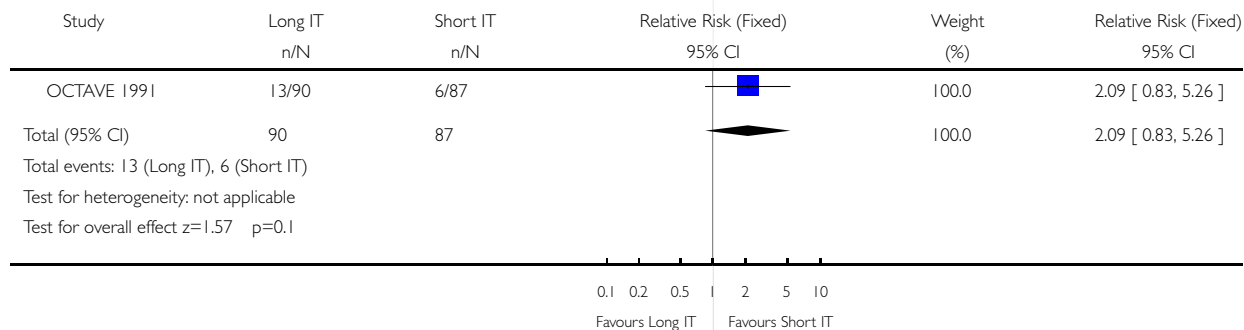


Analysis 01.08. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 08 Visual impairment in survivors less than 33 weeks gestation at birth

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 08 Visual impairment in survivors less than 33 weeks gestation at birth

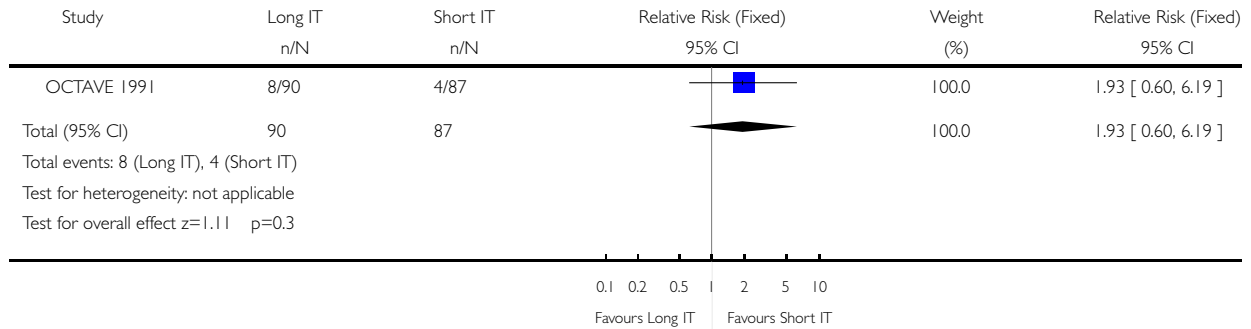


Analysis 01.09. Comparison 01 Long vs Short IT as defined by investigators (all trials), Outcome 09 Sensorineural hearing loss in survivors less than 33 weeks gestation at birth

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 01 Long vs Short IT as defined by investigators (all trials)

Outcome: 09 Sensorineural hearing loss in survivors less than 33 weeks gestation at birth

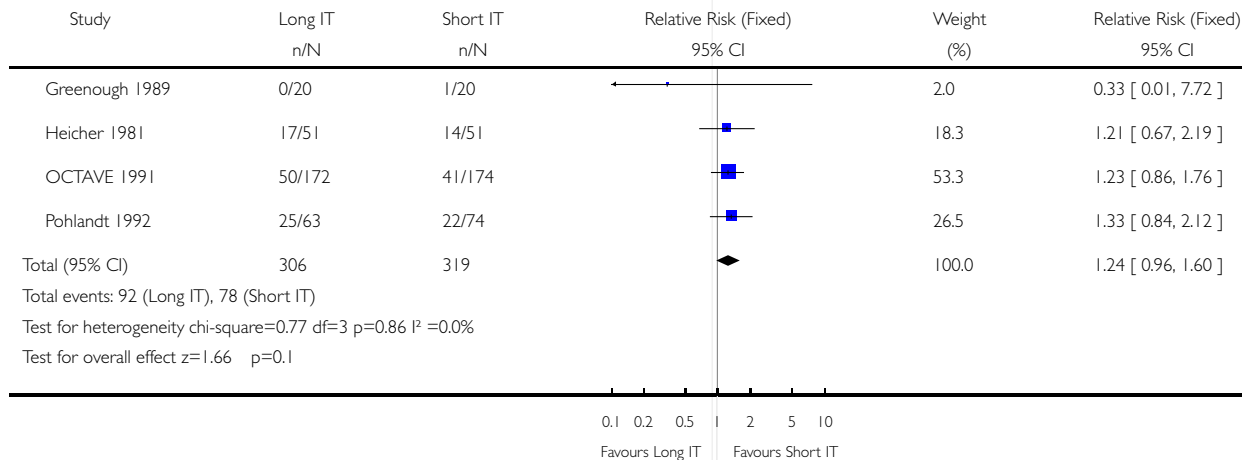


Analysis 02.01. Comparison 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 01 Mortality before discharge

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

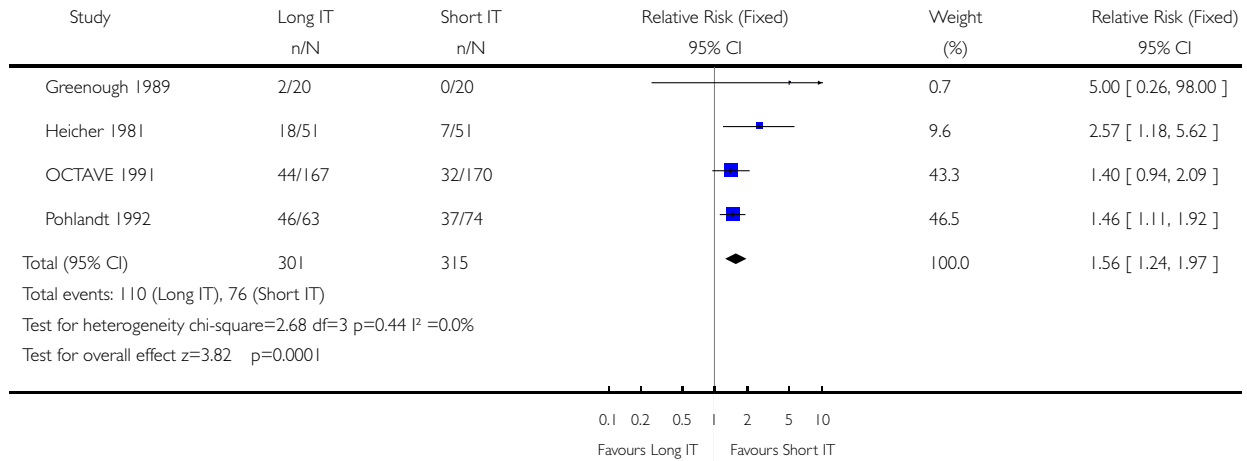
Comparison: 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

Outcome: 01 Mortality before discharge



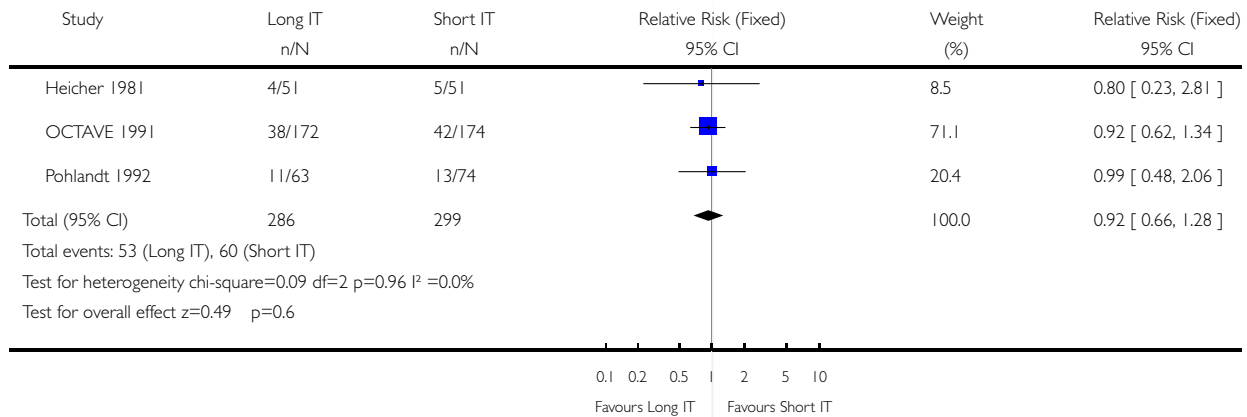
Analysis 02.02. Comparison 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 02 Air leak

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation
 Comparison: 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)
 Outcome: 02 Air leak



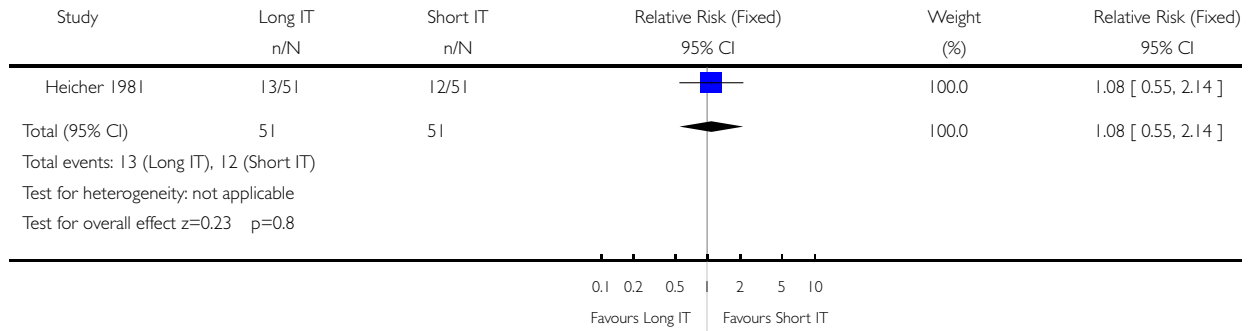
Analysis 02.03. Comparison 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 03 BPD (supplemental oxygenation at 28 days)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation
 Comparison: 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)
 Outcome: 03 BPD (supplemental oxygenation at 28 days)



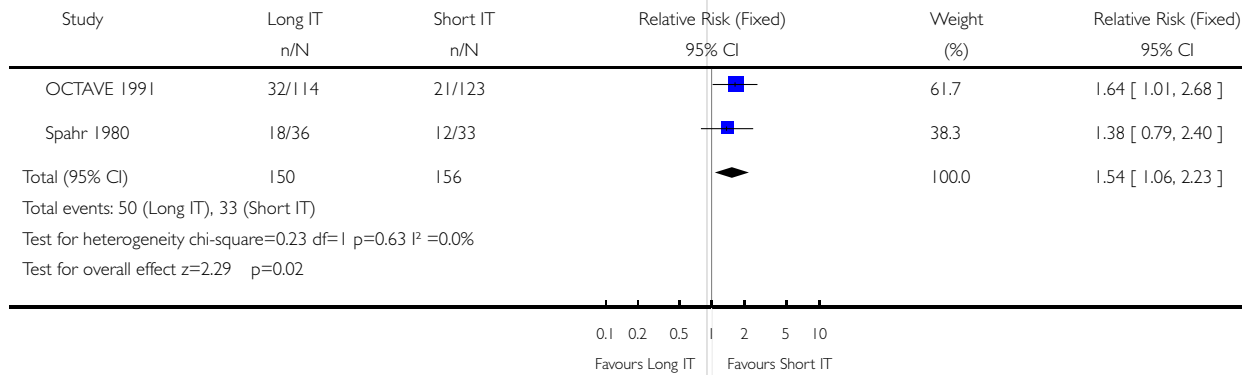
Analysis 02.04. Comparison 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 04 IVH (all grades)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation
 Comparison: 02 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)
 Outcome: 04 IVH (all grades)



Analysis 03.01. Comparison 03 Long vs Short IT in HMD (subgroup analysis by diagnosis), Outcome 01 Mortality before hospital discharge

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation
 Comparison: 03 Long vs Short IT in HMD (subgroup analysis by diagnosis)
 Outcome: 01 Mortality before hospital discharge

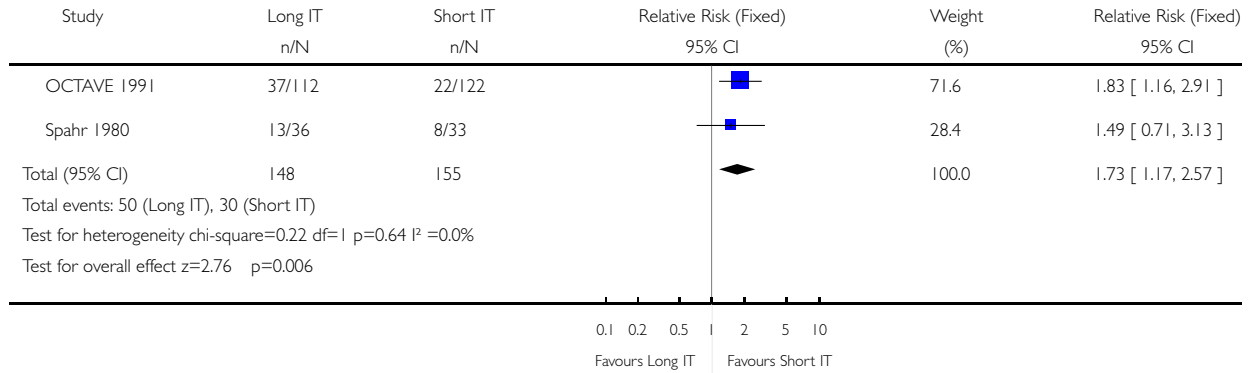


Analysis 03.02. Comparison 03 Long vs Short IT in HMD (subgroup analysis by diagnosis), Outcome 02 Air leak

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 03 Long vs Short IT in HMD (subgroup analysis by diagnosis)

Outcome: 02 Air leak

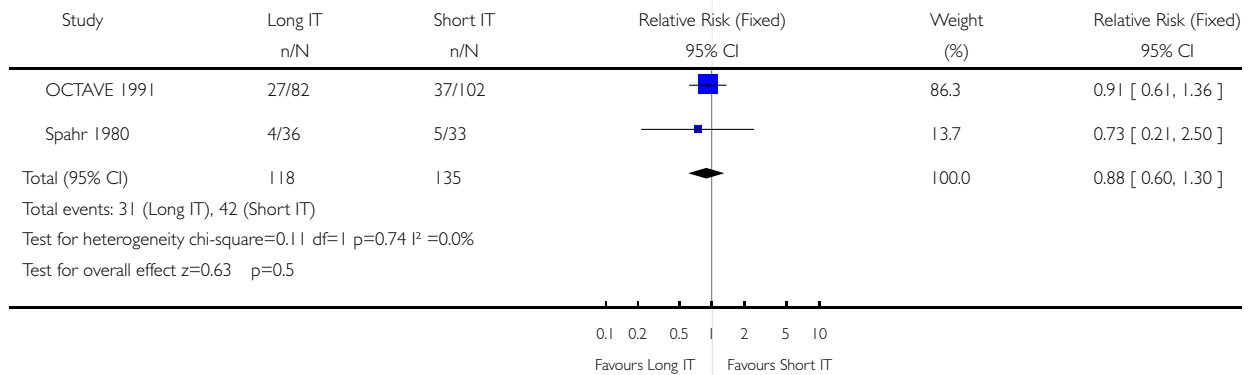


Analysis 03.03. Comparison 03 Long vs Short IT in HMD (subgroup analysis by diagnosis), Outcome 03 BPD (supplemental oxygen at 28 days)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 03 Long vs Short IT in HMD (subgroup analysis by diagnosis)

Outcome: 03 BPD (supplemental oxygen at 28 days)

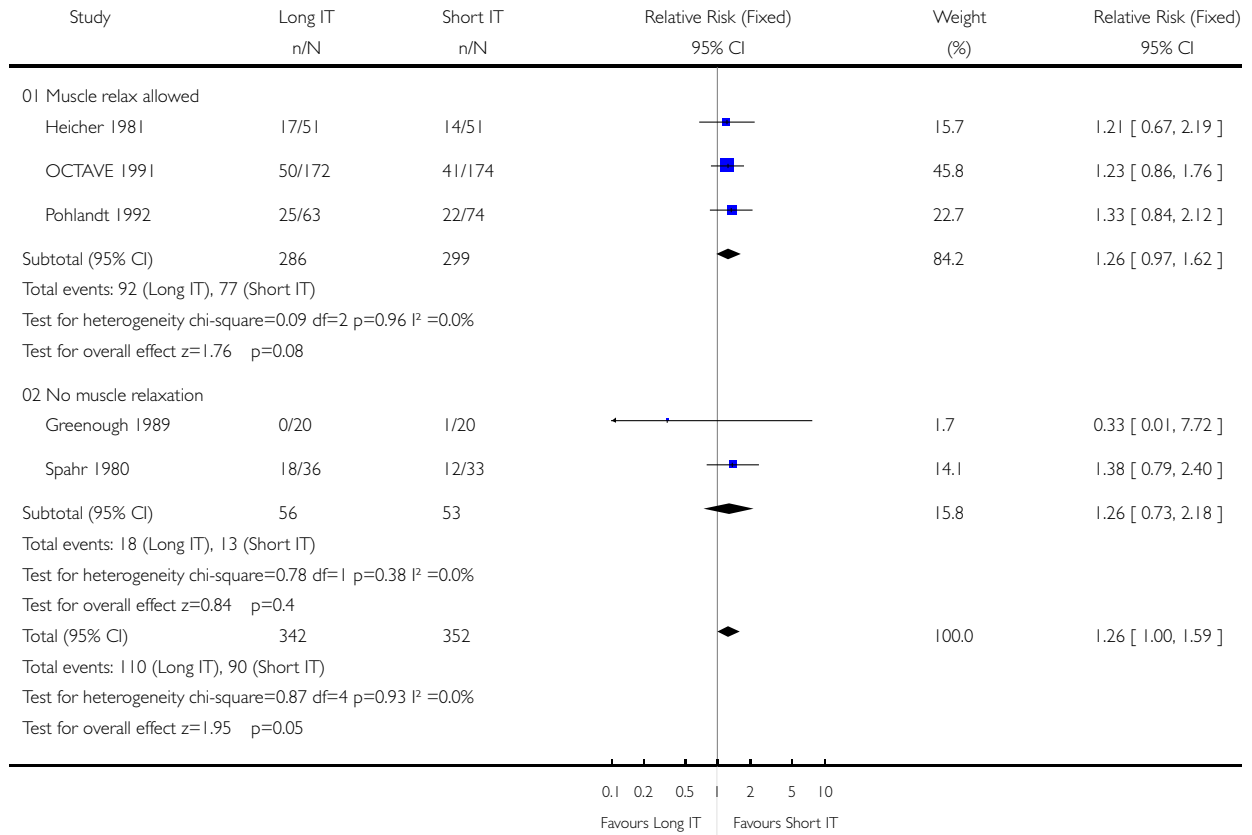


Analysis 04.01. Comparison 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 01 Mortality before discharge

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome: 01 Mortality before discharge

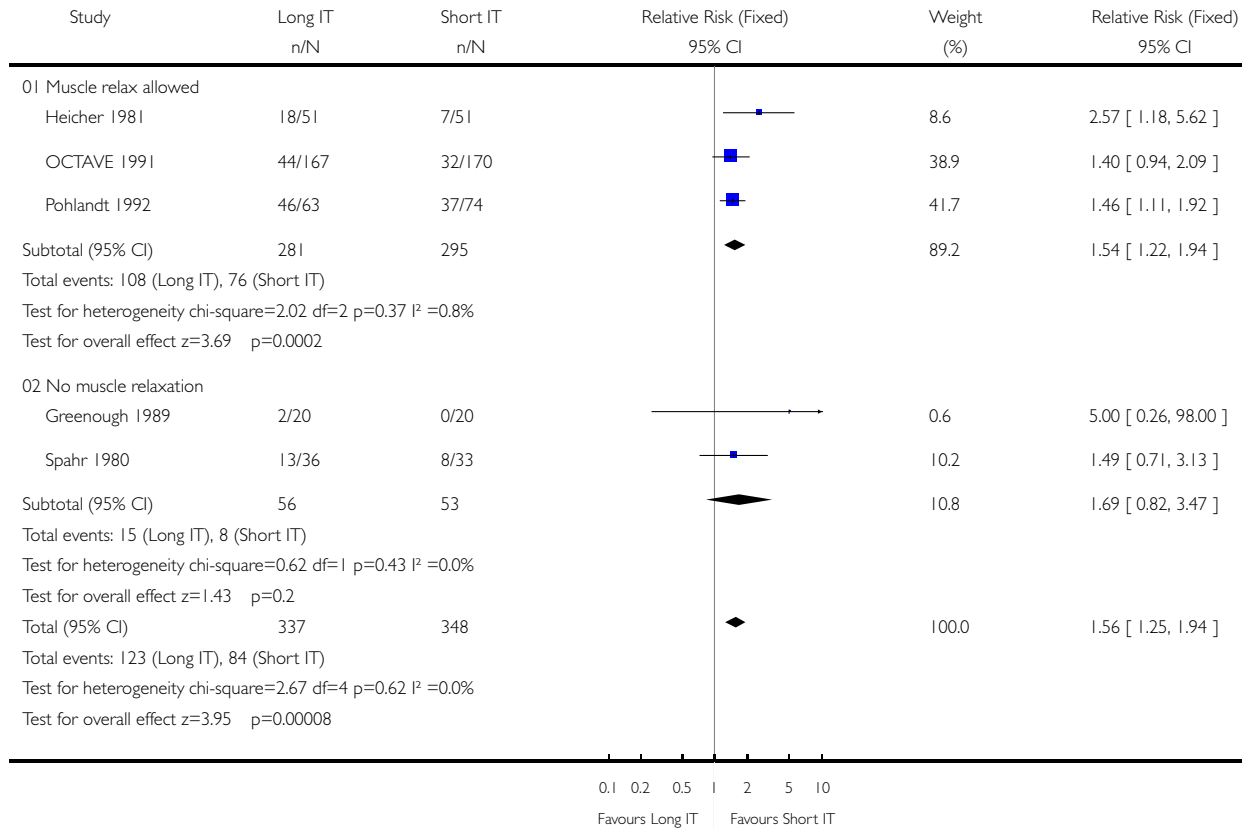


Analysis 04.02. Comparison 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 02 Air leak

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome: 02 Air leak

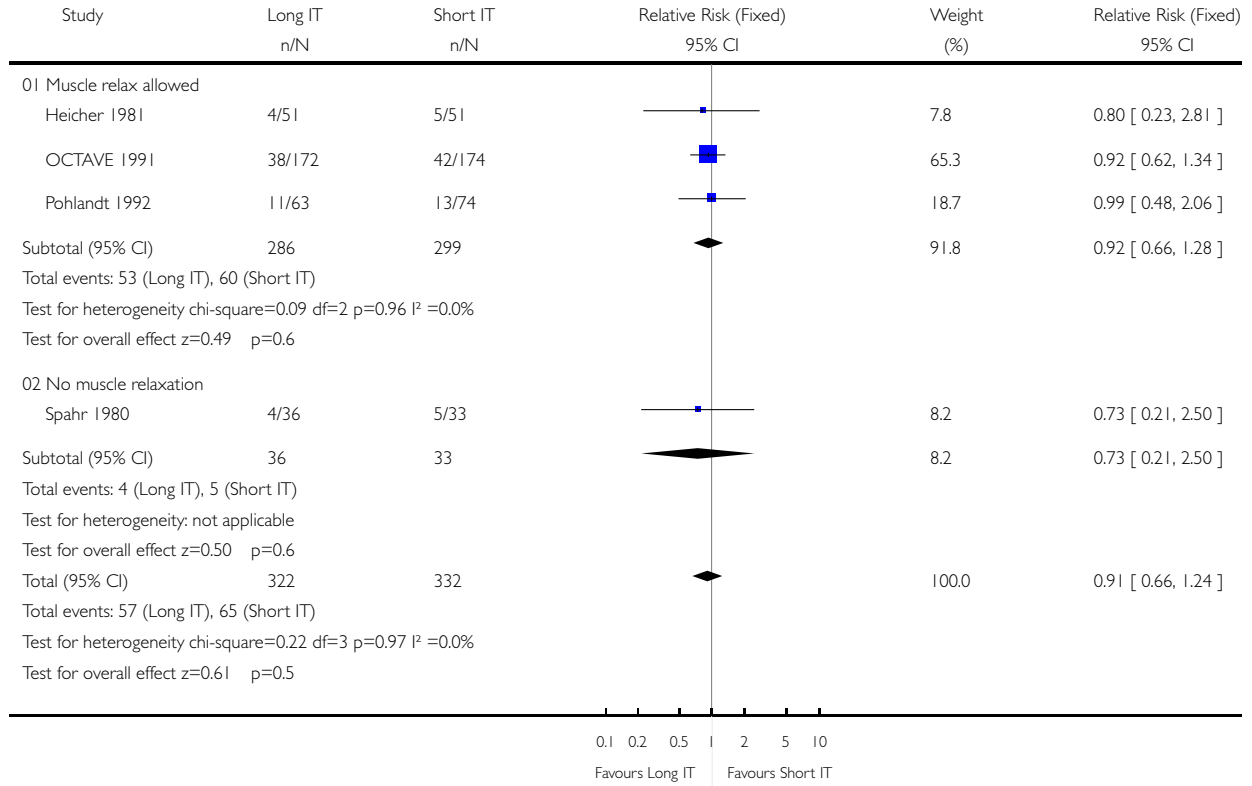


Analysis 04.03. Comparison 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 03 BPD (supplemental oxygen at 28 days)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome: 03 BPD (supplemental oxygen at 28 days)



Analysis 04.04. Comparison 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 04 IVH (all grades)

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 04 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome: 04 IVH (all grades)

