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Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes (Review)

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[Intervention Review]

Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

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ABSTRACT

Background

At birth, infants' lungs are fluid-filled. For newborns to have a successful transition, this fluid must be replaced by air to enable effective breathing. Some infants are judged to have inadequate breathing at birth and are resuscitated with positive pressure ventilation (PPV). Giving prolonged (sustained) inflations at the start of PPV may help clear lung fluid and establish gas volume within the lungs.

Objectives

To assess the efficacy of an initial sustained (> 1 second duration) lung inflation versus standard inflations (≤ 1 second) in newly born infants receiving resuscitation with intermittent PPV.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1), MEDLINE via PubMed (1966 to 17 February 2017), Embase (1980 to 17 February 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 17 February 2017). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles to identify randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs comparing initial sustained lung inflation (SLI) versus standard inflations given to infants receiving resuscitation with PPV at birth.

Data collection and analysis

We assessed the methodological quality of included trials using Cochrane Effective Practice and Organisation of Care Group (EPOC) criteria (assessing randomisation, blinding, loss to follow-up, and handling of outcome data). We evaluated treatment effects using a fixed-effect model with risk ratio (RR) for categorical data and mean, standard deviation (SD), and weighted mean difference (WMD) for continuous data. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Main results

Eight trials enrolling 941 infants met our inclusion criteria. Investigators in seven trials (932 infants) administered sustained inflation with no chest compressions. Use of sustained inflation had no impact on the primary outcomes of this review - mortality in the delivery room (typical RR 2.66, 95% confidence interval (CI) 0.11 to 63.40; participants = 479; studies = 5; I^2 not applicable) and mortality during hospitalisation (typical RR 1.01, 95% CI 0.67 to 1.51; participants = 932; studies = 7; I^2 = 19%); the quality of the evidence was low for death in the delivery room (limitations in study design and imprecision of estimates) and was moderate for death before discharge (limitations in study design of most included trials). Amongst secondary outcomes, duration of mechanical ventilation was shorter in the SLI group (mean difference (MD) -5.37 days, 95% CI -6.31 to -4.43; participants = 524; studies = 5; I^2 = 95%; low-quality evidence). Heterogeneity, statistical significance, and magnitude of effects of this outcome are largely influenced by a single study: When this study was removed from the analysis, the effect was largely reduced (MD -1.71 days, 95% CI -3.04 to -0.39, I^2 = 0%). Results revealed no differences in any of the other secondary outcomes (e.g. rate of endotracheal intubation outside the delivery room by 72 hours of age (typical RR 0.93, 95% CI 0.79 to 1.09; participants = 811; studies = 5; I^2 = 0%); need for surfactant administration during hospital admission (typical RR 0.97, 95% CI 0.86 to 1.10; participants = 932; studies = 7; I^2 = 0%); rate of chronic lung disease (typical RR 0.95, 95% CI 0.74 to 1.22; participants = 683; studies = 5; I^2 = 47%); pneumothorax (typical RR 1.44, 95% CI 0.76 to 2.72; studies = 6, 851 infants; I^2 = 26%); or rate of patent ductus arteriosus requiring pharmacological treatment (typical RR 1.08, 95% CI 0.90 to 1.30; studies = 6, 745 infants; I^2 = 36%). The quality of evidence for these secondary outcomes was moderate (limitations in study design of most included trials - GRADE) except for pneumothorax (low quality: limitations in study design and imprecision of estimates - GRADE).

Authors' conclusions

Sustained inflation was not better than intermittent ventilation for reducing mortality in the delivery room and during hospitalisation. The number of events across trials was limited, so differences cannot be excluded. When considering secondary outcomes, such as need for intubation, need for or duration of respiratory support, or bronchopulmonary dysplasia, we found no evidence of relevant benefit for sustained inflation over intermittent ventilation. The duration of mechanical ventilation was shortened in the SLI group. This result should be interpreted cautiously, as it can be influenced by study characteristics other than the intervention. Future RCTs should aim to enrol infants who are at higher risk of morbidity and mortality, should stratify participants by gestational age, and should provide more detailed monitoring of the procedure, including measurements of lung volume and presence of apnoea before or during the SLI.

PLAIN LANGUAGE SUMMARY

Prolonged lung inflation for neonatal resuscitation

Review question

Does the use of prolonged (or sustained, > 1 second duration) lung inflation rather than standard inflations (≤ 1 second) improve survival and other important outcomes among newly born babies receiving resuscitation at birth?

Background

At birth, the lungs are filled with fluid, which must be replaced by air for babies to breathe properly. Some babies have difficulty establishing effective breathing at birth, and 1 in every 20 to 30 babies receives help to do so. A variety of devices are used to help babies begin normal breathing. Some of these devices allow caregivers to give long (or sustained) inflations. These sustained inflations may help inflate the lungs and may keep the lungs inflated better than if they are not used.

Study characteristics

We collected and analysed all relevant studies to answer the review question and found eight studies enrolling 941 infants. In all studies, babies were born before the due date (from 23 to 36 weeks of gestational age). The sustained inflation lasted between 15 and 20 seconds

at pressure between 20 and 30 cmH_2O. Most studies provided one or more additional sustained inflations in cases of poor clinical response, for example, persistent low heart rate. We analysed one study (which included only nine babies) separately because researchers combined use of sustained or standard inflations with chest compressions.

Key results

The included studies showed no important differences among babies who received sustained versus standard inflations in terms of mortality, need for intubation during the first three days of life, or chronic lung disease. Babies receiving sustained inflation at birth may spend fewer days on mechanical ventilation. Several ongoing studies might help us to clarify whether differences between the two techniques may occur, as now we cannot exclude that small to moderate differences exist.

Quality of evidence

The quality of evidence is low to moderate because overall only a small number of studies have looked at this intervention; few babies were included in these studies; and some studies could have been better designed.

How up-to-date is this review?

We searched for studies that had been published up to February 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Use of initial sustained inflation compared with standard inflations in newborns receiving resuscitation with no chest compressions during resuscitation

Patient or population: preterm infants resuscitated using PPV at birth
Settings: delivery room in Europe (Austria, Germany, Italy), Canada, Egypt, Thailand
Intervention: sustained inflation with no chest compressions
Comparison: standard inflations with no chest compressions

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard inflations in newborns receiving resuscitation with no chest compressions	Use of initial sustained inflation				
Death - death in the delivery room	Study population		RR 2.66 (0.11 to 63.4)	479 (5 studies)	⊕⊕◯◯ low[a,b]	
	0 per 1000	0 per 1000 (0 to 0)				
Death - death before discharge	Study population		RR 1.01 (0.67 to 1.51)	932 (7 studies)	⊕⊕⊕◯ moderate[a]	
	82 per 1000	83 per 1000 (55 to 124)				
Need for mechanical ventilation	Study population		RR 0.87 (0.74 to 1.03)	484 (3 studies)	⊕⊕⊕◯ moderate[a]	
	487 per 1000	424 per 1000 (360 to 502)				
Chronic lung disease - BPD any grade	Study population		RR 0.9 (0.69 to 1.19)	220 (2 studies)	⊕⊕⊕◯ moderate[a]	

	483 per 1000	**435 per 1000** (333 to 575)			
Chronic lung disease - moderate to severe BPD	**Study population**		**RR 0.95** (0.74 to 1.22)	683 (5 studies)	⊕⊕⊕◯ **moderate**[a]
	257 per 1000	**244 per 1000** (190 to 314)			
Pneumothorax - any time	**Study population**		**RR 1.44** (0.76 to 2.72)	851 (6 studies)	⊕⊕◯◯ **low**[a,c]
	33 per 1000	**48 per 1000** (25 to 90)			
Cranial ultrasound abnormalities - intraventricular haemorrhage grade 3 to 4	**Study population**		**RR 0.89** (0.58 to 1.37)	635 (5 studies)	⊕⊕⊕◯ **moderate**[a]
	120 per 1000	**107 per 1000** (70 to 164)			

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

Assumed risk is the risk of the control arm.
[a]Limitations in study design: all studies at high or unclear risk of bias in at least one domain
[b]Imprecision: few events
[c]Imprecision: wide confidence intervals

BACKGROUND

Description of the condition

At birth, infants' lungs are filled with fluid, which must be cleared for effective respiration to occur. Most newly born infants achieve this spontaneously and may use considerable negative pressure (up to -50 cmH_2O) for initial inspirations (Karlberg 1962; Milner 1977). However, it is estimated that 3% to 5% of newly born infants receive some help to breathe at delivery (Saugstad 1998). Adequate ventilation is the key to successful neonatal resuscitation and stabilisation (Wyckoff 2015). Positive pressure ventilation (PPV) is recommended for infants who have absent or inadequate respiratory efforts, bradycardia, or both, at birth (Wyckoff 2015). Use of manual ventilation devices - self-inflating bags, flow-inflating (or anaesthetic) bags, and T-piece devices - with a face mask or endotracheal tube (ETT) is advised. Although it is not included in the International Liaison Committee on Resuscitation (ILCOR) guidelines, respiratory support of infants in the delivery room with a mechanical ventilator and a nasopharyngeal tube has been described (Lindner 1999).

Description of the intervention

Devices recommended for PPV in the delivery room differ in terms of physical characteristics and ability to deliver sustained lung inflation (SLI). The most commonly used self-inflating bag (O'Donnell 2004a; O'Donnell 2004b) may be of insufficient size to support sustained inflation (> 1 second). Both flow-inflating bags and T-pieces may be used to consistently deliver inflations > 1 second. Although target inflation pressures and long inspiratory times are achieved more consistently in mechanical models when T-piece devices rather than bags are used, no recommendation can be made as to which device is preferable (Wyckoff 2015; Wyllie 2015). Positive end-expiratory pressure (PEEP) is very important for aerating the lungs and improving oxygenation; SLI consists of prolonged high-level PEEP.

How the intervention might work

When airways are liquid-filled, it might be unnecessary to interrupt inflation pressures to allow the lung to deflate and exhale CO_2 (Hooper 2016). Boon 1979 described a study of 20 term infants delivered by Caesarean section under general anaesthesia who were resuscitated with a T-piece via an ETT. Trial authors reported that gas continued to flow through the flow sensor placed between the T-piece and the ETT toward the infant at the end of a standard inflation of 1 second on respiratory traces obtained (Boon 1979). On the basis of this observation, this group performed a non-randomised trial of sustained inflations given via a T-piece and an ETT to nine term infants during delivery room resuscitation. Investigators reported that initial inflation with a T-piece lasting 5 seconds produced a two-fold increase in inflation volume compared with standard resuscitation techniques (Vyas 1981). Citing these findings, a retrospective cohort study described the effects of a change in management strategy for extremely low birth weight infants in the delivery room (Lindner 1999). The new management strategy included the introduction of an initial sustained inflation of 15 seconds obtained with a mechanical ventilator via a nasopharyngeal tube. This change in strategy was associated with a reduction in the proportion of infants intubated for ongoing respiratory support without an apparent increase in adverse outcomes. Pulmonary morbidity in very low birth weight infants was reported to be related directly to mortality in 50% of cases of death (Drew 1982). Moreover, multiple SLIs in very preterm infants improved both heart rate and cerebral tissue oxygen saturation, in the absence of any detrimental effects (Fuchs 2011). An observational study showed that sustained inflation of 10 seconds at 25 cmH_2O in 70 very preterm infants at birth was not effective for infants who were not breathing, possibly owing to active glottic adduction (van Vonderen 2014). Newly born infants frequently take a breath and then prolong expiration via glottic closure and diaphragmatic braking, giving themselves prolonged end-expiratory pressure.

Why it is important to do this review

Recommendations regarding use of sustained inflation at birth have varied between international bodies. Although European Resuscitation Council guidelines suggest giving five inflation breaths if the newborn is gasping or is not breathing (Wyllie 2015), the American Heart Association states that evidence is insufficient to recommend an optimum inflation time (Wyckoff 2015). Differences between these guidelines and their algorithms are intriguing (Klingenberg 2016). A narrative review reported that sustained inflation may reduce the need for mechanical ventilation among preterm infants at risk for respiratory distress syndrome (RDS) (Lista 2010). The same review showed that respiratory outcomes among infants receiving sustained inflation (25 cmH_2O for 15 seconds) were improved over those reported for an historical group (Lista 2011).

This review updates the existing review "Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes", which was published in the *Cochrane Database of Systematic Reviews* in 2015 (O'Donnell 2015).

OBJECTIVES

To assess the efficacy of an initial sustained (> 1 second duration) lung inflation (SLI) versus standard inflations ($\leq$ 1 second) in newborn infants receiving resuscitation with intermittent PPV.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs. We excluded observational studies (case-control studies, case series) and cluster-RCTs.

Types of participants

Term and preterm infants resuscitated via PPV at birth.

Types of interventions

Interventions included resuscitation with initial sustained (> 1 second) inflation versus resuscitation with regular (≤ 1 second) inflations:

- with no chest compressions as part of the initial resuscitation (primary comparison); or
- with chest compressions as part of the initial resuscitation (secondary comparison).

Types of outcome measures

Primary outcomes

- Death in the delivery room
- Death during hospitalisation
- Death to latest follow-up

Secondary outcomes

- Apgar scores at 1 and 5 minutes
- Heart rate at 5 minutes
- Endotracheal intubation in the delivery room
- Endotracheal intubation outside the delivery room during hospitalisation
- Surfactant administration in the delivery room or during hospital admission
- Need for mechanical ventilation
- Duration in hours of respiratory support (i.e. nasal continuous airway pressure and ventilation via an ETT considered separately and in total)
- Duration in days of supplemental oxygen requirement
- Chronic lung disease: need for supplemental oxygen at 28 days of life; need for supplemental oxygen at 36 weeks of gestational age for infants born at or before 32 weeks of gestation
- Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported individually or as a composite outcome
- Cranial ultrasound abnormalities: any intraventricular haemorrhage (IVH), grade 3 or 4 according to the Papile classification (Papile 1978), and cystic periventricular leukomalacia
- Seizures including clinical and electroencephalographic
- Hypoxic ischaemic encephalopathy for term and late preterm infants (grade 1 to 3 (Sarnat 1976))
- Long-term neurodevelopmental outcomes (rates of cerebral palsy on physician assessment, developmental delay (i.e. intelligence quotient (IQ) 2 standard deviations (SDs) < mean on validated assessment tool (e.g. Bayley's Mental Developmental Index))
- Retinopathy of prematurity (ROP) (all stages and ≥ stage 3)
- Patent ductus arteriosus (PDA) (pharmacological treatment and surgical ligation)

Search methods for identification of studies

See Cochrane Neonatal Review Group (CNRG) search strategy.

Electronic searches

We used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal search strategy for specialized register).

We conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) in the Cochrane Library; MEDLINE via PubMed (1966 to 17 February 2017); Embase (1980 to 17 February 2017); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 17 February 2017), using the following search terms: (sustained inflation) OR (sustained AND inflation) OR (sustained AND (inflat* AND (lung OR pulmonary))), plus database-specific limiters for RCTs and neonates (see Appendix 1 for full search strategy for each database). We did not apply language restrictions.

We searched clinical trials registries for ongoing and recently completed trials (clinicaltrials.gov; the World Health Organization International Trials Registry and Platform - www.whoint/ictrp/search/en/; and the ISRCTN Registry).

Searching other resources

We also searched abstracts of the Pediatric Academic Society (PAS) from 2000 to 2017, electronically through the PAS website (abstractsonline), using the following key words: "sustained inflation" AND "clinical trial".

Data collection and analysis

Selection of studies

For this update, two review authors (MB, MGC) independently screened all titles and abstracts to determine which trials met the inclusion criteria. We retrieved full-text copies of all papers that were potentially relevant. We resolved disagreements by discussion between review authors.

Data extraction and management

Two review authors (MB, MGC) independently undertook data abstraction using a data extraction form developed *ad hoc* and integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group (EPOC) data collection checklist (EPOC 2015).

We extracted the following characteristics from each included trial.

- Administrative details: study author(s); published or unpublished; year of publication; year in which trial was conducted; details of other relevant papers cited.
- Trial details: study design; type, duration, and completeness of follow-up; country and location of study; informed consent; ethics approval.
- Details of participants: birth weight; gestational age; number of participants.
- Details of intervention: type of ventilation device used; type of interface; duration and level of pressure of sustained lung inflation (SLI).
- Details of outcomes: death during hospitalisation or to latest follow-up; heart rate at 5 minutes; duration in hours of respiratory support; duration in days of supplemental oxygen requirement; long-term neurodevelopmental outcomes; any adverse events.

We resolved disagreements by discussion between review authors. When available, we described ongoing trials identified by detailing primary trial author, research question(s) posed, and methods and outcome measures applied, together with an estimate of the reporting date.

When queries arose or additional data were required, we contacted trial authors.

Assessment of risk of bias in included studies

Two review authors (MB, SZ) independently assessed risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

We resolved disagreements by discussion or via consultation with a third assessor. See Appendix 2 for a detailed description of risk of bias for each domain.

Selection bias (random sequence generation and allocation concealment)

Random sequence generation

For each included trial, we categorised risk of bias regarding random sequence generation as follows.

- Low risk - adequate (any truly random process, e.g. random number table; computer random number generator).
- High risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number).
- Unclear risk - no or unclear information provided.

Allocation concealment

For each included trial, we categorised risk of bias regarding allocation concealment as follows.

- Low risk - adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes).
- High risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth).
- Unclear risk - no or unclear information provided.

Performance bias

Owing to the nature of the intervention, all trials were unblinded, leading to high risk of performance bias.

Detection bias

For each included trial, we categorised the methods used to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or different classes of outcomes.

Attrition bias

For each included trial and for each outcome, we described completeness of data including attrition and exclusions from analysis. We noted whether attrition and exclusions were reported, numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes.

Reporting bias

For each included trial, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed methods as follows.

- Low risk - adequate (when it is clear that all of a trial's prespecified outcomes and all expected outcomes of interest to the review have been reported).
- High risk - inadequate (when not all of a trial's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so cannot be used; or the trial failed to include results of a key outcome that would have been expected to be reported).
- Unclear risk - no or unclear information provided (study protocol was not available).

Other bias

For each included trial, we described any important concerns that we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific trial design, whether the trial was stopped early owing to some data-dependent process). We assessed whether each trial was free of other problems that could put it at risk of bias as follows.

- Low risk - no concerns of other bias raised.
- High risk - concerns raised about multiple looks at data with results made known to investigators, differences in numbers of participants enrolled in abstract, and final publications of the paper.
- Unclear - concerns raised about potential sources of bias that could not be verified by contacting trial authors.

We did not score blinding of the intervention because this was not applicable.
One review author entered data into RevMan 2014, and a second review author checked entered data for accuracy.

Measures of treatment effect

We conducted measures of treatment effect data analysis using RevMan 2014. We determined outcome measures for dichotomous data (e.g. death, endotracheal intubation in the delivery room, frequency of retinopathy) as risk ratios (RRs) with 95% confidence intervals (CIs). We calculated continuous data (e.g. duration of respiratory support, Apgar score) using mean differences (MDs) and SDs.

Unit of analysis issues

The unit of randomisation was the intended unit of analysis (individual neonate).

Dealing with missing data

We contacted trial authors to request missing data when needed.

Assessment of heterogeneity

As a measure of consistency, we used the I^2 statistic and the Q (Chi^2) test (Deeks 2011). We judged statistical significance of the Q (Chi^2) statistic by $P < 0.10$ because of the low statistical power of the test. We used the following cut-offs for heterogeneity: < 25% no (none) heterogeneity; 25% to 49% low heterogeneity; 50% to 74% moderate heterogeneity; and ≥ 75% high heterogeneity (Higgins 2003). We combined trial results using the fixed-effect model, regardless of statistical evidence of heterogeneity effect sizes.

Assessment of reporting biases

See Appendix 2.

Data synthesis

We performed statistical analyses using RevMan 2014. We used the standard methods of the Cochrane Neonatal Review Group. For categorical data, we used RRs, relative risk reductions, and absolute risk difference (RDs). We obtained means and SDs for continuous data and performed analyses using MDs and WMDs when appropriate. We calculated 95% CIs. We presented the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), as appropriate. For each comparison reviewed, meta-analysis could be feasible if we identified more than one eligible trial, and if homogeneity among trials was sufficient with respect to participants and interventions. We combined trials using the fixed-effect model, regardless of statistical evidence of heterogeneity effect sizes. For estimates of RR and RD, we used the Mantel-Haenszel method.

Quality of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: death in the delivery room or during hospitalisation; endotracheal intubation in the delivery room or outside the delivery room during hospitalisation; surfactant administration in the delivery room or during hospital admission; need for mechanical ventilation; chronic lung disease; air leaks; and cranial ultrasound abnormalities.
Two review authors independently assessed the quality of evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded evidence one level for serious (or two levels for very serious) limitations on the basis of the

following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of evidence.

The GRADE approach yields an assessment of the quality of a body of evidence according to one of four grades.

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses of the safety and efficacy of sustained inflation during resuscitation in subgroups.

- Term (≥ 37 weeks of gestation) and preterm (< 37 weeks of gestation) infants.
- Type of ventilation device used (self-inflating bag, flow-inflating bag, T-piece, mechanical ventilator).
- Interface used (i.e. face mask, ETT, nasopharyngeal tube).
- Duration of sustained lung inflation (i.e. > 1 second to 5 seconds, > 5 seconds).

Sensitivity analysis

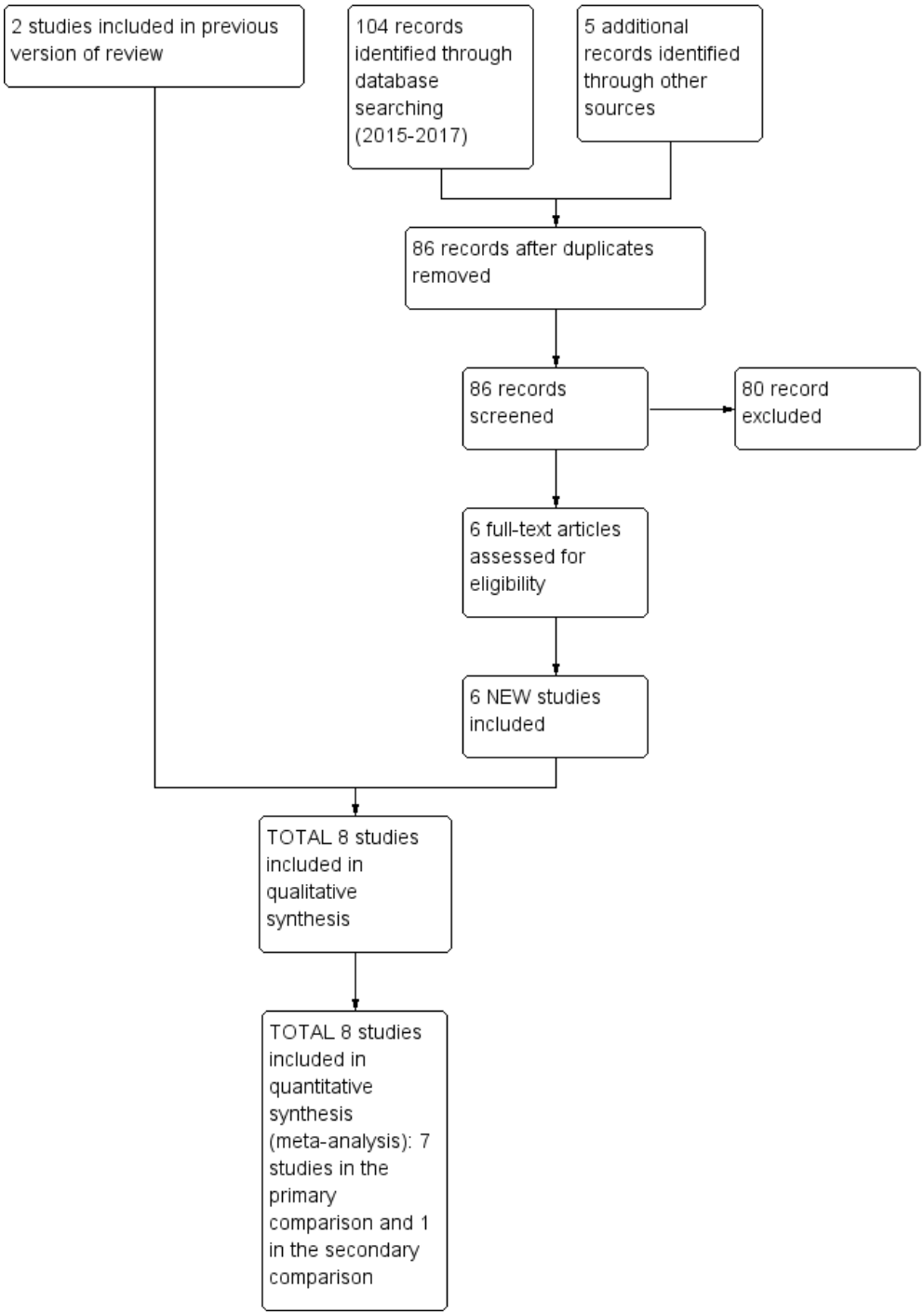
We planned to conduct sensitivity analyses to explore effects of the methodological quality of trials and checked to ascertain whether studies with high risk of bias overestimated treatment effects.

RESULTS

Description of studies

We have provided results of the search for this review update in the study flow diagram (Figure 1).

Figure 1. Study flow diagram: review update.



See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies sections for details.

Included studies

Eight trials recruiting 941 infants (473 in SLI groups, 468 in control groups) met the inclusion criteria (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schmölzer 2015; Schwaberger 2015). We pooled seven trials (with 932 infants) in the primary comparison (i.e. use of sustained inflation with no chest compressions) (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schwaberger 2015). In contrast to other trials, Schwaberger 2015 sought to use near-infrared spectroscopy (NIRS) to investigate whether SLI affected physiological changes in cerebral blood volume and oxygenation. We could not perform any meta-analysis in the secondary comparison (intervention superimposed on uninterrupted chest compressions) because we included only one trial (a pilot study of nine preterm infants) (Schmölzer 2015).
We have listed characteristics of populations and interventions and comparisons of the eight trials under Characteristics of included studies and in Table 1.

Settings and populations

Researchers conducted the included studies on four different continents: two in Italy (Lista 2015; Mercadante 2016), two in Canada by the same contact author (Ngan 2017; Schmölzer 2015), one in Germany (Lindner 2005), one in Austria (Schwaberger 2015), one in Egypt (El-Chimi 2017), and one in Thailand (Jiravisitkul 2017). Only one study was conducted at multiple centres (Lista 2015). Five of the six trials identified for this update included infants with mean birth weight > 1 kg (El-Chimi 2017; Jiravisitkul 2017; Mercadante 2016; Ngan 2017; Schwaberger 2015), whereas the two previously included studies (Lindner 2005; Lista 2015) and the pilot trial (Schmölzer 2015) enrolled extremely low birth weight infants. Mercadante 2016 was the only trial conducted in late preterm infants. No trials enrolled full-term infants. Table 1 shows additional information on populations.

Interventions

Trials pooled in the primary comparison (i.e. without chest compressions) reported that peak inspiratory pressure (PIP) was sustained for 15 seconds in six trials (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Schwaberger 2015) and for 20 seconds in Ngan 2017. However, levels of PIP ranged from 20 cmH_2O (El-Chimi 2017; Lindner 2005) to 24 (Ngan 2017), 25 (Jiravisitkul 2017; Lista 2015; Mercadante 2016), and 30 cmH_2O (Schwaberger 2015). Investigators provided additional SLIs in cases of poor response, with the same (Jiravisitkul 2017; Mercadante 2016; Schwaberger 2015) or higher PIP (El-Chimi 2017; Lindner 2005); researchers in Ngan 2017 based the duration of the second SLI on exhaled CO_2 values. As regards interface and ventilation devices, most included trials used mask and T-piece. However, Lindner 2005 used nasopharyngeal tube and ventilator, and El-Chimi 2017 introduced a relevant bias into the study design by using a T-piece ventilator in the SLI group and a self-inflating bag in the control group (mask in both SLI and control groups). No trials reported whether prespecified levels of pressure for the SLI were actually delivered according to the protocol. Study authors did not monitor leaks at the mask and lung volumes during the manoeuvre. Whether the infant breathed before or during the SLI was not recorded: Apnoeic newborns at birth are known to show less gain in lung volume during an SLI than actively breathing infants (Lista 2017).
For the secondary comparison, in which infants in both SLI and control groups were resuscitated with chest compressions, duration of SLI was 20 + 20 seconds (Schmölzer 2015).
Table 1 shows additional information on interventions.

Excluded studies

We have summarised the reasons for exclusion of potentially eligible trials (Bouziri 2011; Harling 2005; te Pas 2007) in the Characteristics of excluded studies table.
In particular, we excluded te Pas 2007 because sustained inflation was only one element of the intervention, and because it is not possible to determine the relative contributions of various elements of this intervention to differences observed between groups. We excluded Harling 2005, as investigators randomised infants in this trial to receive inflation for 2 seconds or 5 seconds at initiation of PPV. All infants thus received sustained (> 1 second) inflations as defined in our protocol (O'Donnell 2004).
For the 2017 update, we excluded no eligible studies.

Risk of bias in included studies

We have presented a summary of the 'Risk of bias' assessment in Figure 2 and Figure 3. We have provided details of the methodological quality of included trials in the Characteristics of included studies section.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

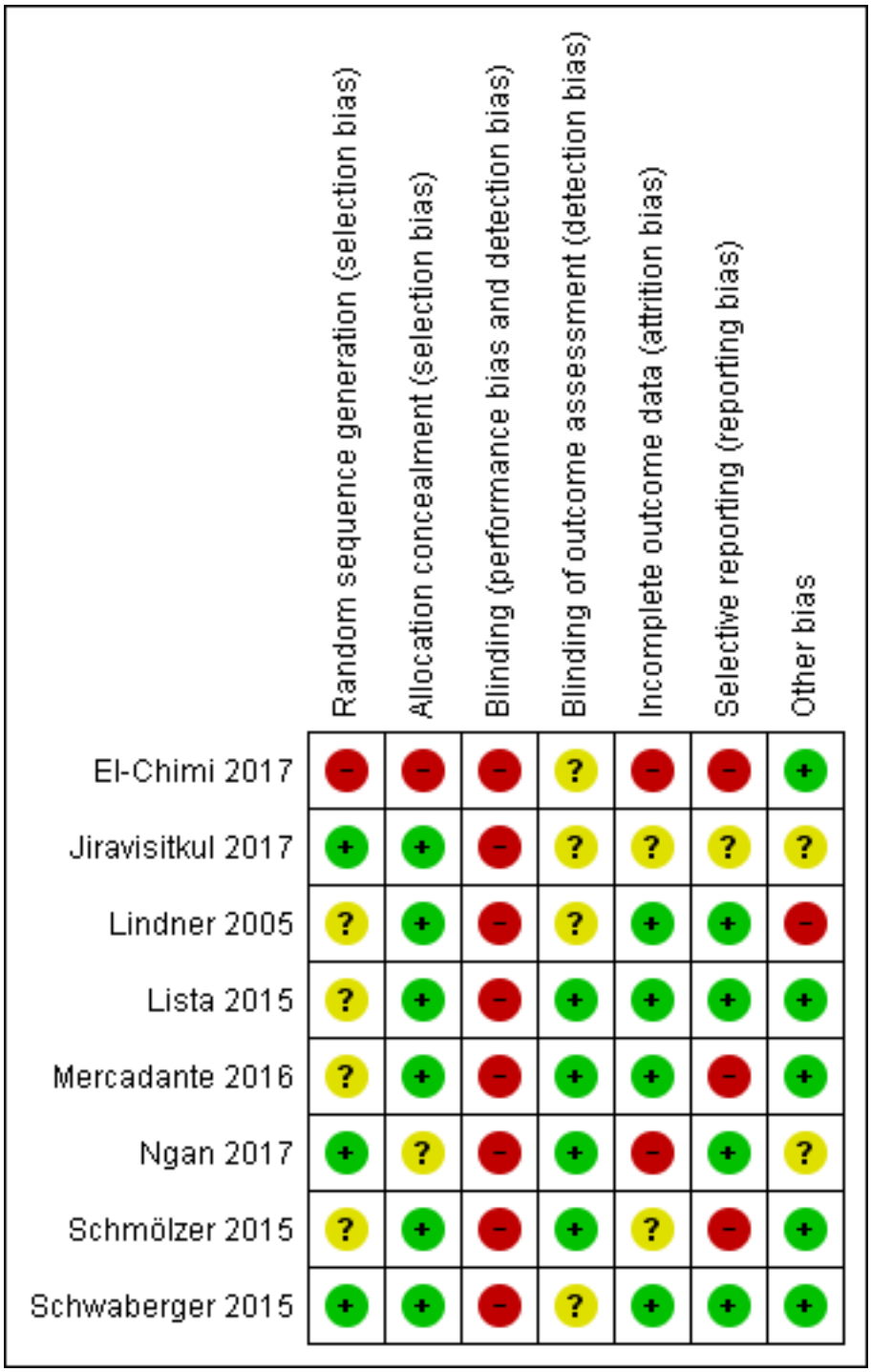
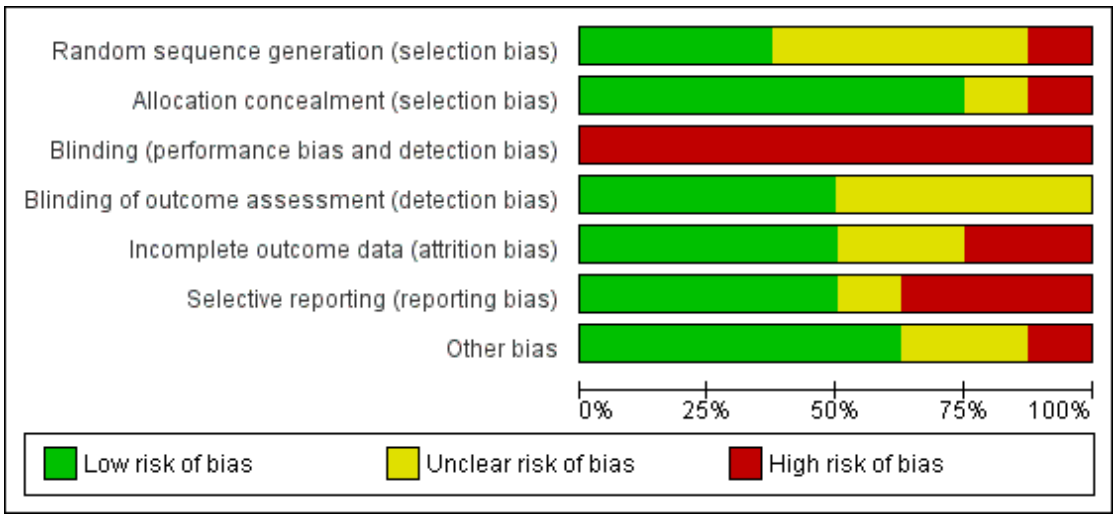


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.



Allocation

One trial had high risk of selection bias: This quasi-randomised trial (odd-numbered sheets indicated allocation to the SLI group, and even-numbered sheets to the control group) did not use opaque envelopes (information provided by study authors) (El-Chimi 2017). In Jiravisitkul 2017 and Schwaberger 2015, risk of selection bias was low as regards random sequence generation and allocation concealment (opaque, numbered envelopes). In Ngan 2017, risk of selection bias was low as regards random sequence generation and was unclear for allocation concealment: Timing of randomisation resulted in many post-randomisation exclusions, as results showed more post-randomisation exclusions in the SLI group than in the control group. In the other four trials, risk of selection bias was unclear as regards random sequence generation and was low as regards allocation concealment (opaque, numbered envelopes) (Lindner 2005; Lista 2015; Mercadante 2016; Schmölzer 2015).

Blinding

Owing to the nature of the intervention, all trials were unblinded, leading to high risk of performance bias. However, four trials blinded researchers assessing trial endpoints to the nature of study treatments (Lista 2015; Mercadante 2016; Ngan 2017; Schmölzer 2015).

Incomplete outcome data

El-Chimi 2017 referred almost half of enrolled infants to other NICUs; we excluded these studies from analysis owing to failure of follow-up, although the primary outcome of the study (treatment failure/success within 72 hours) could have been determined and reported for these infants. In Ngan 2017, post-randomisation exclusion (27%) resulted in fewer included infants in the SLI group. Most trials accounted for all outcomes (Lindner 2005; Lista 2015; Mercadante 2016; Schwaberger 2015).

Selective reporting

Four trials provided complete results for all reported outcomes (Lindner 2005; Lista 2015; Ngan 2017; Schwaberger 2015).

Other potential sources of bias

El-Chimi 2017 and Schwaberger 2015 did not report sample size calculations. For Schwaberger 2015, investigators registered the protocol after study initiation. Jiravisitkul 2017 planned sample sizes of 40 infants for each group but allocated only 38 to the control group. Lindner 2005 was stopped after the interim analysis. It was unclear why study authors made this decision. Ngan 2017 did not achieve the planned sample size; in addition, the incidence of the primary outcome in the control group was less than that

assumed for the sample size calculation, leading to lack of power to detect the chosen effect size. The other trials appear free of other bias.

We were unable to explore possible bias through generation of funnel plots because fewer than ten trials met the inclusion criteria of this Cochrane review.

Effects of interventions

See: **Summary of findings for the main comparison** Use of initial sustained inflation compared with standard inflations in newborns receiving resuscitation with no chest compressions during resuscitation; **Summary of findings 2** Use of initial sustained inflation compared with standard inflations in newborns receiving resuscitation with chest compressions during resuscitation

Primary comparison: use of initial sustained inflation versus standard inflations in newborns receiving resuscitation with no chest compressions

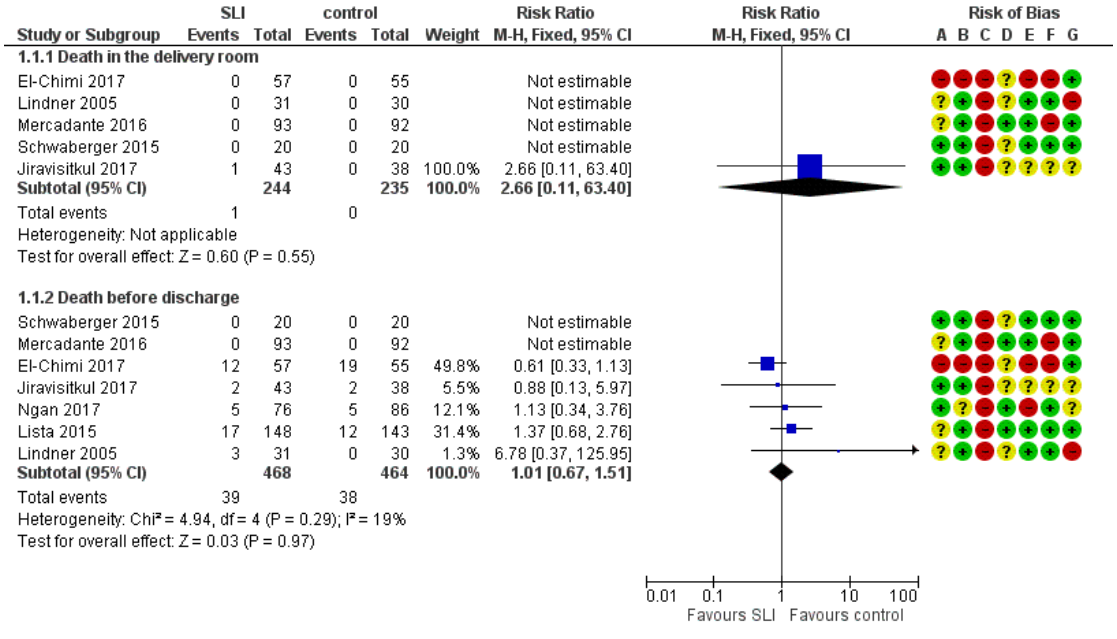
Primary outcomes

Death (Outcome 1.1)

Death in the delivery room (Outcome 1.1.1)

Five trials (N = 479) reported this outcome (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Schwaberger 2015); one event occurred in the SLI group in Jiravisitkul 2017 (death in delivery room at 15 to 20 minutes of life, severe birth asphyxia as the result of a prolapsed cord), and none in the other four trials (typical RR 2.66, 95% CI 0.11 to 63.40; typical RD 0.00, 95% CI -0.02 to 0.02; participants = 479; studies = 5; I^2 not applicable for RR and I^2 = 0% for RD; Analysis 1.1 and Figure 4). We obtained data for this outcome directly from trial authors (Jiravisitkul 2017; Lindner 2005).

Figure 4. Forest plot of comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, outcome: 1.1 Death.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Death during hospitalisation (Outcome 1.2.1)

All trials included in the primary comparison (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schwaberger 2015) reported mortality during hospitalisation (typical RR 1.01, 95% CI 0.67 to 1.51; typical RD 0.00, 95% CI -0.03 to 0.03; participants = 932; studies = 7; I^2 = 19% for RR and I^2 = 0% for RD; Analysis 1.1 and Figure 4).

We obtained data for this outcome directly from trial authors (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005).

In El-Chimi 2017, 12 and 19 infants in SLI and control groups, respectively, died. In Jiravisitkul 2017, two infants in each group died: In the SLI group, one died of severe birth asphyxia as the result of a prolapsed cord, and the other died at 3 hours of life of suspected umbilical catheter migration with haemothorax; in the control group, one died of severe respiratory distress syndrome at 2 hours of life, and the other of septic shock at 168 days of life. In Lindner 2005, three deaths occurred in the sustained inflation group: at day 1 (respiratory failure), at day 36 (necrotising enterocolitis), and at day 107 (liver fibrosis of unknown origin). In Lista 2015, 12 infants in the control group and 17 in the sustained inflations group died during the trial. Mercadante 2016 and Schwaberger 2015 reported no events.

Secondary outcomes

Apgar score at one minute (Outcome 1.2)

Five trials (N = 529) (Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Ngan 2017; Schwaberger 2015) reported this outcome (MD -0.08, 95% CI -0.26 to 0.09; participants = 529; studies = 5; I^2 = 0%; Analysis 1.2). We obtained data for this outcome directly from trial authors (Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Ngan 2017; Schwaberger 2015).

Apgar score at five minutes (Outcome 1.3)

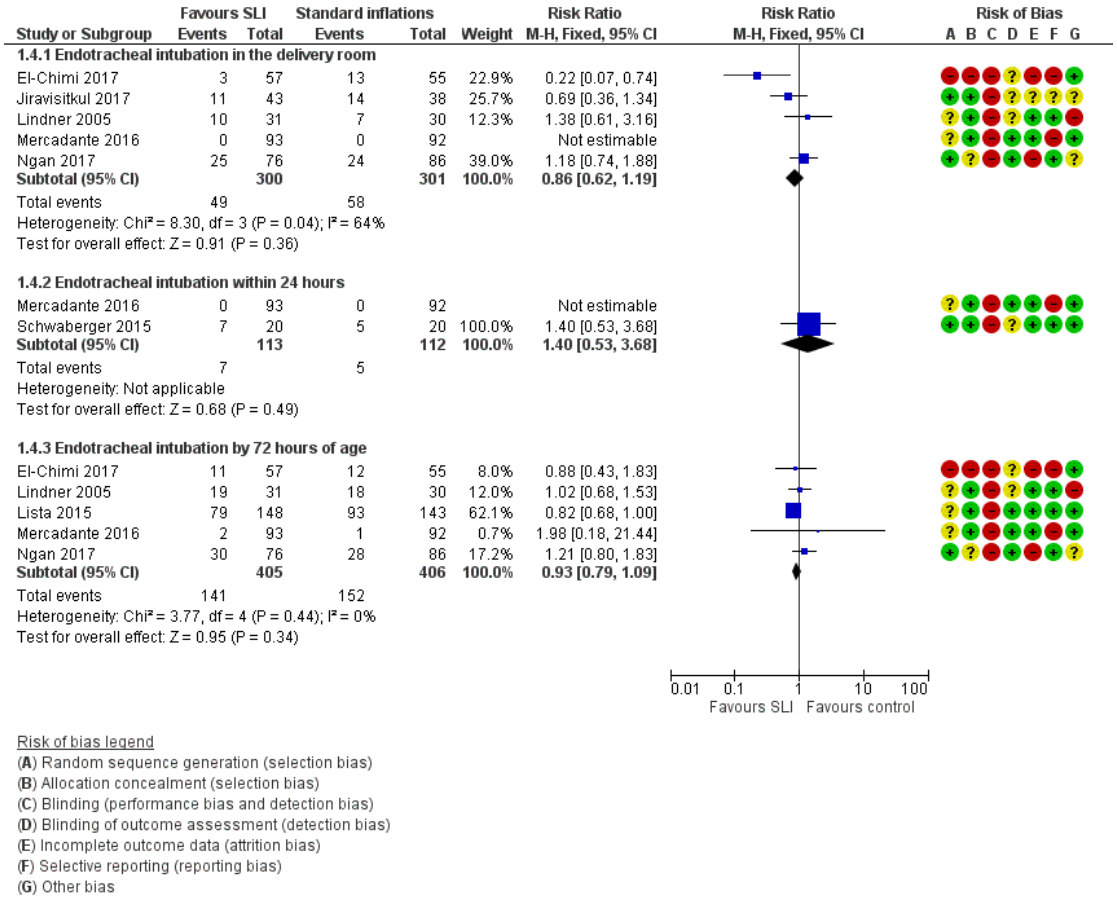
Six trials (N = 641) (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Ngan 2017; Schwaberger 2015) reported this outcome (MD -0.02, 95% CI -0.13 to 0.08; participants = 641; studies = 6; I^2 = 46%; Analysis 1.3). We obtained data for this outcome directly from trial authors (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Ngan 2017; Schwaberger 2015).

Endotracheal intubation (Outcome 1.4)

Endotracheal intubation in the delivery room (Outcome 1.4.1)

Five trials (N = 601) (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Ngan 2017) reported this outcome (typical RR 0.86, 95% CI 0.62 to 1.19; typical RD -0.03, 95% CI -0.08 to 0.03; participants = 601; studies = 5; I^2 = 64% for RR and I^2 = 74% for RD; Analysis 1.4; Figure 5). We obtained data for this outcome directly from trial authors (Mercadante 2016).

Figure 5. Forest plot of comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, outcome: 1.4 Endotracheal intubation.



Endotracheal intubation outside the delivery room within 24 hours (Outcome 1.4.2)

Two trials (N = 225) (Mercadante 2016; Schwaberger 2015) reported this outcome (RR 1.40, 95% CI 0.53 to 3.68; RD 0.02, 95% CI -0.04 to 0.07; participants = 225; studies = 2). The test for heterogeneity was not applicable because only one trial (Lindner 2005) reported events (Analysis 1.4; Figure 5). We obtained data for this outcome directly from trial authors (Mercadante 2016).

Endotracheal intubation outside the delivery room by 72 hours (Outcome 1.4.3)

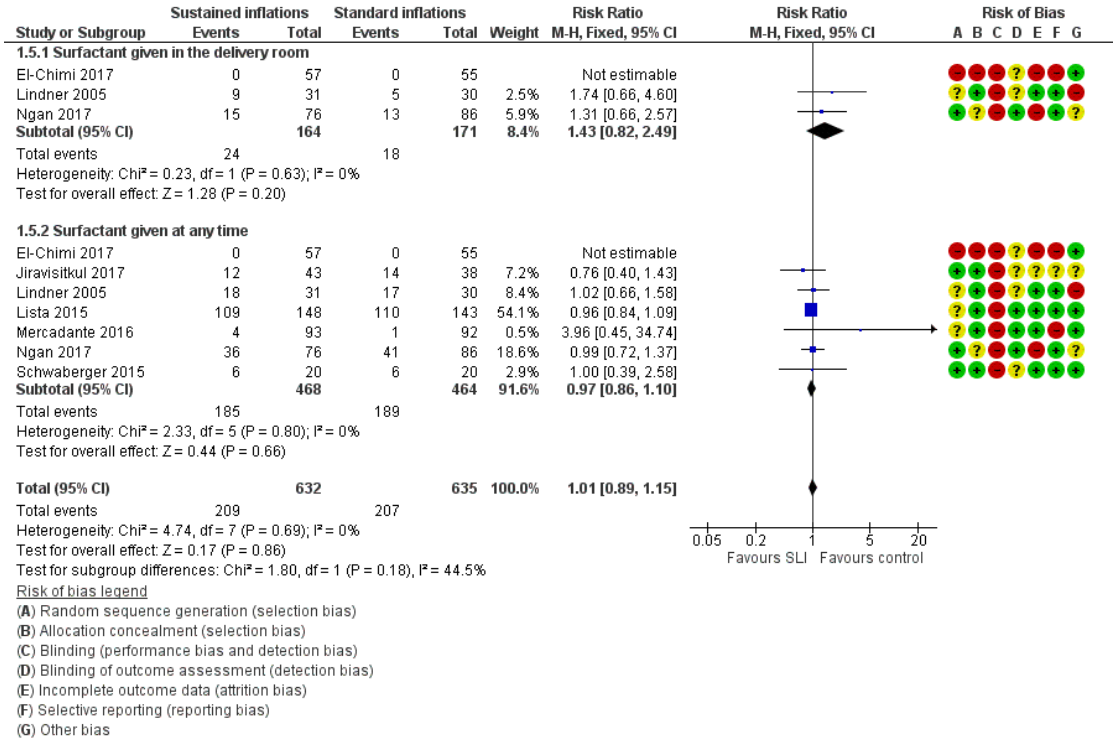
Five included trials (N = 811) (El-Chimi 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017) reported this outcome (typical RR 0.93, 95% CI 0.79 to 1.09; typical RD -0.03, 95% CI -0.09 to 0.03; participants = 811; studies = 5; I^2 = 0% for RR and I^2 = 53% for RD) (Analysis 1.4; Figure 5). We obtained data for this outcome directly from trial authors (Mercadante 2016).

Surfactant administration (Outcome 1.5)

Surfactant administration in the delivery room (Outcome 1.5.1)

Three trials (N = 335) (El-Chimi 2017; Lindner 2005; Ngan 2017) reported this outcome (typical RR 1.43, 95% CI 0.82 to 2.49; typical RD 0.04, 95% CI -0.02 to 0.11; participants = 335; studies = 3; I^2 = 0% for RR and I^2 = 72% for RD; Analysis 1.5; Figure 6). We obtained data for this outcome directly from trial authors (El-Chimi 2017).

Figure 6. Forest plot of comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, outcome: 1.5 Surfactant administration.



Surfactant administration during hospital admission (Outcome 1.5.2)

All trials included in the primary comparison (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schwaberger 2015) (N = 932) reported this outcome (typical RR 0.97, 95% CI 0.86 to 1.10; typical RD -0.01, 95% CI -0.06 to 0.04; participants = 932; studies = 7; I^2 = 0% for RR and I^2 = 0% for RD; Analysis 1.5; Figure 6). We obtained data for this outcome directly from trial authors (El-Chimi 2017; Lindner 2005; Mercadante 2016).

Need for mechanical ventilation (Outcome 1.6)

Three trials (N = 484) reported this outcome (El-Chimi 2017; Jiravisitkul 2017; Lista 2015) (typical RR 0.87, 95% CI 0.74 to 1.03; typical RD -0.06, 95% CI -0.14 to 0.01; participants = 484; studies = 3; I^2 = 0% for RR and I^2 = 85% for RD) (Analysis 1.6). We obtained data for this outcome directly from trial authors (El-Chimi 2017).

Duration of nasal continuous airway pressure (Outcome 1.7)

Three trials (N = 355) reported this outcome (El-Chimi 2017; Lindner 2005; Mercadante 2016) (MD 0.26 days, 95% CI -0.19 to 0.72; participants = 355; studies = 3; I^2 = 59%) (Analysis 1.7). We obtained data for this outcome directly from trial authors; data for this outcome refer to survivors at time of assessment (El-Chimi 2017; Lindner 2005; Mercadante 2016).

Duration of ventilation via an ETT (Outcome 1.8)

Five trials (N = 524) reported this outcome (Jiravisitkul 2017; Lindner 2005; Mercadante 2016; Ngan 2017; Schwaberger 2015) (MD -5.37 days, 95% CI -6.31 to -4.43; participants = 524; studies = 5; I^2 = 95%; Analysis 1.8). Data for this outcome refer to survivors at time of assessment (Jiravisitkul 2017; Lindner 2005; Mercadante 2016). We obtained data for this outcome directly from trial authors (Jiravisitkul 2017; Mercadante 2016; Ngan 2017; Schwaberger 2015). Heterogeneity, statistical significance, and magnitude of effects of this outcome are largely influenced by a single study (Ngan 2017): when this study was removed from the analysis, the effect was largely reduced (MD -1.71 days, 95% CI -3.04 to -0.39, I^2 = 0%).

Duration of respiratory support (nasal continuous airway pressure and ventilation via an ETT, considered in total) (Outcome 1.9)

Two trials (N = 243) reported this outcome (Lindner 2005; Mercadante 2016) (MD 0.69 days, 95% CI 0.23 to 1.16; participants = 243; studies = 2; I^2 = 0%; Analysis 1.9). We obtained data for this outcome directly from trial authors; data refer to survivors at time of assessment (Lindner 2005; Mercadante 2016).

Duration of supplemental oxygen requirement (days) (Outcome 1.10)

One trial (N = 81) reported this outcome (Jiravisitkul 2017) (MD -9.73, 95% CI -25.06 to 5.60; participants = 81; studies = 1; Analysis 1.10). The test for heterogeneity was not applicable. We obtained data for this outcome directly from trial authors (Jiravisitkul 2017).

Chronic lung disease (i.e. need for supplemental oxygen at 36 weeks of gestational age for infants born at or before 32 weeks of gestation) (Outcome 1.11)

Bronchopulmonary dysplasia (BPD) any grade (Outcome 1.11.1)

Two trials (N = 220) reported this outcome (Lindner 2005; Ngan 2017) (typical RR 0.90, 95% CI 0.69 to 1.19; typical RD -0.05, 95% CI -0.17 to 0.08; participants = 220; studies = 2; I^2 = 0% for RR and I^2 = 0% for RD). We obtained data for this outcome directly from trial authors; data refer to survivors at time of assessment (Lindner 2005; Analysis 1.11).

Moderate to severe BDP (Outcome 1.11.2)

Five included trials (N = 683) (El-Chimi 2017; Jiravisitkul 2017; Lista 2015; Ngan 2017; Schwaberger 2015) reported this outcome (typical RR 0.95, 95% CI 0.74 to 1.22; typical RD -0.01, 95% CI -0.07 to 0.05; participants = 683; studies = 5; I^2 = 47% for RR and I^2 = 57% for RD; Analysis 1.11).

Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported individually or as a composite outcome (Outcome 1.12)

Pneumothorax in first 48 hours of life (Outcome 1.12.1)

One trial (N = 81) (Jiravisitkul 2017) reported this outcome (RR 0.88, 95% CI 0.06 to 13.65; RD -0.00, 95% CI -0.07 to 0.06). The test for heterogeneity was not applicable (Analysis 1.12).

Pneumothorax at any time (Outcome 1.12.2)

Six included studies (N = 851) (El-Chimi 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schwaberger 2015) reported this outcome (typical RR 1.44, 95% CI 0.76 to 2.72; typical RD 0.02, 95% CI -0.01 to 0.04; studies = 6; 851 infants; I^2 = 26% for RR and I^2 = 2% for RD; Analysis 1.12).

Cranial ultrasound abnormalities (Outcome 1.13)

Intraventricular haemorrhage (IVH), grade 3 or 4 according to the Papile classification (Papile 1978) (Outcome 1.13.1)

Five included trials (N = 635) (Jiravisitkul 2017; Lindner 2005; Lista 2015; Ngan 2017; Schwaberger 2015) reported this outcome (typical RR 0.89, 95% CI 0.58 to 1.37; typical RD -0.01, 95% CI -0.06 to 0.03; studies = 5; 635 infants; I^2 = 4% for RR and I^2 = 0% for RD; Analysis 1.13).

IVH any grade (Outcome 1.13.2)

Two included trials (N = 152) (El-Chimi 2017; Schwaberger 2015) reported this outcome (typical RR 0.82, 95% CI 0.40 to 1.69; typical RD -0.03, 95% CI -0.15 to 0.08; studies = 3; 152 infants; I^2 = 0% for RR and I^2 = 0% for RD; Analysis 1.13).

Cystic periventricular leukomalacia (Outcome 1.13.3)

Five included trials (N = 635) (Jiravisitkul 2017; Lindner 2005; Lista 2015; Ngan 2017; Schwaberger 2015) reported this outcome (typical RR 0.59, 95% CI 0.24 to 1.44; typical RD -0.04, 95% CI -0.04 to 0.01; studies = 5; 635 infants; I^2 = 0% for RR and I^2 = 0% for RD; Analysis 1.13).

Retinopathy of prematurity (ROP) ≥ stage 3 (Outcome 1.14)

Five trials (N = 632) (Jiravisitkul 2017; Lindner 2005; Lista 2015; Ngan 2017; Schwaberger 2015) reported this outcome (typical RR 0.69, 95% CI 0.44 to 1.10; typical RD -0.04, 95% CI -0.08 to 0.01; studies = 5; 632 infants; I^2 = 42% for RR and I^2 = 40% for RD; Analysis 1.14). For Lindner 2005, data refer to survivors at time of assessment (Analysis 1.14).

Patent ductus arteriosus (PDA) (Outcome 1.15)

Rate of PDA - pharmacological treatment (Outcome 1.15.1)

Six included trials (N = 745) (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Ngan 2017; Schwaberger 2015) reported this outcome (typical RR 1.08, 95% CI 0.90 to 1.30; typical RD 0.03, 95% CI -0.04 to 0.09; studies = 6; 745 infants; I^2 = 36% for RR and I^2 = 58% for RD; Analysis 1.15). We obtained data for this outcome directly from trial authors (Schwaberger 2015).

Rate of PDA - surgical closure (Outcome 1.15.2)

Three trials (N = 412) (Jiravisitkul 2017; Lista 2015; Schwaberger 2015) reported this outcome (typical RR 0.73, 95% CI 0.27 to 1.99; typical RD -0.01, 95% CI -0.05 to 0.03; studies = 3; 412 infants; I^2 = 0% for RR and I^2 = 26% for RD; Analysis 1.15). We obtained data for this outcome directly from trial authors (Schwaberger 2015).

The data refer to all randomised infants, unless otherwise specified. No data were reported for the following outcomes: heart rate; need for supplemental oxygen at 28 days of life; seizures including clinical and electroencephalographic; hypoxic ischaemic encephalopathy in term and late preterm infants (grade 1 to 3; Sarnat 1976); and long-term neurodevelopmental outcomes.

Death to latest follow-up: No data were provided in addition to those already presented for death during hospitalisation (Analysis 1.1).

Subgroup analysis for the primary comparison

For the primary comparison, we were unable to conduct any of the four prespecified subgroup analyses because:

- no term infants were included;
- for ventilation devices, all trials used a T-piece except Lindner 2005 (mechanical ventilator): We did not perform a separate analysis because of the very small sample size and the presence of high or unclear risk of bias in most GRADE domains. Moreover, El-Chimi 2017 used a T-piece ventilator in the SLI group and a self-inflating bag in the control group; thus we could not include this as a subgroup;
- for interface, all trials used a face mask, except Lindner 2005 (nasopharyngeal tube): As for ventilation devices, we did not perform a separate analysis for Lindner 2005; and
- no trials used SLI < 5 seconds.

Secondary comparison: use of initial sustained inflation versus standard inflations in newborns receiving resuscitation with chest compressions

Primary outcomes

Death (Outcome 2.1)

Death in the delivery room (Outcome 2.1.1)

The included trial (N = 9) did not report this outcome (Schmölzer 2015).

Death during hospitalisation (Outcome 2.1.2)

One trial (N = 9) reported this outcome (RR 1.60, 95% CI 0.21 to 11.92; RD 0.15, 95% CI -0.45 to 0.75); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.1). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Secondary outcomes

Endotracheal intubation in the delivery room (Outcome 2.2)

One trial (N = 9) reported this outcome (RR 1.00, 95% CI 0.68 to 1.46; RD 0.00, 95% CI -0.34 to 0.34); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.2). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Surfactant administration in the delivery room (Outcome 2.3)

One trial (N = 9) reported this outcome (RR 1.60, 95% CI 0.55 to 4.68; RD 0.30, 95% CI -0.30 to 0.90); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.3). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Chronic lung disease (2.4, 2.5, 2.6)

Moderate to severe BDP (Outcome 2.4)

One trial (N = 9) reported this outcome (RR 0.89, 95% CI 0.33 to 2.37; RD -0.08, 95% CI -0.76 to 0.60); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.3). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Pneumothorax at any time (Outcome 2.5)

One trial (N = 9) reported this outcome: No events occurred (Analysis 2.5). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Cranial ultrasound abnormalities (Outcome 2.6)

Intraventricular haemorrhage (IVH), grade 3 or 4 according to the Papile classification (Papile 1978) *(Outcome 2.6.1)*

One trial (N = 9) reported this outcome (RR 0.40, 95% CI 0.05 to 2.98; RD -0.30, 95% CI -0.90 to 0.30); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.6). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

IVH any grade *(Outcome 2.6.2)*

One trial (N = 9) reported this outcome (RR 0.28, 95% CI 0.07 to 1.15; RD -0.80, 95% CI -1.23 to -0.37); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.6). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Retinopathy of prematurity (ROP) ≥ stage 3 (Outcome 2.7)

One trial (N = 9) reported this outcome (RR 0.27, 95% CI 0.04 to 1.68; RD -0.55, 95% CI -1.10 to 0.00); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.7). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

Rate of PDA - pharmacological treatment (Outcome 2.8)

One trial (N = 9) reported this outcome (RR 0.46, 95% CI 0.17 to 1.25; RD -0.60, 95% CI -1.07 to -0.13); thus, the test for heterogeneity was not applicable for this outcome (Schmölzer 2015; Analysis 2.8). We obtained data for this outcome directly from trial authors (Schmölzer 2015).

For the secondary comparison, investigators provided no data on other prespecified outcomes.

Subgroup analysis for the secondary comparison

For the secondary comparison, we were unable to conduct any subgroup analysis, as we included only one trial.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Use of initial sustained inflation compared with standard inflations in newborns receiving resuscitation with chest compressions during resuscitation

Patient or population: preterm infants resuscitated by PPV at birth
Settings: delivery room in Europe (Austria, Germany, Italy), Canada, Egypt, Thailand
Intervention: sustained inflation with chest compressions
Comparison: standard inflations with chest compressions

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard inflations in newborns receiving resuscitation with chest compressions	Use of initial sustained inflation				
Death - death before discharge	See comment	See comment	Not estimable	9 (1 study)	⊕◯◯◯ very low[a,b]	Only 1 trial included
Chronic lung disease - moderate to severe BPD	See comment	See comment	Not estimable	7 (1 study)	⊕◯◯◯ very low[a,b]	Only 1 trial included
Pneumothorax - any time	See comment	See comment	Not estimable	9 (1 study)	⊕◯◯◯ very low[a,b]	Only 1 trial included
Cranial ultrasound abnormalities - intraventricular haemorrhage grade 3 to 4	See comment	See comment	Not estimable	9 (1 study)	⊕◯◯◯ very low[a,b]	Only 1 trial included

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

Assumed risk is the risk of the control arm.
[a]Limitations in study design: included study at high or unclear risk of bias in four domains
[b]Imprecision (downgraded by two levels): extremely low sample size, few events

DISCUSSION

Summary of main results

We evaluated the merits of sustained lung inflation (SLI) versus intermittent ventilation in infants requiring resuscitation and stabilisation at birth. Eight trials enrolling 941 preterm infants met review inclusion criteria (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schmölzer 2015; Schwaberger 2015). Whereas the two trials included in the previous version of this review enrolled infants at 25^{+0} to 28^{+6} weeks (Lindner 2005; Lista 2015), the five more recent trials enrolled larger infants (El-Chimi 2017; Jiravisitkul 2017; Mercadante 2016; Ngan 2017; Schwaberger 2015). One of the trials included in this update was not pooled with the other studies for analysis because investigators superimposed the intervention on chest compressions (Schmölzer 2015).

Sustained lung inflation was not better than intermittent ventilation for reducing mortality - the primary outcome of this review. We rated the quality of evidence as moderate (GRADE) for death before discharge (limitations in study design of most included trials) and as low (GRADE) for death in the delivery room (limitations in study design and imprecision of estimates). When considering secondary outcomes, such as need for intubation, need for or duration of respiratory support, bronchopulmonary dysplasia, or pneumothorax, we found no benefit of SLI over intermittent ventilation. The quality of evidence for secondary outcomes was moderate (limitations in study design of most included trials - GRADE), except for pneumothorax (low quality: limitations in study design and imprecision of estimates - GRADE). Duration of mechanical ventilation was shorter in the SLI group (low quality: limitations in study design and imprecision of estimates - GRADE). The first version of this review reported an increased rate of patent ductus arteriosus (PDA) in the sustained lung inflation group. However, this effect was not seen when the most recent trials were added to the analysis. We identified six ongoing trials.

Overall completeness and applicability of evidence

To date, seven trials comparing sustained versus standard inflations for initial resuscitation have enrolled 941 newborns. Available data were insufficient for assessment of clinically important outcomes, which were identified *a priori*. Study authors did not report outcomes such as duration of supplemental oxygen requirement and long-term neurodevelopmental outcomes and did not enrol term infants. We could not perform an *a priori* subgroup analysis (gestational age, ventilation device, interface, duration of sustained inflation) to detect differential effects because of the paucity of included trials. Relevant questions such as the following remain unanswered: What is the optimal duration for an SLI? Which level of positive end-expiratory pressure (PEEP) should follow? Which is the optimal interface/device? (McCall 2016) We were able to summarise available evidence in a comprehensive way, as we obtained additional information about study design and outcome data from all included trials (El-Chimi 2017; Jiravisitkul 2017; Lindner 2005; Lista 2015; Mercadante 2016; Ngan 2017; Schmölzer 2015; Schwaberger 2015) and from two excluded trials (Harling 2005; te Pas 2007). The five ongoing trials that we identified reported important differences in choice of gestational age (NCT02139800; NCT02493920; NCT02846597; NCT02858583; NCT02887924). NCT02139800 enrols infants at 23 to 26 weeks, NCT02493920 at 25 to 36 weeks, NCT02887924 at 26 to 29 weeks, and NCT02846597 at < 33 weeks, whereas NCT02858583 enrols term and preterm infants. These differences among study populations might prove to be important, as trials have reported that sustained inflation was more effective in infants at 28 to 30 weeks than at < 28 or > 30 weeks of gestation (te Pas 2007).

Quality of the evidence

According to the GRADE approach, we rated the overall quality of evidence for clinically relevant outcomes as low to moderate (see Summary of findings for the main comparison). We downgraded the overall quality of evidence for critical outcomes because of limitations in study design (i.e. selection bias due to lack of allocation concealment) and imprecision of results (few events for death in the delivery room and wide confidence intervals for pneumothorax). In addition, two trials did not report sample size calculations (El-Chimi 2017; Schwaberger 2015), and the other three did not achieve them (Jiravisitkul 2017; Lindner 2005; Ngan 2017). Results of smaller studies are subject to greater sampling variation, and hence are less precise. Indeed, imprecision is reflected in the confidence interval around the intervention effect estimate from each study and in the weight given to the results of each study included in the meta-analysis (Higgins 2011).

Potential biases in the review process

A major limitation of this Cochrane review is the definition of sustained lung inflation, as trials used different pressures, which may have impacted study results. No trials were blinded owing to the nature of the intervention. We excluded a potentially relevant trial (te Pas 2007) because sustained inflation was only one element of the intervention, and it is not possible to determine the relative contributions of various elements of this intervention to differences observed between groups. We excluded Harling 2005 because the control group received 2 seconds of inflation (5 seconds for the intervention group), whereas we defined sustained as > 1 second. For this update, we made a *post hoc* decision to add a

comparison based on the presence of chest compressions during resuscitation.

Agreements and disagreements with other studies or reviews

Several systematic reviews of SLI have been recently published. Schmölzer 2014 conducted a systematic review of randomised clinical trials comparing SLI versus intermittent positive-pressure ventilation (IPPV) as the primary respiratory intervention during respiratory support in preterm individuals at < 33 weeks of gestational age in the delivery room. This review included four trials, including two that we excluded from our systematic review (Harling 2005; te Pas 2007). Schmölzer 2014 reported a significant reduction in the need for mechanical ventilation within 72 hours after birth (typical risk ratio (RR) 0.87, 95% confidence interval (CI) 0.74 to 1.03). As in our analysis, significantly more infants treated with SLI received treatment for PDA (RR 1.27, 95% CI 1.05 to 1.54). Results showed no differences in bronchopulmonary dysplasia (BPD), death at latest follow-up, or the combined outcome of death or BPD among survivors between groups. The findings of Schmölzer 2014 differ from the findings of this Cochrane review because of differences in the definition of duration of the intervention, and therefore in determination of included trials. A narrative review (Foglia 2016) including five trials (Harling 2005; Lindner 2005; Lista 2015; Mercadante 2016; te Pas 2007) concluded that at present, data are insufficient to support the use of SLI in clinical practice. An observational analytical cross-sectional case-control study of 78 preterm infants showed that SLI resulted in lower rates of intubation in the delivery room, lower rates of invasive mechanical ventilation, and higher rates of intraventricular haemorrhage (Grasso 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Sustained lung inflation was not better than intermittent ventilation for reducing mortality in the delivery room (low-quality evidence - GRADE) and during hospitalisation (moderate-quality evidence - GRADE) - primary outcomes of this review. When considering secondary outcomes, such as need for intubation, need for or duration of respiratory support, or bronchopulmonary dysplasia, we found no benefit of sustained inflation over intermittent ventilation (moderate-quality evidence - GRADE). Duration of mechanical ventilation was shortened in the SLI group (low-quality evidence - GRADE); however, this result should be interpreted cautiously, as it might have been influenced by study characteristics other than the intervention.

Implications for research

Additional studies of SLI for infants receiving respiratory support at birth should provide more detailed monitoring of the procedure, such as measurements of lung volume and presence of apnoea before or during SLI. Future randomised controlled trials should aim to enrol infants who are at higher risk of morbidity and mortality, and should stratify participants by gestational age. Researchers should also measure long-term neurodevelopmental outcomes (e.g. Bayley Scales of Infant Development administered at two years of corrected age).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

El-Chimi 2017

Methods	Prospective quasi-randomised parallel controlled trial Setting: delivery room of Maternity Hospital, Ain Shams University, Cairo, Egypt Conducted: April 2012 to March 2014
Participants	Inclusion criteria (as specified in the protocol): gestational age 26 to 33 weeks, birth weight > 750 grams Exclusion criteria (as specified in the protocol): major congenital anomalies; meconium aspiration syndrome, congenital diaphragmatic hernia, anterior abdominal wall defect, maternal chorioamnionitis
Interventions	• SLI group: PIP of 20 cmH_2O for 15 seconds, using a neonatal mask and a T-piece ventilator, followed by PEEP of 5 cmH_2O. If response was not satisfactory (i.e. breathing remained insufficient and/or heart rate was < 100 bpm and/or the infant was cyanotic): A second 15 second SLI of 25 cmH_2O for 15 seconds, followed by PEEP of 6 cmH_2O. If still not satisfactory, a third SLI of 30 cmH_2O for 15 seconds, followed by PEEP of 7 cmH_2O. If still not satisfactory, intubation inside DR and ventilation (rate of 40 to 60 breaths/min, PIP of 25 to 35 cmH_2O, PEEP of 7 to 8 cmH_2O) until transfer to NICU • Control group: intermittent bag/mask inflation: rate of 40 to 60 breaths/min, maximum PIP of 40 cmH_2O for 30 seconds using a self-inflating bag with an oxygen reservoir. After adequate circulation and breathing achieved, CPAP of 5 to 7 cmH_2O during transfer to NICU. In cases of poor response, intubation and ventilation (rate of 40 to 60 breaths/min, PIP of 25 to 35 cmH_2O, PEEP of 7 to 8 cmH_2O) until transfer to NICU
Outcomes	Primary outcome was either "success" (defined as no need for further ventilatory support, need for exclusive NCPAP, or need for intubation beyond the first 72 hours after delivery) or "failure" (defined as need for intubation within first 72 hours of life, including DR intubation) Secondary outcomes were blood IL-1b and TNF-a levels, air leaks, BPD, IVH, PDA, and NEC
Notes	Study was registered at ClinicalTrials.gov (Identifier: NCT01255826)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	For randomisation, sequentially numbered sheets were used to assign eligible infants to resuscitation: Odd-numbered sheets indicated those allocated to the SLI group, and even-numbered to the control group

El-Chimi 2017 (*Continued*)

Allocation concealment (selection bias)	High risk	No opaque envelopes were used (information provided by study authors)
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	After enrolment (n = 202), infants referred to other NICUs were excluded from analysis owing to failure of follow-up. At study end, SLI group comprised 57 babies and CBMI group comprised 55 babies
Selective reporting (reporting bias)	High risk	Some outcomes were specified at https://clinicaltrials.gov/ct2/show/NCT01255826 but were not reported in the manuscript (e.g. duration of oxygen therapy, length of NICU stay)
Other bias	Low risk	Appears free of other bias

Jiravisitkul 2017

Methods	Prospective randomised parallel controlled trial Setting: delivery room of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand Conducted: November 2013 to March 2015
Participants	Included: 81 preterm infants (25 to 32 weeks of gestational age) requiring positive-pressure ventilation or continuous positive airway pressure Exclusion criteria: major congenital anomalies, hydrops foetalis, prenatal diagnosis of upper airway obstruction, meconium-stained amniotic fluid
Interventions	• SLI group (n = 43): SLI at 25 cmH_2O for 15 seconds with neonatal mask via a T-piece resuscitator, followed by delivery of CPAP at 6 cmH_2O via a face mask for 5 to 10 seconds. Cardiorespiratory status was then re-evaluated: If HR was ≥100 beats/min and respiratory effort was improved, CPAP was continued via face mask. If HR was < 60 beats/min, PPV was initiated. If HR was 60 to 100 beats/min and/or respiratory effort was poor, a second SLI manoeuvre similar to the first SLI manoeuvre was initiated. If HR was < 100 beats/min or gasping/apnoea was present during the second SLI manoeuvre, PPV was initiated and additional resuscitation steps performed. If HR was ≥ 100 beats/min and no apnoea/gasping was present during the second SLI manoeuvre, CPAP was performed via face mask • Non-SLI group (n = 38): standard resuscitation alone. PPV was given via a T-piece resuscitator with PIP of 15 to 20 cmH_2O and positive end-expiratory pressure of

	5 cmH_2O for 30 seconds. Infants were placed on CPAP at 6 cmH_2O via face mask if breathing was still laboured All enrolled infants were resuscitated with an initial fraction of inspired oxygen (FiO_2) of 0.3, which was adjusted by 0.1 every 30 seconds to achieve the target SpO_2. Criteria for intubation included 1 of the following: remaining apnoeic after PPV, HR of 30 seconds before the start of chest compressions, or SpO_2 < 80% despite CPAP via mask with FiO_2 of 1.0 for 5 to 10 minutes Infants of multiple gestations were enrolled in the same intervention group
Outcomes	Primary outcomes: change in oxygen requirements, HR, and SpO_2 during resuscitation; proportion of infants on room air during first 10 minutes after birth; need for intubation in the delivery room Secondary outcomes: survival at discharge, duration of hospitalisation, proportion of infants on MV within first 72 hours of life, duration of MV, duration of oxygen supplementation, need for surfactant, need for postnatal steroids, pneumothorax within first 48 hours after NICU admission, moderate to severe BPD as defined by Jobe and Bancalari, Apgar score at 5 minutes, PDA and need for surgical closure, grade 3 to 4 IVH, cystic periventricular leukomalacia, stage > 2 ROP, ROP requiring treatment
Notes	Study was registered in the Thai Clinical Trials Registry (TCTR20140418001)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block of 4 randomisation stratified by GA: 25 to 28 weeks and 29 to 32 weeks. Random sequence was generated by computer random number generator (information provided by study authors)
Allocation concealment (selection bias)	Low risk	Sequence numbers were kept in opaque sealed envelopes that were opened just before birth in the delivery room by a person not involved in resuscitation of infants
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear why 43 infants in SLI group and 38 in control group

Jiravisitkul 2017 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	According to the Thai Clinical Trials Registry (TCTR20140418001), the only primary outcome was intubation in DR; only a key secondary outcome was specified: BPD
Other bias	Unclear risk	Planned sample size: 40 infants in each group; however, only 38 in control group

Lindner 2005

Methods	Prospective randomised parallel controlled trial Setting: Delivery Room, Ulm, Germany Conducted: August 1999 to February 2002
Participants	Inclusion criteria: newly born infants at 25 to 28 weeks of gestation inclusive Exclusion criteria: severe malformations, oligo-anhydramnios before 20 weeks of gestation, foeto-foetal transfusion syndrome A total of 61 infants were enrolled (31 in sustained inflation group and 30 in control group)
Interventions	• SLI group: PIP 20 cmH_2O for 15 seconds. Infants who did not respond satisfactorily (persistent poor or laboured respiratory effort, bradycardia or cyanosis, and low oxygen saturation (SpO_2)): up to 2 additional inflations of 15 seconds at higher inflating pressures (25 and 30 cmH_2O). Infants whose response remained unsatisfactory were intubated and mechanically ventilated • Control group: NIMV (PIP 20 cmH_2O, PEEP 4 to 6 cmH_2O; inflation time 0.5 seconds; inflation rate 60/min) for 30 seconds before the start of NCPAP at 4 to 6 cmH_2O Infants received support from a mechanical ventilator via a nasopharyngeal tube Infants in both groups who had apnoea on NCPAP could be treated with NIMV (PIP 20 cmH_2O; inflation time 0.3 seconds; inflation rate 60/min) for up to 4 minutes Treatment was deemed to have failed if infants had shown persistently poor respiratory effort, bradycardia, or cyanosis/low SpO_2 in the delivery room; or if criteria combining clinical assessments of respiratory distress and evidence of impaired oxygenation, impaired ventilation (high CO_2), or apnoea were met within 48 hours of birth
Outcomes	Primary outcome: rate of infants reaching criteria for intubation and mechanical ventilation at < 48 hours of life Secondary outcomes: mortality, Apgar score, endotracheal intubation, surfactant administration, duration of respiratory support, chronic lung disease, air leak, intraventricular haemorrhage, cystic periventricular leukomalacia, retinopathy of prematurity, PDA
Notes	Trial was stopped before target sample was recruited owing to slow enrolment. Clinical outcomes were reported for all randomised infants
Risk of bias	

Lindner 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomised, stratified for gestational age (25 to 26 weeks, 27 to 28 weeks)
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes used
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants accounted for
Selective reporting (reporting bias)	Low risk	All reported outcomes provided with complete results
Other bias	High risk	Trial lacks power because only 61 infants were enrolled (instead of 110)

Lista 2015

Methods	Multi-centre prospective randomised parallel controlled trial Setting: Delivery Room, Italy Conducted: October 2011 to January 2013 Infants were assigned immediately after birth before the first breath to receive SLI manoeuvres and NCPAP or NCPAP alone in a 1:1 ratio in permuted blocks of variable size. Randomisation was stratified according to centre and gestational age (25 or 26 weeks and 27 or 28 weeks). Group assignment was contained in sequentially numbered, sealed, opaque envelopes that were prepared by an independent statistician. The trial was not blinded
Participants	Newly born infants at 25 to 28 weeks of gestation inclusive without major congenital malformations (i.e. congenital heart, cerebral, lung, abdominal malformations), foetal hydrops, and lack of parental consent. A total of 294 infants were enrolled (150 in the sustained lung inflation group and 144 in the control group)
Interventions	• SLI group: PIP 25 cmH_2O for 15 seconds, followed by delivery of 5 cmH_2O CPAP, via a neonatal mask and a T-piece ventilator. Participants were observed for the next 6 to 10 seconds for evaluation of cardiorespiratory function. If respiratory failure persisted (i.e. apnoea, gasping) or heart rate was 60 and 100 beats/min despite CPAP, the SLI manoeuvre (again 25 cmH_2O for 15 seconds) was repeated. If heart rate remained 60 and 100 beats/min after the second SLI manoeuvre, the infant was resuscitated according to AAP guidelines

	• Control group: NCPAP at 5 cmH_2O with assistance according to AAP guidelines Infants in both groups who were not intubated in the delivery room were transferred to the NICU on NCPAP at 5 cmH_2O with a fraction of inspired oxygen (FiO_2) of 0.21 to 0.40 (in agreement with local protocols)
Outcomes	Primary outcome: rate of infants reaching mechanical ventilation within the first 72 hours of life Secondary outcomes: MV in the first 3 hours of life, highest FiO_2, duration of NCPAP, need for and duration of bi-level NCPAP, nasal IMV, conventional or high-frequency ventilation, duration of hospitalisation, need for and number of doses of surfactant, occurrence of RDS, BPD, and mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomised (1:1 ratio), stratified for gestational age (25 to 26 weeks, and 27 to 28 weeks)
Allocation concealment (selection bias)	Low risk	Group assignment was contained in sequentially numbered, automatically generated, sealed, opaque envelopes that were prepared by an independent statistician and distributed to participating centres
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff performing the study also cared for infants later on. However, the decision to start MV was made by clinicians other than investigators involved in the study according to specific guidelines, and researchers assessing study endpoints were blinded to the nature of study treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 0.7% (control group) and 1.3% (SLI group) of participants were lost
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Appears free of other bias

Mercadante 2016

Methods	Prospective randomised parallel controlled trial Setting: Delivery Room, Neonatal Intensive Care Unit (NICU) in Milan, Italy Conducted: September 2013 to June 2014
Participants	Inclusion criteria: inborn infants with a gestational age of 34 to 36 weeks after parental consent is obtained Exclusion criteria: major congenital anomalies
Interventions	• SLI group: PIP 25 cmH_2O for 15 seconds in the delivery room, followed by PEEP of 5 cmH_2O. In case of persistent hearth failure (HR < 100 bpm), a second SLI manoeuvre will be repeated • Control group: CPAP 5 cmH_2O with mask In both groups, mask and T-piece system were used
Outcomes	Primary outcome: need for respiratory support Secondary outcomes: air leak syndromes, NICU admission, NICU admission for respiratory disease, length of stay, exclusive breastfeeding at discharge
Notes	Sample size described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The decision to start respiratory support was made by clinicians other than investigators involved in the study according to specific guidelines, and researchers assessing study endpoints were blinded to the nature of study treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes accounted for
Selective reporting (reporting bias)	High risk	We could not ascertain whether deviations from the original protocol were evident in the final publication
Other bias	Low risk	

Ngan 2017

Methods	Prospective randomised parallel controlled trial Setting: Delivery Room, Neonatal Intensive Care Unit (NICU), Royal Alexandra Hospital (RAH), Edmonton, Canada Conducted: June 2013 to August 2014
Participants	Inclusion criteria: infants between 23^{+0} and 32^{+6} weeks of gestation who require respiratory support for resuscitation in the delivery room Exclusion criteria: congenital abnormality or condition that might have an adverse effect on breathing or ventilation; absence of parents' consent for inclusion in the study
Interventions	• SLI group: 2 PIPs of 24 cmH_2O. Duration of first SLI was 20 seconds. Duration of second SLI was 20 or 10 seconds if ECO_2 value was < or > 20 mmHg, respectively. After SLIs, CPAP if breathing spontaneously or, if found to have apnoea or laboured breathing, mask IPPV at a rate of 40 to 60 bpm • Control group: mask IPPV, ventilation rate of 40 to 60 inflations/min until spontaneous breathing, at which time CPAP will be provided
Outcomes	Primary outcome: BPD (need for respiratory support or supplemental oxygen at corrected gestational age of 36 weeks) Secondary outcomes: rate of endotracheal intubation in the DR or the NICU, duration of MV and non-invasive ventilation, neonatal death, air leak, PDA (medical or surgical), NEC, ROP, periventricular leukomalacia, abnormal cranial ultrasound (including IVH, parenchymal injury, and ventriculomegaly), surfactant administration, postnatal steroids, respiratory support or oxygen requirements at 28 days, neonatal death before discharge
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Com- puter-generated randomisation scheme (1:1 ratio). Randomisation stratified according to gestational age (to infants 23^{+0} to 27^{+6} and 28^{+0} to 32^{+6} weeks). Twins and/or triplets were randomised as individuals
Allocation concealment (selection bias)	Unclear risk	A sequentially numbered, brown, sealed envelope contained a folded card box with treatment allocation opened by the clinical team immediately before delivery Timing of randomisation resulted in many post-randomisation exclusions with the potential of inadequate allocation concealment, as more post-randomisation exclusions occurred in the SLI group than in the control group

Ngan 2017 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After admission into the NICU, the clinical team was not made aware of treatment allocation. In addition, both data collector and outcome assessor were unaware of group allocation. The research team was not involved in clinical care of the infants
Incomplete outcome data (attrition bias) All outcomes	High risk	Post-randomisation exclusion (27%) resulted in fewer included infants in the SLI group; this discrepancy might have yielded different results
Selective reporting (reporting bias)	Low risk	Protocol was registered at Clinicaltrials.gov (NCT01739114)
Other bias	Unclear risk	Planned sample size of 93 infants in each group was not achieved. Moreover, incidence of the primary outcome in the control group was lower than assumed for the sample size calculation, further underpowering the trial to detect the desired effect size

Schmölzer 2015

Methods	Prospective randomised parallel controlled trial Pilot (5 infants randomised to each group) Setting: Royal Alexandra Hospital, Edmonton, Alberta, Canada
Participants	Inclusion criteria: inborn infants between 23^{+0} and 32^{+6} weeks of postmenstrual age who required chest compressions in the delivery room Exclusion criteria: congenital abnormality or condition that might have an adverse effect on breathing or ventilation (e.g. congenital pulmonary or airway anomalies, congenital diaphragmatic hernia, congenital heart disease requiring intervention in neonatal period)
Interventions	• SLI group: SLI of 20 + 20 seconds, plus uninterrupted chest compression at a rate of 90/min • Control group: 3:1 compression:ventilation (C:V) ratio according to current resuscitation guidelines Default settings for airway pressures: PIP of 24 cmH_2O and PEEP of 6 cmH_2O
Outcomes	Primary outcome: return of spontaneous circulation Secondary outcomes (we obtained the following information directly from trial authors) : all mortality before discharge from hospital, delivery room interventions (rate of in-

Schmölzer 2015 (*Continued*)

	tubation, use of epinephrine), mechanical ventilation, use of inotropic agents, NEC, moderate to severe BPD, ROP, brain injury as indicated by abnormal neuroimaging
Notes	Available as an abstract only (Canadian Paediatric Society 92nd Annual Conference) Trial was registered at ClinicalTrials.gov: NCT02083705

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Although not reported in the abstract, we obtained the following information directly from trial authors: A sequentially numbered, brown, sealed envelope contained a folded card box with treatment allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although not reported in the abstract, we obtained the following information directly from trial authors: Both data collector and outcome assessor were unaware of group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	Trial was registered at ClinicalTrials.gov: NCT02083705. However, secondary outcomes were not specified
Other bias	Low risk	Appears free of other bias

Schwaberger 2015

Methods	Prospective randomised parallel controlled trial Setting: Delivery Room, Graz, Austria Conducted: April 2012 to December 2013
Participants	Inclusion criteria: preterm infants (28 weeks 0 days to 33 weeks 6 days) delivered by elective Caesarean section with HR < 100 or irregular breathing and/or pronounced signs of respiratory distress (grunting, tachypnoea, and increased work of breathing)

Schwaberger 2015 (*Continued*)

	Exclusion criteria: major congenital malformations, inherited disorders of metabolism and necessity of primary intubation within first 15 minutes after birth. In cases of multiple birth, only 1 of the infants was included
Interventions	Cord clamping within 30 seconds after delivery. Respiratory support with a T-piece system in the delivery room • SLI group: PIP 30 cmH_2O for 15 seconds, with mask, to be repeated once or twice with HR remaining below 100 bpm. Infants with HR > 100 bpm were supported by PPV at 30 cmH_2O PIP or CPAP at a PEEP level of 5 cmH_2O depending on respiratory rate • Control group: Respiratory support was provided according to AHA guidelines. CPAP (5 cmH_2O PEEP) was applied in infants with respiratory rate > 30 breaths per minute and signs of respiratory distress. Insufficient breathing efforts (HR < 100 bpm, respiratory rate < 30 breaths per minute or irregular breathing) indicated PPV at 30 cmH_2O PIP via face mask Initial fraction of inspired oxygen (FiO_2) of 0.3 was adapted to achieve defined oxygen saturation targets (3': > 60%; 5': > 75%; 10': > 85%)
Outcomes	Primary outcome: changes in cerebral blood volume and cerebral tissue oxygenation index during immediate postnatal transition Secondary outcomes: SpO_2, HR, VT, face mask leak, FiO_2 within first 15 minutes after birth
Notes	Trial was registered at the German Clinical Trials Register (DRKS00005161) in July 2013, after study initiation (April 2012)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated blocked randomisation, 1:1 ratio, with a block size of 8 (www.randomizer.at)
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used. We obtained the following information directly from trial authors: Envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Assigned intervention could not be blinded to the resuscitation team
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Cerebral ultrasound pictures were evaluated by a neonatologist blinded to participants. No information was provided for the other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes accounted for

Schwaberger 2015 (*Continued*)

Selective reporting (reporting bias)	Low risk	Protocol for this trial is available as supporting information. Reporting of the study conforms to Consolidated Standards of Reporting Trials (CONSORT) 2010 statement
Other bias	Low risk	Appears free of other bias.

AAP: American Academy of Pediatrics
AHA: American Heart Association
BPD: bronchopulmonary dysplasia
C:V: compression:ventilation
CBMI: conventional bag/mask inflation
CPAP: continuous positive airway pressure
DR: delivery room
ECO2: enzymatic carbonate (measure of carbon dioxide in the blood)
FiO2: fraction of inspired oxygen
HR: heart rate
IL-1b: interleukin-1beta
IMV: intermittent mandatory ventilation
IPPV: intermittent positive pressure ventilation
IVH: intraventricular haemorrhage
MV: mandatory ventilation
NCPAP: nasal continuous positive airway pressure
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
NIMV: nasal intermittent mandatory ventilation
PDA: patent ductus arteriosus
PEEP: positive end-expiratory pressure
PIP: peak inspiratory pressure
PPV: positive pressure ventilation
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity
SLI: sustained lung inflation
SpO2: blood oxygen saturation level
TNF-a: tumour necrosis factor-alpha
VT: ventricular tachycardia

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

Study	Reason for exclusion
Bouziri 2011	Not a clinical trial. Does not investigate sustained lung inflation
Harling 2005	Control group consisted of inflation for 2 seconds (5 seconds for intervention): As we defined sustained if > 1 second, this trial could not be included Infants in the SLI group were born more preterm and had lower median birth weight than those in the conventional group, although the P value was not provided. Median birth weight (range) was 885 (518 to 1460) grams in the SLI group and 1095 (560 to 1562) grams in the conventional group. Median gestational age (range) was 27 (23 to 30) weeks in the SLI group and 28 (23 to 31) weeks in the conventional group
te Pas 2007	This RCT enrolled newly born infants born at < 33 weeks of gestation free of known major congenital anomalies with respiratory distress Infants were randomised to inflation of 10 seconds at 20 cmH_2O with a T-piece via a nasal tube, or to intermittent PPV with a self-inflating bag via a face mask. Infants randomised to the T-piece received inflation for 10 seconds at 20 cmH_2O followed by NCPAP at 5 to 6 cmH_2O. If the infant's clinical response was unsatisfactory, another inflation of 10 seconds at 25 cmH_2O and NIMV (PIP 20 to 25 cmH_2O, inflation rate 60 per minute) could be given. If the infants' condition improved (satisfactory heart rate and colour) but they had irregular breathing, they could receive NIMV for several minutes. Infants who were judged to have inadequate breathing, remain bradycardic, or remain cyanosed in the delivery room after these interventions were intubated and mechanically ventilated. Infants randomised to the self-inflating bag received initial inflations of 30 to 40 cmH_2O, followed by inflations not > 20 cmH_2O (inflation time was not specified or recorded) for 30 seconds. Infants judged to have inadequate breathing, remain bradycardic, or remain cyanosed in the delivery room after this intervention were intubated and mechanically ventilated. Infants in the sustained lung inflation group who were not intubated were transferred to the neonatal intensive care unit (NICU) on NCPAP at 5 to 6 cmH_2O; non-intubated infants in the control group were transferred to the NICU with supplemental oxygen and were monitored with pulse oximetry The intervention in this trial was multi-faceted. In addition to a sustained inflation, many other aspects of respiratory care provided at birth differed between groups (ventilation device used; interface used; whether PEEP was used; whether NIMV was used; time allowed for stabilisation before intubation was considered; time of starting NCPAP) . It is not possible to determine the relative contribution (if any) of each element of this intervention to differences in outcomes observed between groups

NCPAP: nasal continuous positive airway pressure
NICU: neonatal intensive care unit
NIMV: nasal intermittent mandatory ventilation
PEEP: positive end-expiratory pressure
PIP: peak inspiratory pressure
PPV: positive pressure ventilation
RCT: randomised controlled trial
SLI: sustained lung inflation

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

NCT02139800

Trial name or title	Sustained aeration of infant lungs trial (SAIL)
Methods	Two-arm randomised controlled multi-centre clinical trial
Participants	Infants of 23 to 26 weeks of gestational age requiring respiratory support at birth. Sample size: 600 infants Inclusion criteria: gestational age at least 23 weeks but less than 27 completed weeks by best obstetrical estimate; requiring resuscitation/respiratory intervention at birth Exclusion criteria: considered non-viable by attending neonatologist; refusal of antenatal informed consent; known major anomalies, pulmonary hypoplasia. Mothers unable to provide consent for medical care and who do not have a surrogate guardian will not be approached for consent
Interventions	SLI group: sustained inflation in the delivery room. The first sustained inflation will use inflation pressure of 20 cmH_2O for 15 seconds Control group: CPAP of 5 to 7 cmH_2O in the delivery room
Outcomes	Primary outcome: combined endpoint of death or BPD at 36 weeks of gestational age Secondary outcomes: oxygen profile over first 24 hours; oxygen profile with highest fraction of inspired oxygen (FiO_2) level up to 48 hours; highest FiO_2 level recorded during first 48 hours; heart rate in the delivery room (DR); detailed status on departure from DR; type of respiratory support (CPAP, PPV) and FiO_2 on departure from DR; use of inotropic agents on arrival in NICU; circulatory support; need for intubation in DR or by 24 hours of age; pressure-volume characteristics in DR; chest x-ray reports showing pneumothorax or new chest drains in first 48 hours of life; duration of any chest drain in situ; head ultrasound and/or MRI findings of intraventricular haemorrhage; chest x-ray between days 7 and 10; death or need for positive pressure ventilation at 7 days; highest FiO_2 and area under the FiO_2 curve for first week of life; pneumothorax and pulmonary interstitial emphysema (PIE); survival to discharge home without BPD, retinopathy of prematurity (grades 3 and 4), or significant brain abnormalities on head ultrasound; duration of respiratory support (ventilation, CPAP, supplemental oxygen); death in hospital; retinopathy of prematurity (ROP) stage 3 or greater requiring treatment; use of postnatal steroids for treatment of BPD; length of hospital stay; neurodevelopmental and respiratory outcome at 22 to 26 months of corrected gestational age
Starting date	August 2014.
Contact information	Haresh Kirpalani, BM, MSc; kirpalanih@email.chop.edu Sarah J Ratcliffe, PhD; sratclif@upenn.edu.
Notes	Estimated enrolment: 600 Estimated primary completion date: December 2017

NCT02493920

Trial name or title	Evaluation of pulmonary mechanics in preterm infant treated with sustained lung inflation at birth
Methods	Prospective randomised parallel controlled trial
Participants	Preterm infants at 25 to 36 weeks

NCT02493920 (*Continued*)

Interventions	SLI group: PIP of 25 cmH_2O for 15 seconds followed by PEEP of 5 cmH_2O; second SLI in case of poor response Control group: CPAP of 5 cmH_2O with mask
Outcomes	Primary outcomes: change in reactance values measured by forced oscillation technique Secondary outcomes: need for intubation within first 72 hours of life; duration of respiratory support; death in hospital; number of surfactant doses; ROP stage 3 or greater requiring treatment; PDA requiring treatment; BPD; IVH
Starting date	July 2015
Contact information	Mariarosa Colnaghi, MD; mariarosa.colnaghi@mangiagalli.it Domenica Mercadante, MD; domenica.mrc@hotmail.it
Notes	Estimated enrolment: 48 Estimated primary completion date: December 2015

NCT02846597

Trial name or title	Sustained lung inflation at birth for preterm infants at risk of respiratory distress syndrome: the proper pressure and duration: prospective randomised study
Methods	Prospective randomised parallel controlled trial
Participants	Preterm infants $\leq$ 32 weeks of gestation with respiratory distress syndrome at birth
Interventions	Five arms: evaluating 2 different pressures - 20 and 15 cmH_2O, and for 2 different durations - 10 and 20 seconds, during application of sustained lung inflation in resuscitation of preterm infants with respiratory distress in the delivery room, plus a control group without any SLI (CPAP 5 cmH_2O)
Outcomes	Primary outcome: need for endotracheal intubation in the delivery room Secondary outcomes: need for mechanical ventilation; need for surfactant; neonatal mortality; death before hospital discharge; BPD; IVH; ROP; NEC; length of NICU and hospital stay; air leak syndrome
Starting date	March 2013
Contact information	Nehad Nasef, Associate Professor Mansoura University Children Hospital, El Dakahlya, Egypt
Notes	Estimated enrolment: 100 Estimated primary completion date: October 2016 (for primary outcome)

NCT02858583

Trial name or title	SURV1VE-Trial - Sustained inflation and chest compression versus 3:1 chest compression to ventilation ratio during cardiopulmonary resuscitation of asphyxiated newborns: a randomised controlled trial
Methods	Prospective randomised parallel controlled trial
Participants	Infants (term or preterm infants) requiring chest compressions in the delivery room
Interventions	SLI group: PIP of 25 to 30 cmH_2O for 45 seconds while receiving chest compression. This will be followed by PEEP of 5 to 8 cmH_2O. If heart rate < 60/min, continue with chest compression + SLI for another 45 seconds. If heart rate remains < 60/min, continue with CC + SI Control group: chest compression at a rate of 90/min and 30 ventilations/min in a 3:1 C:V ratio
Outcomes	Primary outcomes: return of spontaneous circulation; duration of chest compression heart rate is > 60/min for 15 seconds
Starting date	January 2017
Contact information	Georg Schmolzer, MD, PhD; georg.schmoelzer@me.com University of Alberta
Notes	Estimated enrolment: 118 Estimated primary completion date: December 2018

NCT02887924

Trial name or title	The effect of sustained lung inflation maneuver applied through nasal prong on early and late respiratory morbidities in preterm infants
Methods	Prospective randomised parallel controlled trial
Participants	Preterm infants of 26 weeks 0 days and 29 weeks 6 days
Interventions	SLI group: PIP 25 cmH_2O for 15 seconds with T-piece and bi-nasal prongs; second SLI in case of poor response Control group: CPAP
Outcomes	Primary outcome: surfactant need, intubation and mechanical ventilation needs within first 72 hours of life Secondary outcomes: heart rate, fractional inspiratory oxygen, CPAP pressure and oxygen saturation within first 72 hours of life in preterm infants; total non-invasive, invasive respiratory support time; BPD; PDA; IVH, NEC; ROP; feeding intolerance, reaching birth weight; transition to full oral feeding time
Starting date	August 2016
Contact information	Zekai Tahir Burak Women's Health Research and Education Hospital, Ankara, Turkey
Notes	Estimated enrolment: 250 Estimated primary completion date: September 2017

BPD: bronchopulmonary dysplasia
CC: chest compression
C:V: compression: ventilation
CPAP: continuous positive airway pressure
DR: delivery room
FiO2: fraction of inspired oxygen
IVH: intraventricular haemorrhage
NICU: neonatal intensive care unit
PEEP: positive end-expiratory pressure
PIE: pulmonary interstitial emphysema
PIP: peak inspiratory pressure
PPV: positive pressure ventilation
ROP: retinopathy of prematurity
SI: sustained inflation
SLI: sustained lung inflation

DATA AND ANALYSES

Comparison 1. Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Death in the delivery room	5	479	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [0.11, 63.40]
1.2 Death before discharge	7	932	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.67, 1.51]
2 Apgar at 1 minute	5	529	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.26, 0.09]
3 Apgar at 5 minutes	6	641	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.13, 0.08]
4 Endotracheal intubation	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Endotracheal intubation in the delivery room	5	601	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.19]
4.2 Endotracheal intubation within 24 hours	2	225	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.53, 3.68]
4.3 Endotracheal intubation by 72 hours of age	5	811	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
5 Surfactant administration	7	1267	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.89, 1.15]
5.1 Surfactant given in the delivery room	3	335	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.82, 2.49]
5.2 Surfactant given at any time	7	932	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.10]
6 Need for mechanical ventilation	3	484	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.74, 1.03]
7 Duration of NCPAP	3	355	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.19, 0.72]
8 Duration of mechanical ventilation	5	524	Mean Difference (IV, Fixed, 95% CI)	-5.37 [-6.31, -4.43]
9 Duration of respiratory support (NCPAP + MV)	2	243	Mean Difference (IV, Fixed, 95% CI)	0.69 [0.23, 1.16]
10 Duration of supplemental oxygen requirement	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Chronic lung disease	6	903	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.13]
11.1 BPD any grade	2	220	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.19]
11.2 Moderate to severe BPD	5	683	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.74, 1.22]
12 Pneumothorax	7	932	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.76, 2.61]
12.1 During first 48 hours	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.06, 13.65]
12.2 At any time	6	851	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.76, 2.72]
13 Cranial ultrasound abnormalities	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Intraventricular haemorrhage grade 3-4	5	635	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.37]
13.2 IVH any grade	2	152	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.69]
13.3 Cystic periventricular leukomalacia	5	635	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.24, 1.44]
14 Retinopathy of prematurity (ROP) stage ≥ 3	5	632	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.44, 1.10]

15 Patent ductus arteriosus (PDA)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 PDA - pharmacological treatment	6	745	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.90, 1.30]
15.2 PDA - surgical closure	3	412	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.27, 1.99]

Comparison 2. Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

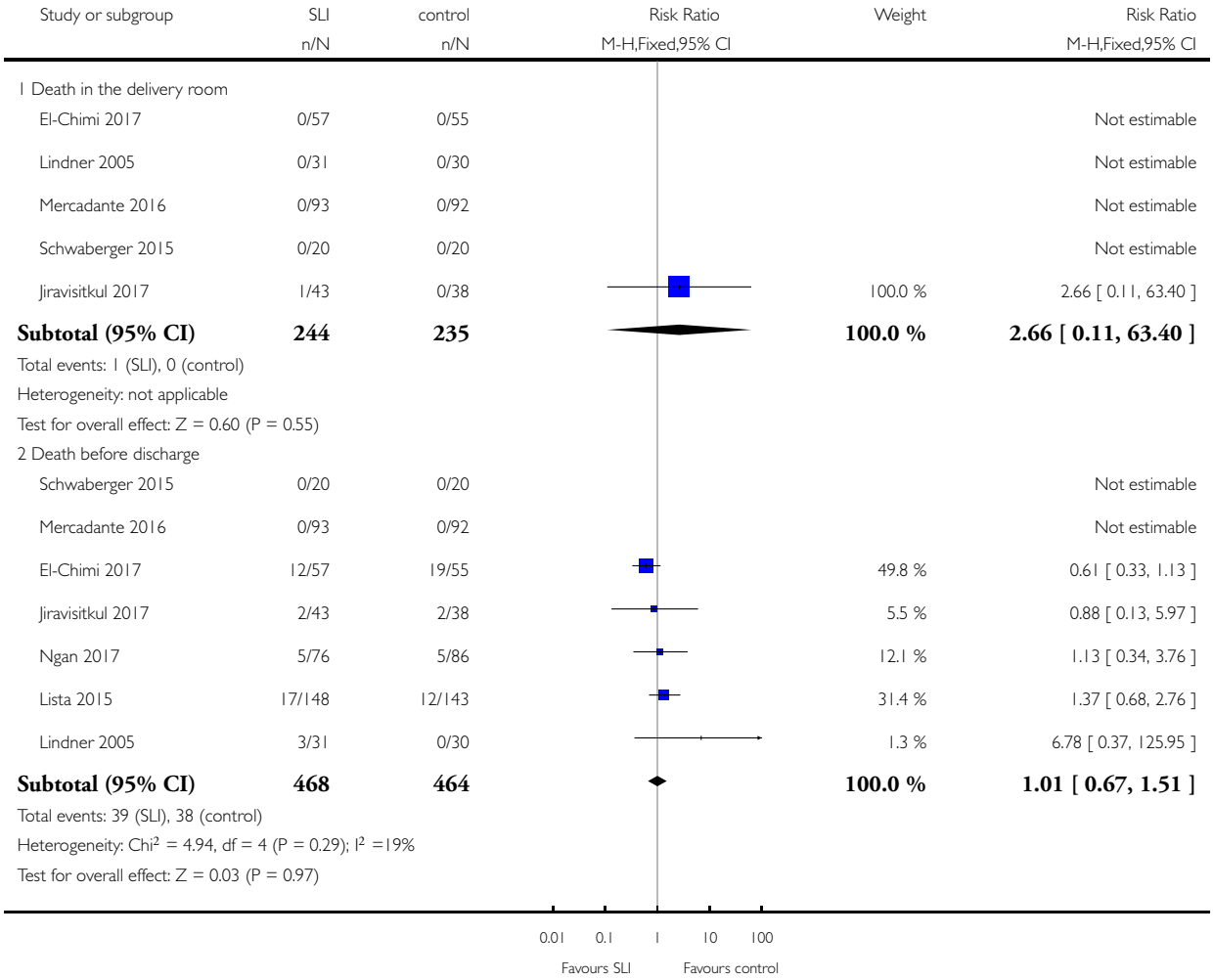
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Death before discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Endotracheal intubation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Endotracheal intubation in the delivery room	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Surfactant administration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Surfactant given in the delivery room	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Chronic lung disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Moderate to severe BPD	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Pneumothorax	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 At any time	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Cranial ultrasound abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Intraventricular haemorrhage grade 3 to 4	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 IVH any grade	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Retinopathy of prematurity (ROP) stage ≥ 3	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Patent ductus arteriosus (PDA)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 PDA - pharmacological treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 1 Death.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 1 Death



Analysis 1.2. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 2 Apgar at 1 minute.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 2 Apgar at 1 minute

Study or subgroup	SLI		control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Jiravisitkul 2017	43	4.77 (2.59)	38	4.35 (2.76)		2.3 %	0.42 [-0.75, 1.59]
Lindner 2005	31	4.2 (1.9)	30	3.8 (1.9)		3.4 %	0.40 [-0.55, 1.35]
Mercadante 2016	93	8.4 (0.67)	92	8.5 (0.73)		76.6 %	-0.10 [-0.30, 0.10]
Ngan 2017	76	4 (2)	86	4 (2)		8.2 %	0.0 [-0.62, 0.62]
Schwaberger 2015	20	7.6 (1.14)	20	7.9 (0.64)		9.5 %	-0.30 [-0.87, 0.27]
Total (95% CI)	**263**		**266**			**100.0 %**	**-0.08 [-0.26, 0.09]**

Heterogeneity: $Chi^2 = 2.34$, df = 4 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 3 Apgar at 5 minutes.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 3 Apgar at 5 minutes

Study or subgroup	Sustained inflations		Standard inflations		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
El-Chimi 2017	57	7.61 (0.65)	55	7.24 (0.86)		13.8 %	0.37 [0.09, 0.65]
Jiravisitkul 2017	43	7.36 (2.1)	38	7.1 (2.34)		1.2 %	0.26 [-0.71, 1.23]
Lindner 2005	31	8 (2)	30	8 (2)		1.1 %	0.0 [-1.00, 1.00]
Mercadante 2016	93	9.4 (0.43)	92	9.5 (0.44)		70.1 %	-0.10 [-0.23, 0.03]
Ngan 2017	76	7 (1)	86	7 (2)		4.8 %	0.0 [-0.48, 0.48]
Schwaberger 2015	20	8.7 (0.47)	20	8.75 (0.64)		9.1 %	-0.05 [-0.40, 0.30]
Total (95% CI)	**320**		**321**			**100.0 %**	**-0.02 [-0.13, 0.08]**

Heterogeneity: $Chi^2 = 9.21$, df = 5 (P = 0.10); $I^2 = 46\%$

Test for overall effect: Z = 0.39 (P = 0.70)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 4 Endotracheal intubation.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 4 Endotracheal intubation

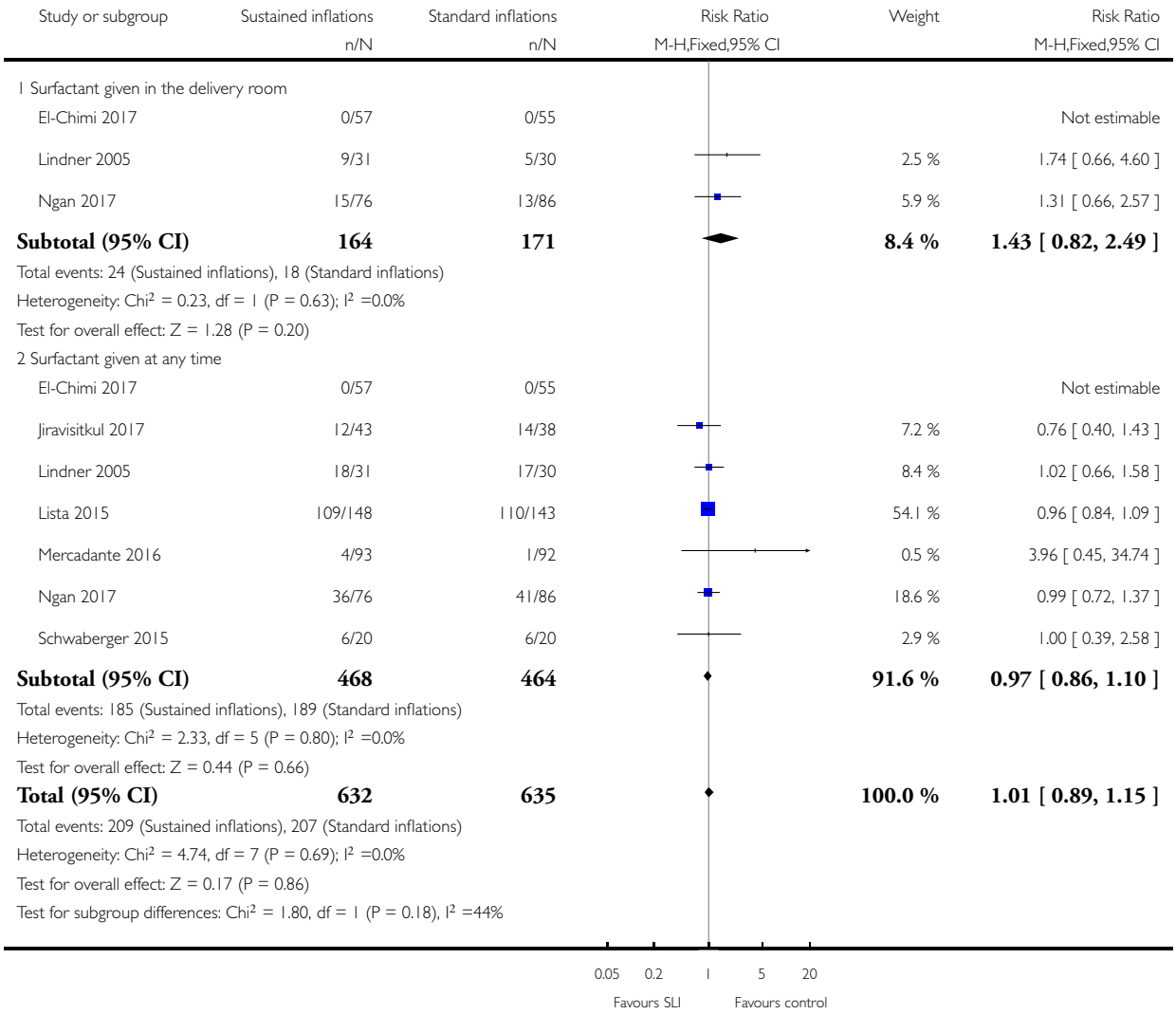
Study or subgroup	Favours SLI n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Endotracheal intubation in the delivery room					
El-Chimi 2017	3/57	13/55		22.9 %	0.22 [0.07, 0.74]
Jiravisitkul 2017	11/43	14/38		25.7 %	0.69 [0.36, 1.34]
Lindner 2005	10/31	7/30		12.3 %	1.38 [0.61, 3.16]
Mercadante 2016	0/93	0/92			Not estimable
Ngan 2017	25/76	24/86		39.0 %	1.18 [0.74, 1.88]
Subtotal (95% CI)	**300**	**301**		**100.0 %**	**0.86 [0.62, 1.19]**
Total events: 49 (Favours SLI), 58 (Standard inflations)					
Heterogeneity: Chi^2 = 8.30, df = 3 (P = 0.04); I^2 =64%					
Test for overall effect: Z = 0.91 (P = 0.36)					
2 Endotracheal intubation within 24 hours					
Mercadante 2016	0/93	0/92			Not estimable
Schwaberger 2015	7/20	5/20		100.0 %	1.40 [0.53, 3.68]
Subtotal (95% CI)	**113**	**112**		**100.0 %**	**1.40 [0.53, 3.68]**
Total events: 7 (Favours SLI), 5 (Standard inflations)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.49)					
3 Endotracheal intubation by 72 hours of age					
El-Chimi 2017	11/57	12/55		8.0 %	0.88 [0.43, 1.83]
Lindner 2005	19/31	18/30		12.0 %	1.02 [0.68, 1.53]
Lista 2015	79/148	93/143		62.1 %	0.82 [0.68, 1.00]
Mercadante 2016	2/93	1/92		0.7 %	1.98 [0.18, 21.44]
Ngan 2017	30/76	28/86		17.2 %	1.21 [0.80, 1.83]
Subtotal (95% CI)	**405**	**406**		**100.0 %**	**0.93 [0.79, 1.09]**
Total events: 141 (Favours SLI), 152 (Standard inflations)					
Heterogeneity: Chi^2 = 3.77, df = 4 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.95 (P = 0.34)					

Analysis 1.5. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 5 Surfactant administration.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 5 Surfactant administration

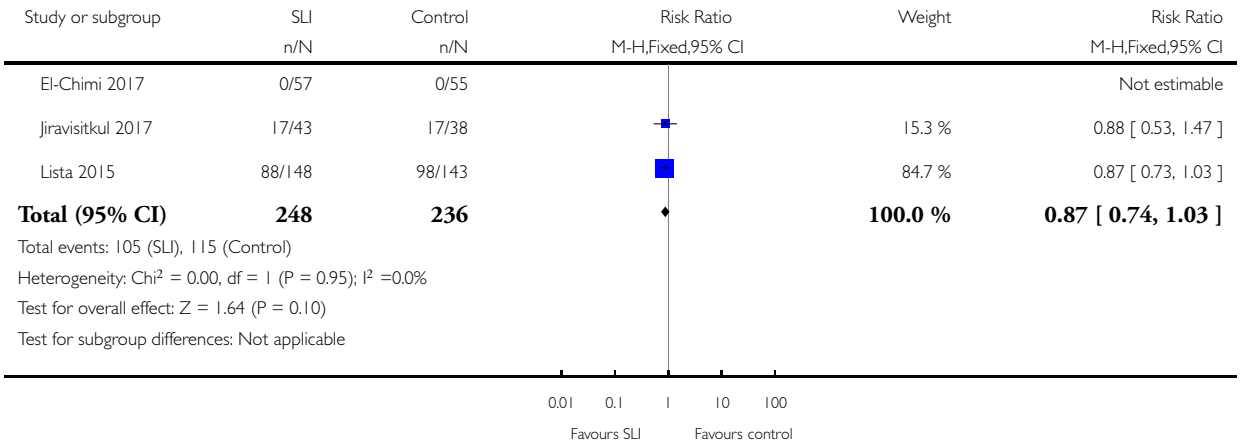


Analysis 1.6. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 6 Need for mechanical ventilation.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 6 Need for mechanical ventilation



Analysis 1.7. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 7 Duration of NCPAP.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 7 Duration of NCPAP

Study or subgroup	Sustained inflations		Standard inflations		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[days]	N	Mean(SD)[days]	IV,Fixed,95% CI		IV,Fixed,95% CI
El-Chimi 2017	57	6.89 (10.39)	55	9.71 (10.79)		1.4 %	-2.82 [-6.75, 1.11]
Lindner 2005	28	14.5 (9.5)	30	19.9 (17.3)		0.4 %	-5.40 [-12.52, 1.72]
Mercadante 2016	93	2.96 (1.7)	92	2.63 (1.5)		98.2 %	0.33 [-0.13, 0.79]
Total (95% CI)	**178**		**177**			**100.0 %**	**0.26 [-0.19, 0.72]**

Heterogeneity: $Chi^2 = 4.88$, df = 2 (P = 0.09); $I^2 = 59\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 8 Duration of mechanical ventilation.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 8 Duration of mechanical ventilation

Study or subgroup	SLI		control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[days]	N	Mean(SD)[days]	IV,Fixed,95% CI		IV,Fixed,95% CI
Mercadante 2016	93	3.5 (2.8)	92	0.08 (0)			Not estimable
Lindner 2005	28	15.3 (20.5)	30	14.6 (17.9)		0.9 %	0.70 [-9.23, 10.63]
Jiravisitkul 2017	42	1.5 (3.35)	37	4.13 (5.65)		20.2 %	-2.63 [-4.71, -0.55]
Schwaberger 2015	20	0.75 (2.02)	20	1.9 (3.42)		29.0 %	-1.15 [-2.89, 0.59]
Ngan 2017	76	7.54 (3.8)	86	16.58 (4.8)		49.9 %	-9.04 [-10.37, -7.71]
Total (95% CI)	**259**		**265**			**100.0 %**	**-5.37 [-6.31, -4.43]**

Heterogeneity: Chi² = 60.07, df = 3 (P<0.00001); I² =95%

Test for overall effect: Z = 11.23 (P < 0.00001)

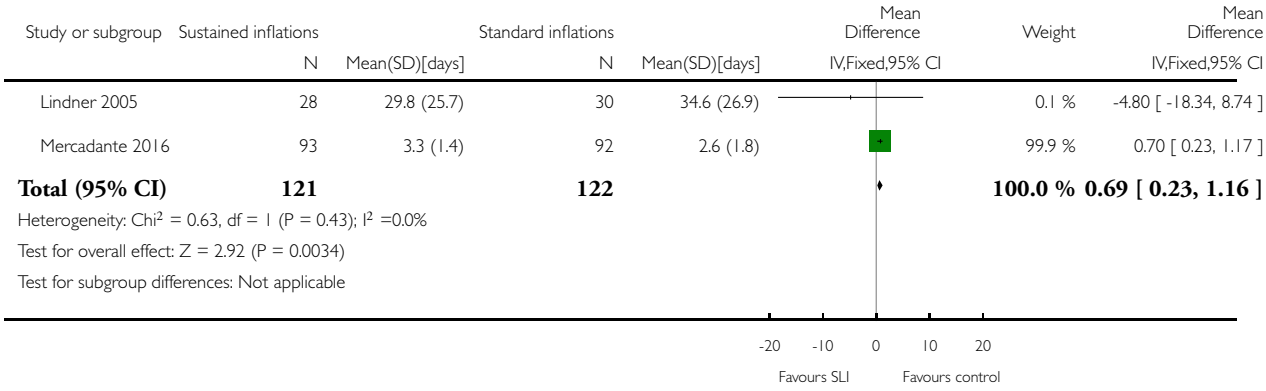
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 9 Duration of respiratory support (NCPAP + MV).

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 9 Duration of respiratory support (NCPAP + MV)

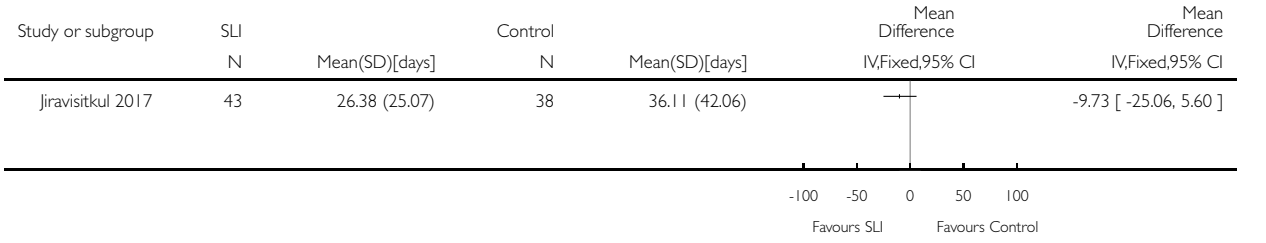


Analysis 1.10. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 10 Duration of supplemental oxygen requirement.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 10 Duration of supplemental oxygen requirement

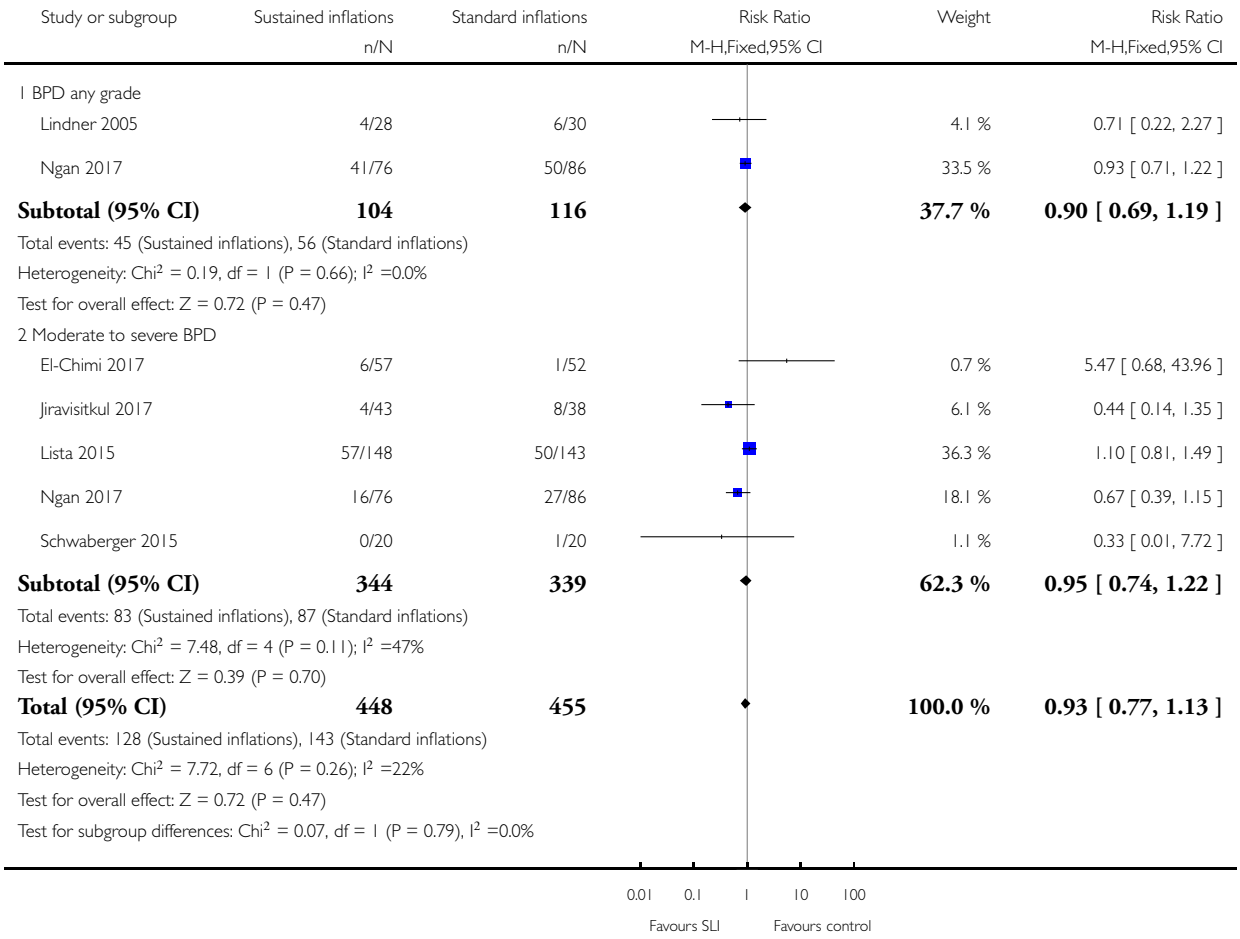


Analysis 1.11. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 11 Chronic lung disease.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 11 Chronic lung disease

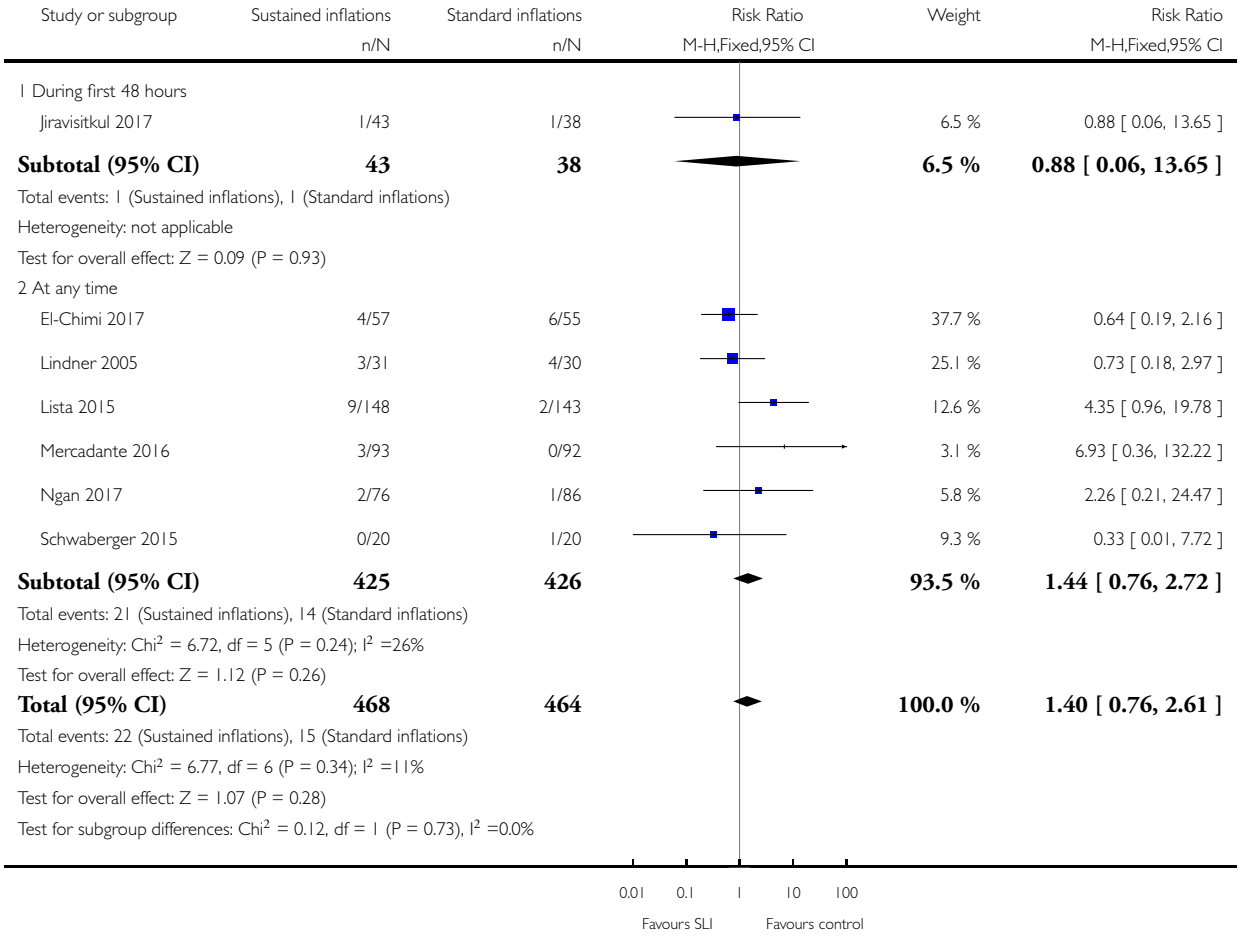


Analysis 1.12. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 12 Pneumothorax.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 12 Pneumothorax

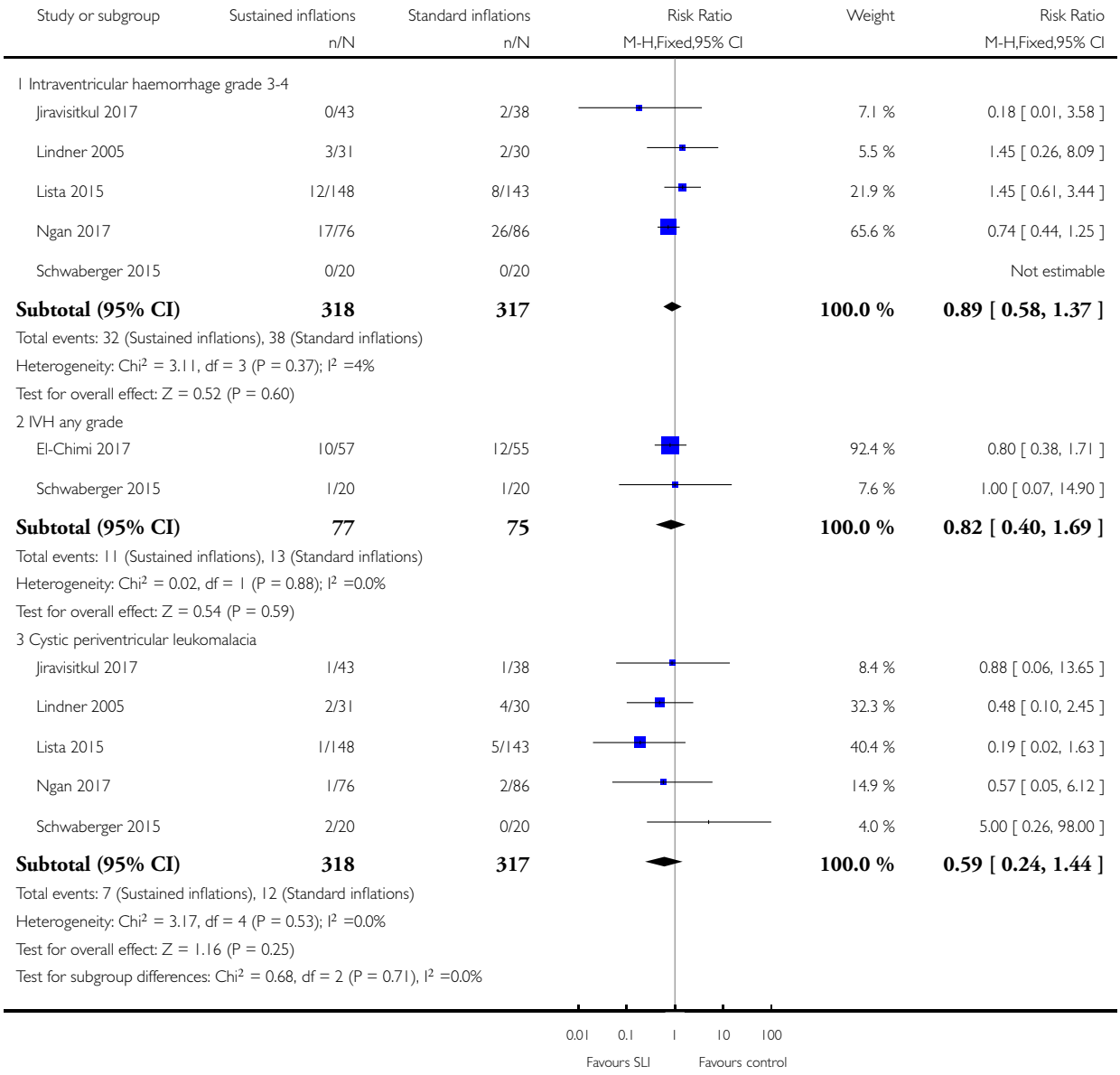


Analysis 1.13. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 13 Cranial ultrasound abnormalities.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 13 Cranial ultrasound abnormalities



Analysis 1.14. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 14 Retinopathy of prematurity (ROP) stage ≥ 3.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 14 Retinopathy of prematurity (ROP) stage ≥ 3

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jiravisitkul 2017	0/43	4/38		12.3 %	0.10 [0.01, 1.77]
Lindner 2005	5/28	5/30		12.5 %	1.07 [0.35, 3.31]
Lista 2015	14/148	12/143		31.5 %	1.13 [0.54, 2.35]
Ngan 2017	7/76	18/86		43.6 %	0.44 [0.19, 1.00]
Schwaberger 2015	0/20	0/20			Not estimable
Total (95% CI)	**315**	**317**		**100.0 %**	**0.69 [0.44, 1.10]**

Total events: 26 (Sustained inflations), 39 (Standard inflations)

Heterogeneity: $Chi^2 = 5.19$, df = 3 (P = 0.16); $I^2 = 42\%$

Test for overall effect: Z = 1.54 (P = 0.12)

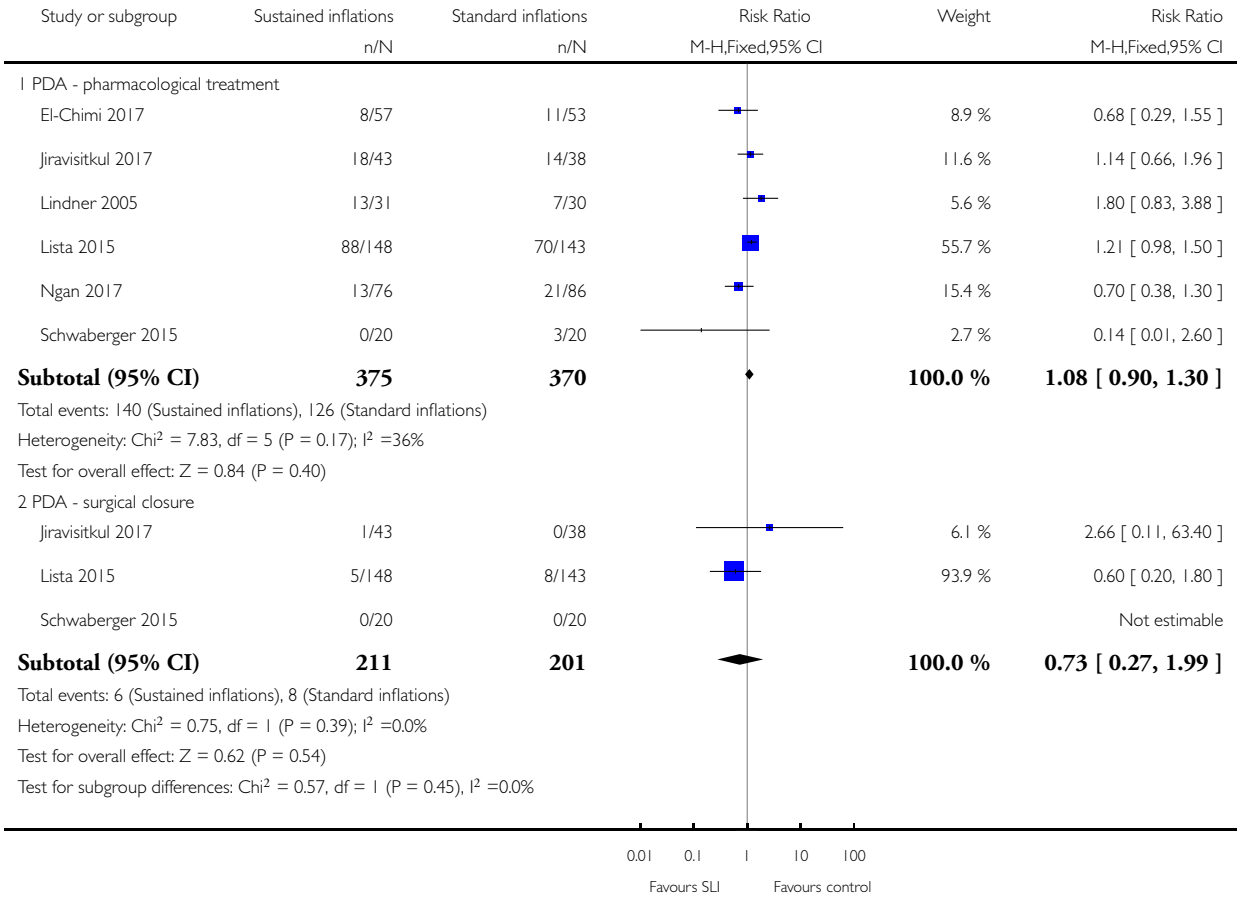
Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions, Outcome 15 Patent ductus arteriosus (PDA).

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 1 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with no chest compressions

Outcome: 15 Patent ductus arteriosus (PDA)

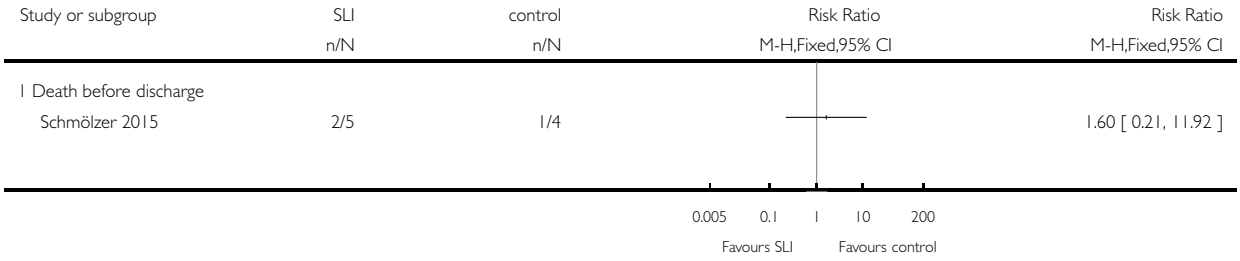


Analysis 2.1. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 1 Death.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 1 Death

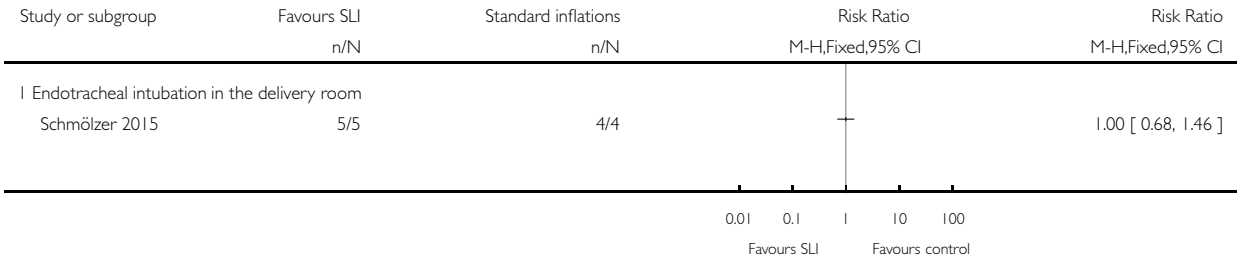


Analysis 2.2. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 2 Endotracheal intubation.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 2 Endotracheal intubation



Analysis 2.3. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 3 Surfactant administration.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 3 Surfactant administration

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Surfactant given in the delivery room				
Schmölzer 2015	4/5	2/4		1.60 [0.55, 4.68]

Analysis 2.4. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 4 Chronic lung disease.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 4 Chronic lung disease

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Moderate to severe BPD				
Schmölzer 2015	2/3	3/4		0.89 [0.33, 2.37]

Analysis 2.5. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 5 Pneumothorax.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 5 Pneumothorax

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 At any time				
Schmölzer 2015	0/5	0/4		Not estimable

Analysis 2.6. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 6 Cranial ultrasound abnormalities.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 6 Cranial ultrasound abnormalities

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Intraventricular haemorrhage grade 3 to 4				
Schmölzer 2015	1/5	2/4		0.40 [0.05, 2.98]
2 IVH any grade				
Schmölzer 2015	1/5	4/4		0.28 [0.07, 1.15]

Analysis 2.7. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 7 Retinopathy of prematurity (ROP) stage ≥ 3.

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 7 Retinopathy of prematurity (ROP) stage ≥ 3

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Schmölzer 2015	1/5	3/4		0.27 [0.04, 1.68]

Analysis 2.8. Comparison 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions, Outcome 8 Patent ductus arteriosus (PDA).

Review: Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes

Comparison: 2 Use of initial sustained inflation vs standard inflations in newborns receiving resuscitation with chest compressions

Outcome: 8 Patent ductus arteriosus (PDA)

Study or subgroup	Sustained inflations n/N	Standard inflations n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 PDA - pharmacological treatment				
Schmölzer 2015	2/5	4/4		0.46 [0.17, 1.25]

ADDITIONAL TABLES

Table 1. Populations and interventions in included trials

Trial (no. infants)	Antenatal steroids		Gestational age, weeks		Birth weight, grams		Device/ Interface	Interventions/Controls	
	SLI	Control	SLI	Control	SLI	Control	SLI and control	SLI	Control
El-Chimi 2017 (112)	39%	34.5%	mean 31.1 (SD 1.7)	mean 31.3 (SD 1.7)	mean 1561 (SD 326)	mean 1510 (SD 319)	Mask and T-piece in SLI group Mask and self-inflating bag with an oxygen reservoir in control group	PIP of 20 cmH_2O for 15 seconds, followed by PEEP of 5 cmH_2O If needed: a second SLI of 15 seconds of 25 cmH_2O for 15 seconds, followed by PEEP of 6 cmH_2O; then a third SLI of 15 seconds of 30 cmH_2O for 15 seconds, followed by PEEP of 7 cmH_2O If still not satisfactory: intubated in delivery room	PIP maximum 40 cmH_2O, rate of 40 to 60 breaths/ min for 30 seconds
Jiravisitkul 2017 (81)	63%	74%	25 to 28 weeks: n = 17; 29 to 32 weeks: n = 26	25 to 28 weeks: n = 16; 29 to 32 weeks: n = 22	mean 1206 (SD 367)	mean 1160 (SD 411)	Mask and T-piece	PIP of 25 cmH_2O for 15 seconds If	PIP 15 to 20 cmH_2O, PEEP 5 cmH_2O

Table 1. Populations and interventions in included trials (*Continued*)

								HR 60 to 100 beats/min and/or poor respiratory effort: a second SLI (25 cmH_2O, 15 seconds)	for 30 seconds, followed by resuscitation according to AHA guidelines
Lindner 2005 (61)	81%	80%	median 27.0 (IQR 25.0 to 28.9)	median 26.7 (IQR 25.0 to 28.9)	median 870 (IQR 410 to 1320)	median 830 (IQR 370 to 1370)	Nasopharyngeal tube (fixed at 4 to 5 cm) and mechanical ventilator	PIP of 20 cmH_2O for 15 seconds If response was not satisfactory: 2 further SLIs of 15 seconds (25 and 30 cmH_2O). Then PEEP at 4 to 6 cmH_2O	PIP 20 cmH_2O, PEEP 4 to 6 cmH_2O; inflation time 0.5 seconds; inflation rate 60 per min. Then, PEEP at 4 to 6 cmH_2O
Lista 2015 (301)	87%	91%	mean 26.8 (SD 1.2); 25 to 26 weeks: n = 55 27 to 28 weeks: n = 88	mean 26.8 (SD 1.1); 25 to 26 weeks: n = 52; 27 to 28 weeks: n = 96	mean 894 (SD 247)	mean 893 (SD 241)	Mask and T-piece	PIP 25 cmH_2O for 15 seconds. Then reduced to PEEP of 5 cmH_2O	PEEP 5 cmH_2O, followed by resuscitation according to AHA guidelines
Mercadante 2016 (185)	40%	32%	mean 35.2 (SD 0.8)	mean 35.2 (SD 0.8)	mean 2345 (SD 397)	mean 2346 (SD 359)	Mask and T-piece	PIP 25 cmH_2O for 15 seconds, followed by PEEP of 5 cmH_2O. In case of persistent	PEEP 5 cmH_2O, followed by resuscitation according to AAP guidelines

Table 1. Populations and interventions in included trials (*Continued*)

								heart failure (HR < 100 bpm) : SLI repeated	
Ngan 2017 (162)	78%	70%	mean 28 (SD 2.5)	mean 28 (SD 2.5)	mean 1154 (SD 426)	mean 1140 (SD 406)	Mask and T-piece	Two PIPs of 24 cmH_2O. Duration of first SLI was 20 seconds. Duration of second SLI was 20 or 10 seconds, guided by ECO_2 values. After SLIs, CPAP if breathing spontaneously or, if found to have apnoea or laboured breathing, mask IPPV at a rate of 40 to 60 bpm	IPPV, rate of 40 to 60 inflations/min until spontaneous breathing, at which time CPAP will be provided
Schmölzer 2015 (9)	80%[a]	100%[a]	mean 24.6 (SD 1.3)[a]	mean 25.6 (SD 2.3)[a]	mean 707 (SD 208)[a]	mean 808 (SD 192)[a]	Mask and T-piece[a]	PIP for 20 + 20 seconds[a] during chest compressions	3: 1 compression:ventilation ratio according to resuscitation guidelines
Schwaberger 2015 (40)	not reported	not reported	mean 32.1 (SD 1.4)	mean 32.1 (SD 1.6)	mean 1692 (SD 297)	mean 1722 (SD 604)	Mask and T-piece	PIP 30 cmH_2O for 15 seconds, to be	Resuscitation according to AHA

Table 1. Populations and interventions in included trials (*Continued*)

								repeated once or twice with HR remaining < 100 bpm. Infants with HR > 100 bpm: PPV at 30 cmH_2O PIP or CPAP at PEEP level of 5 cmH_2O depending on respiratory rate	guidelines PEEP 5 cmH_2O if respiratory rate > 30 and signs of respiratory distress PPV at 30 cmH_2O PIP if insufficient breathing efforts

[a] Information provided by study authors

APPENDICES

Appendix 1. Standard search method

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of the trials. For each trial, we sought information regarding the method of randomisation, and the blinding and reporting of all outcomes of all infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. We resolved any disagreement by discussion. We added this information to the table Characteristics of included studies. We evaluated the following issues and entered the findings into the risk of bias table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

a. low risk (any truly random process, e.g. random number table; computer random number generator);
b. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
c. unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

a. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
b. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
c. unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

a. low risk, high risk, or unclear risk for participants; and
b. low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods as:

a. low risk for outcome assessors;
b. high risk for outcome assessors; or
c. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by trial authors, we re-included missing data in the analyses. We categorised the methods as:

a. low risk (< 20% missing data);
b. high risk (≥ 20% missing data); or
c. unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

a. low risk (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
b. high risk (when not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
c. unclear risk.

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

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific study design, whether the trial was stopped early owing to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

a. low risk;
b. high risk; or
c. unclear risk.

If needed, we explored the impact of the level of bias by undertaking sensitivity analyses.

WHAT'S NEW

Last assessed as up-to-date: 17 February 2017.

Date	Event	Description
21 July 2017	Amended	Typo corrected: Schwaberger 2015 used near-infrared spectroscopy (NIRS) not a numerical rating scale (NRS)

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 7, 2015

Date	Event	Description
13 June 2017	New citation required but conclusions have not changed	We included six new studies but made no changes to the main conclusions
13 June 2017	New search has been performed	We updated searches in 2017 and found six new eligible studies for inclusion
6 July 2015	Amended	We updated review author affiliation
10 July 2008	Amended	We converted the review to new review format

CONTRIBUTIONS OF AUTHORS

Dr. Bruschettini and Dr. O'Donnell performed the literature search, extracted and analysed data, and wrote the manuscript. Prof. Davis performed the literature search, extracted data, checked the analysis, and reviewed the manuscript. Prof. Morley and Dr. Moja reviewed the manuscript. Dr. Zappettini performed the literature search, extracted data, and reviewed the manuscript. Dr. Calevo analysed data, checked the analysis, and reviewed the manuscript.

DECLARATIONS OF INTEREST

MB, COD, PD, CM, LM, SZ, and MGC have no known conflicts of interest to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added clinically relevant outcomes (surfactant administration, need for mechanical ventilation, retinopathy of prematurity, and PDA).

We planned subgroup analyses according to gestational age (< 37 weeks, ≥ 37 weeks), ventilation device used (self-inflating bag, flow-inflating bag, T-piece, mechanical ventilator), patient interface used (face mask, ETT, nasopharyngeal tube), and duration of sustained inflation (> 1 second to 5 seconds, > 5 seconds). We were unable to conduct any subgroup analyses as few trials met the inclusion criteria.

For this update, we made the *post hoc* decision to add a comparison based on use of chest compression during resuscitation. Moreover, we specified Unit of analysis issues and Sensitivity analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Ductus Arteriosus, Patent [epidemiology]; Hospital Mortality; Intubation, Intratracheal [methods; mortality]; Positive-Pressure Respiration [*methods; mortality]; Pulmonary Surfactants [administration & dosage]; Randomized Controlled Trials as Topic; Respiration, Artificial [utilization]; Resuscitation [*methods]; Time Factors

MeSH check words

Humans; Infant, Newborn