Thresholds for surfactant use in preterm neonates: a network meta-analysis

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ABSTRACT
Objective To perform a network meta-analysis of randomised controlled trials of different surfactant treatment strategies for respiratory distress syndrome (RDS) to assess if a certain fraction of inspired oxygen (FiO₂) is optimal for selective surfactant therapy. Design Systematic review and network meta-analysis using Bayesian analysis of randomised trials of prophylactic versus selective surfactant for RDS. Setting Cochrane Central Register of Controlled Trials, MEDLINE, Embase and Science Citation Index Expanded. Patients Randomised trials including infants under 32 weeks of gestational age. Interventions Intratracheal surfactant, irrespective of type or dose. Main outcome measures Our primary outcome was neonatal mortality, compared between groups treated with selective surfactant therapy at different thresholds of FiO₂. Secondary outcomes included respiratory morbidity and major complications of prematurity. Results Of 4643 identified references, 14 studies involving 5298 participants were included. We found no statistically significant differences between 30%, 40% and 50% FiO₂ thresholds. A sensitivity analysis of infants treated in the era of high antenatal steroid use suggested an increase in the combined outcome of major morbidity and major complications of prematurity. Conclusion Our results do not show a clear benefit of surfactant treatment at any threshold of FiO₂. The 60% threshold was suggestive of increased morbidity. There was no advantage seen with prophylactic treatment. Randomised trials of different thresholds for surfactant delivery are urgently needed to guide clinicians and provide robust evidence.

PROSPERO registration number CRD42020166620.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Intratracheal surfactant, provided to premature infants with neonatal respiratory distress syndrome (RDS), decreases mortality and the respiratory complications of prematurity.
⇒ Current best practice supports nasal continuous positive airway pressure (NCPAP) and avoidance of mechanical ventilation, with provision of exogenous surfactant with increasing oxygen requirement or need for ventilation.
⇒ Due to insufficient available evidence, clinical guidelines and therefore practice on when surfactant should be provided to these infants vary.

WHAT THIS STUDY ADDS
⇒ This study adds to a limited evidence base on when is most appropriate to provide selective surfactant to infants with RDS.
⇒ A threshold of 60% fraction of inspired oxygen has been shown to increase major morbidity, most notably retinopathy of prematurity, and should be avoided.
⇒ No significant difference was seen between the 30%, 40% and 50% thresholds, which suggests more judicious use of surfactant may be appropriate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ The results of this study suggest that more judicious use of selective surfactant may be appropriate in premature infants managed on NCPAP.
⇒ Well designed and adequately powered randomised trials are required to further evaluate the most appropriate threshold of oxygen to provide surfactant to these infants.

INTRODUCTION
Respiratory distress syndrome (RDS) is a common consequence of prematurity.1 Management is through provision of respiratory support alongside exogenous surfactant.2 Early Cochrane reviews supported prophylactic surfactant and intubation.3 A more recent review compared a prophylactic strategy (administration before first breath or after brief stabilisation) to selective use (after evidence of RDS), including subgroup analysis of current best practice (nasal continuous positive airway pressure (NCPAP) and high antenatal steroid use).4 The risk of chronic lung disease (CLD)/death was lower in the selective group in the subgroup supporting more judicious use.

Best practice dictates stabilisation of preterm infants with NCPAP and early surfactant if the need for intubation arises. However, the threshold at which this should occur is unclear. Despite a large body of work assessing the best use of surfactant, little work has assessed the threshold of fraction of inspired oxygen (FiO₂) that surfactant should be given at, leading to variations in practice and reliance on poor quality evidence.5 6 Differing views exist internationally. The European Consensus Guidelines suggest a 30%
Interventions
Intratracheal surfactant delivery.

Outcomes
The primary outcome was mortality.
Secondary outcomes included
- Bronchopulmonary dysplasia (BPD) (oxygen requirement or need for respiratory support at 36 weeks of corrected gestational age (CGA))
- CLD (oxygen requirement or need for respiratory support at 28 days).
- Pneumothorax (or other air leak).
- Surfactant therapy (proportion requiring surfactant and number of doses required)
- Major morbidity, defined as at least one of severe intraventricular haemorrhage (IVH) (grade 3 or 4), periventricular leucomalacia (PVL), necrotising enterocolitis (NEC) (stage 2A or above), retinopathy of prematurity (ROP) greater than stage 2 or BPD.
- Neurodevelopmental outcome at 2 years of CGA, defined as one of cerebral palsy, mental retardation (Bayley Scales of Infant Development Mental Developmental Index <70), legal blindness (<20/200 visual acuity) and hearing deficit (aided or <60dB on audiometric testing).
- Health-related quality of life (HRQOL).

Search methods
Regarding electronic searches, we searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Embase and Science Citation Index Expanded between inception and December 2021 without language restrictions.
We also searched The US National Institute of Health Ongoing Trials Register (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).
A combination of controlled vocabulary and free-text terms was used for the population (preterm infants) and intervention (surfactant) (see online supplemental eMethods).

Data collection and management
Two authors independently screened titles and abstracts and selected articles for inclusion based on full-text examination. Two authors independently extracted data in a prepiloted form, including outcome data, data on potential effect modifiers and individual study data (see online supplemental eMethods).
We collected data at maximum follow-up and shorter follow-up where applicable. Trial authors were contacted in the case of missing information. Differences were resolved by discussion. The Cochrane Risk of Bias V.2 tool was used. Each domain was classified as ‘low risk’, ‘some concern’ or ‘high risk’, leading to classification of the study.

Measurement of treatment effects
For dichotomous variables the OR with 95% credible intervals (CrI) were calculated. For continuous variables, we calculated the mean difference with 95% CrI. For count outcomes, we calculated the rate ratio with 95% CrI. For time-to-event outcomes, HR with 95% CrI was calculated.
We estimated the ranking probabilities for all interventions (level of FiO2) of being at each possible rank for each intervention. We obtained the surface under the cumulative ranking curve (cumulative probability), rankogram and relative ranking table with CrI for the ranking probabilities.
Table 1  Characteristics of included studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Setting</th>
<th>Participants analysed</th>
<th>Threshold for selective surfactant (%)</th>
<th>Primary outcome</th>
<th>Gestational age range (weeks)</th>
<th>Female gender (%)</th>
<th>Antenatal steroids (any) (%)</th>
<th>Surfactant type</th>
<th>Surfactant dose</th>
<th>Ventilation</th>
<th>Dropout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kattwinkel et al</td>
<td>8 centres, USA</td>
<td>1248</td>
<td>30</td>
<td>Moderate RDS*</td>
<td>29–33</td>
<td>47</td>
<td>No info</td>
<td>Bovine</td>
<td>150 mg/dose</td>
<td>Both</td>
<td>150</td>
</tr>
<tr>
<td>Rojas et al</td>
<td>8 centres,</td>
<td>279</td>
<td>30</td>
<td>Need for MV</td>
<td>27–32</td>
<td>49</td>
<td>86</td>
<td>Bovine</td>
<td>100 mg/kg</td>
<td>CPAP</td>
<td>0</td>
</tr>
<tr>
<td>Walti et al</td>
<td>12 centres,</td>
<td>256</td>
<td>30</td>
<td>Survival without</td>
<td>25–31</td>
<td>46</td>
<td>15</td>
<td>Porcine</td>
<td>200 mg/kg</td>
<td>Intubation</td>
<td>32</td>
</tr>
<tr>
<td>Bevilaqua et al</td>
<td>2 centres:</td>
<td>93</td>
<td>40</td>
<td>Mortality</td>
<td>26–30</td>
<td>54</td>
<td>29</td>
<td>Porcine</td>
<td>200 mg/kg</td>
<td>Both</td>
<td>0</td>
</tr>
<tr>
<td>Dilmen et al</td>
<td>6 centres,</td>
<td>159</td>
<td>40</td>
<td>Necessity for MV</td>
<td>25–30</td>
<td>55</td>
<td>65</td>
<td>Porcine</td>
<td>200 mg/kg</td>
<td>CPAP</td>
<td>0</td>
</tr>
<tr>
<td>Kendig et al</td>
<td>3 centres, USA</td>
<td>479</td>
<td>40</td>
<td>Survival to</td>
<td>&lt;30</td>
<td>45</td>
<td>31</td>
<td>Bovine</td>
<td>90 mg/dose</td>
<td>Intubation</td>
<td>0</td>
</tr>
<tr>
<td>Lefort et al</td>
<td>1 centre, Brazil</td>
<td>75</td>
<td>40</td>
<td>Ventilation</td>
<td>&lt;34</td>
<td>45</td>
<td>No info</td>
<td>Porcine</td>
<td>100 mg/kg</td>
<td>Both</td>
<td>0</td>
</tr>
<tr>
<td>Sandri et al</td>
<td>Multi-centre,</td>
<td>208</td>
<td>40</td>
<td>MV in first 5</td>
<td>25–29</td>
<td>47</td>
<td>97</td>
<td>Porcine</td>
<td>200 mg/kg</td>
<td>CPAP</td>
<td>0</td>
</tr>
<tr>
<td>Finer et al</td>
<td>Multi-centre, USA</td>
<td>1316</td>
<td>50</td>
<td>Death/BPD at</td>
<td>24–28</td>
<td>46</td>
<td>96</td>
<td>Individual unit protocol</td>
<td>CPAP</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Kandraju et al</td>
<td>1 centre, India</td>
<td>153</td>
<td>50</td>
<td>Need for MV in</td>
<td>28–34</td>
<td>49</td>
<td>94</td>
<td>Porcine (Curosurf) or bovine (Survanta)</td>
<td>100 mg/kg</td>
<td>CPAP</td>
<td>0</td>
</tr>
<tr>
<td>Merritt et al</td>
<td>3 centres, USA</td>
<td>148</td>
<td>50</td>
<td>Mortality</td>
<td>26–29</td>
<td>43</td>
<td>4</td>
<td>Human</td>
<td>70 mg/kg</td>
<td>Intubation</td>
<td>98†</td>
</tr>
<tr>
<td>de Winter et al</td>
<td>2 centres,</td>
<td>81</td>
<td>60</td>
<td>TcPO2 and FiO2 at 6 hrs</td>
<td>26–30</td>
<td>48</td>
<td>44</td>
<td>Porcine</td>
<td>200 mg/kg</td>
<td>Intubated</td>
<td>0</td>
</tr>
<tr>
<td>Dunn et al</td>
<td>27 centres:</td>
<td>656</td>
<td>60</td>
<td>Death/BPD at</td>
<td>26–30</td>
<td>49</td>
<td>99</td>
<td>Individual unit protocol</td>
<td>Both</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Egberts et al</td>
<td>4 centres:</td>
<td>147</td>
<td>60%</td>
<td>TcPO2 and FiO2 at 6 hrs</td>
<td>26–30</td>
<td>60</td>
<td>29</td>
<td>Porcine</td>
<td>200 mg/kg</td>
<td>Intubated</td>
<td>2</td>
</tr>
</tbody>
</table>

*Moderate RDS defined as mean airway pressure ≥8 cm H2O or FiO2 ≥40%.
†Including 52 patients in placebo group not included in this analysis.
BPD, bronchopulmonary dysplasia; CGA, corrected gestational age; CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; IVH, Intraventricular haemorrhage; MV, mechanical ventilation; RDS, respiratory distress syndrome; TcPO2, transcutaneous oxygen tension.
Table 2  Summary of findings table for the primary outcome mortality at maximal follow-up

<table>
<thead>
<tr>
<th>Mortality</th>
<th>30% Threshold</th>
<th>40% Threshold</th>
<th>50% Threshold</th>
<th>60% Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies: 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants: 5290</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>123 per 1000</td>
<td>OR 1.81</td>
<td>OR 1.52</td>
<td>OR 0.82</td>
<td>OR 1.16</td>
</tr>
<tr>
<td>(12.3%)</td>
<td>(1.00 to 3.44)</td>
<td>(0.94 to 2.40)</td>
<td>(0.50 to 1.41)</td>
<td>(0.63 to 2.29)</td>
</tr>
<tr>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
</tr>
<tr>
<td>79 more per 1000</td>
<td>(0 fewer to 202 more)</td>
<td>(7 fewer to 128 more)</td>
<td>(7 fewer to 42 more)</td>
<td>(41 fewer to 120 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of evidence:</td>
<td>Based on 1783 participants</td>
<td>Based on 1014 participants</td>
<td>Based on 1617 participants</td>
<td>Based on 876 participants</td>
</tr>
<tr>
<td><strong>Low</strong> *†§</td>
<td>(3 RCTs)</td>
<td>(3 RCTs)</td>
<td>(3 RCTs)</td>
<td>(3 RCTs)</td>
</tr>
<tr>
<td>*The trials all had some concerns or were at high risk of bias.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†There was significant heterogeneity.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>§This is a surrogate outcome or was an indirect comparison.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>¶Less than 300 events in combined groups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>††There is evidence of publication bias.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Summary of findings table for secondary outcomes: respiratory outcomes

<table>
<thead>
<tr>
<th>Threshold 30%</th>
<th>Threshold 40%</th>
<th>Threshold 50%</th>
<th>Threshold 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies: 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants: 3003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>113 per 1000</td>
<td>OR 1.39</td>
<td>OR 0.77</td>
<td>OR 0.93</td>
</tr>
<tr>
<td>(11.3%)</td>
<td>(0.87 to 2.24)</td>
<td>(0.37 to 1.58)</td>
<td>(0.74 to 1.16)</td>
</tr>
<tr>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
</tr>
<tr>
<td>38 more per 1000</td>
<td>(13 fewer to 109 more)</td>
<td>(68 fewer to 55 more)</td>
<td>(27 fewer to 16 more)</td>
</tr>
<tr>
<td>OR 24 fewer per 1000</td>
<td>(1000 (68 fewer to 55 more)</td>
<td>(27 fewer to 16 more)</td>
<td>(27 fewer to 16 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of evidence:</td>
<td>Based on 279 participants</td>
<td>Based on 460 participants</td>
<td>Based on 1469 participants</td>
</tr>
<tr>
<td><strong>Very low</strong> <strong>Low</strong> *†‡</td>
<td>(1 RCT)</td>
<td>(3 RCTs)</td>
<td>(3 RCTs)</td>
</tr>
<tr>
<td>*The trials all had some concerns or were at high risk of bias.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†There was significant heterogeneity.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡This is a surrogate outcome or was an indirect comparison.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>¶Less than 300 events in combined groups.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chronic lung disease

Studies: 9

Participants: 2740

Prophylaxis: 284 per 1000 (28.4%)

OR 1.48

(0.82 to 2.63) Network estimate

86 more per 1000 (40 fewer to 227 more)

OR 1.05

(0.63 to 1.64) Network estimate

10 more per 1000 (84 fewer to 110 more)

OR 4.08

(0.77 to 35.45) Network estimate

334 more per 1000 (50 fewer to 650 more)

Quality of evidence: **Very low** **Low** *†‡

Based on 1504 participants

Based on 855 participants

Based on 153 participants

Based on 228 participants

BPD or CLD or CLD

Studies: 13

Participants: 5142

Prophylaxis: 171 per 1000 (17.1%)

OR 1.45

(0.95 to 2.21) Network estimate

59 more per 1000 (7 fewer to 142 more)

OR 0.91

(0.54 to 1.41) Network estimate

13 fewer per 1000 (71 fewer to 54 more)

OR 0.96

(0.59 to 2.00) Network estimate

6 fewer per 1000 (63 fewer to 121 more)

Quality of evidence: **Very low** **Low** *†‡

Based on 1783 participants

Based on 1014 participants

Based on 1469 participants

Based on 876 participants

Pneumothorax

Studies: 14

Participants: 5290

Prophylaxis: 33 per 1000 (3.3%)

OR 2.41

(0.61 to 10.48) Network estimate

43 more per 1000 (13 fewer to 232 more)

OR 1.26

(0.42 to 3.97) Network estimate

8 more per 1000 (19 fewer to 87 more)

Quality of evidence: **Very low** **Low** *†‡

Based on 1783 participants

Based on 1014 participants

Based on 1617 participants

Based on 876 participants

All results are reported as OR with 95% credible intervals.

*The trials all had some concerns or were at high risk of bias. |

†There was significant heterogeneity. |

‡This is a surrogate outcome or was an indirect comparison. |

§Less than 300 events in combined groups. |

RCT, randomised controlled trial.

Data synthesis

A network meta-analysis was conducted to compare thresholds of FiO₂ simultaneously for each outcome. Our analysis was based on guidance by the National Institute for Clinical Excellence Decision Support Unit.19–21

We conducted a network plot to ensure that the trials were connected by interventions.19 We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method (for further details, see online supplemental eMethods). We
used fixed-effect and random-effect models, reporting the more conservative. We estimated the probability that each intervention ranked at one of the possible positions.

Analysis was carried out using OpenBUGS V.3.2.3 (OpenBUGS Project Management Group, UK).

We assessed inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. In the presence of inconsistency, we assessed whether the inconsistency was due to clinical or methodological heterogeneity. We performed direct comparisons using the same technical details.

Subgroup/sensitivity analysis was planned based on (1) trials at low risk of bias compared with trials at high risk of bias, (2) gestational age and (3) current best practice—use of antenatal steroids and NCPAP.

RESULTS
A total of 4643 references were identified. Of 138 full-text articles reviewed, 112 were excluded (see online supplemental eResults). Twenty-six references describing 14 trials were included (PRISMA diagram, figure 1).

The included studies involved 5588 infants, 5298 after postrandomisation dropouts. Threshold of FiO2 for provision of selective surfactant ranged from 30% (three studies) to 60% (three studies). Five studies provided surfactants at 40% and three studies provided surfactants at 50%. Mean gestational age ranged from 27 weeks to 30 weeks. The range of gestational ages included in trials was variable as shown in table 1. There does not appear to be a systematic difference in the range of gestational ages among the trials using different FiO2 thresholds for selective surfactant provision. Regarding the prophylactic group, in seven studies, surfactant was given straight after birth; in five studies, surfactant was given within 15 min; and in three studies, surfactant was given within 1 hour. The percentage of participants with antenatal steroid exposure ranged from 4% to 99%.

Eight studies used Poractant alfa (Curosurf, Chiesi Farmaceutici, Italy). One study used Poractant alfa or Beractant (Survanta, AbbVie, USA). Of the five remaining studies, two multicentre trials allowed surfactant as per individual unit protocol, one Calfactant (Infasurf, ONY Biotech, USA) and one a self-prepared bovine surfactant. One study used a self-prepared human surfactant (see table 1 for further details). Twelve publications were identified as follow-up of the cohort included trials. Due to the nature of the intervention studied, star-shaped networks were formed for each outcome. No closed loops were present, and each study was connected to the network for each outcome. No studies were found to be at low risk of bias, 12 had some concerns; and 2 had high risk of bias (online supplemental eTable 1). As shown in online supplemental eTable 1, there does not appear to be a systematic difference in the risk of bias among the trials using different FiO2 thresholds.

Primary outcome
Each of the 14 studies measured mortality, including 5298 patients. A random-effect model was used. OR for each comparison, Deviance Information Criteria (DIC), median between-study SD and variance are summarised in online supplemental eTable 2. None of the estimates reached statistical significance with 30% threshold having the highest OR for this outcome (1.81) with 95% CrI of 1.0 to 3.44 (table 2). Sensitivity analysis of current best practice (NCPAP use with high rates of antenatal steroid) did not show any statistically significant difference (online supplemental eTables 3 and 4).

Secondary outcomes
ORs, DIC and variance for each comparison can be found in online supplemental eTable 5. A summary of results is provided (tables 3–5).

Respiratory outcomes
BPD, CLD and CLD/BPD at maximum follow-up were assessed. There was no difference regarding BPD or CLD alone. When evaluated at maximum follow-up, incidence was higher in the 30% group than prophylaxis when directly compared. The other outcomes showed lower point estimates, although not reaching statistical significance.

Use of surfactant
Unsurprisingly, the proportion of infants receiving surfactant was significantly higher in the prophylactic group (online supplemental eTable 5e).

Regarding the number of surfactant doses, there was a significant difference between thresholds. The 60% threshold had the least use of surfactant, 815 fewer doses per 1000. The 30% threshold ranked second at 546 fewer doses per 1000; the 50% threshold ranked third at 384 fewer doses per 1000; and the 40% threshold ranked last at 316 fewer doses per 1000.

Complications of prematurity
We showed no significant differences in incidence of IVH, PVL, NEC or BPD. The 60% threshold showed a higher
incidence of ROP on direct comparison with prophylaxis (OR 2.35, 95% CrI 1.02 to 5.42). Due to the presentation of components of this outcome separately in included studies, we performed a combined count outcome. Studies were included if they provided data from two or more of the five components of the composite outcome. No significant differences were found.

**Neurodevelopment at CGA of 2 years**

One trial reported this outcome. Forty-three of 479 in the prophylactic group and 55 of 511 in the selective group developed one or more component.

Table 5  Summary of findings table for secondary outcome: major morbidities

<table>
<thead>
<tr>
<th>Total major morbidities (n)</th>
<th>30% Threshold</th>
<th>40% Threshold</th>
<th>50% Threshold</th>
<th>60% Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies: 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants: 5134</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis: 316 per 1000 (31.6 per 100 participants)</td>
<td>RaI 1.14 (0.94 to 1.40 Network estimate)</td>
<td>45 more per 1000 (29 fewer to 126 more)</td>
<td>RaI 1.18 (0.89 to 1.56 Network estimate)</td>
<td>56 more per 1000 (34 fewer to 176 more)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Based on 1783 participants (3 RCTs)</td>
<td>Based on 939 participants (4 RCTs)</td>
<td>Based on 1617 participants (3 RCTs)</td>
<td>Based on 795 participants (2 RCTs)</td>
</tr>
</tbody>
</table>

Grade 3/4 Intraventricular haemorrhage

<table>
<thead>
<tr>
<th>Studies: 12</th>
<th>Participants: 5134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis: 44 per 1000 (4.4%)</td>
<td>OR 2.01 (0.83 to 5.46) Network estimate</td>
</tr>
<tr>
<td>Quality of Evidence</td>
<td>Based on 1783 participants (3 RCTs)</td>
</tr>
</tbody>
</table>

Periventricular leukomalacia

<table>
<thead>
<tr>
<th>Studies: 8</th>
<th>Participants: 3087</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis: 34 per 1000 (3.4%)</td>
<td>OR 0.81 (0.51 to 1.28) Network estimate</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Based on 1783 participants (3 RCTs)</td>
</tr>
</tbody>
</table>

Necrotising enterocolitis

<table>
<thead>
<tr>
<th>Studies: 10</th>
<th>Participants: 4690</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis: 75 per 1000 (7.5%)</td>
<td>OR 0.86 (0.55 to 1.35) Network estimate</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Based on 1504 participants (2 RCTs)</td>
</tr>
</tbody>
</table>

Retinopathy of prematurity

<table>
<thead>
<tr>
<th>Stage 2</th>
<th>Studies: 6</th>
<th>Participants: 3727</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis: 52 per 1000 (5.2%)</td>
<td>OR 1.01 (0.01 to 96.83) Network estimate</td>
<td>1 more per 1000 (52 fewer to 790 more)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Based on 1248 participants (1 RCT)</td>
<td>Based on 367 participants (2 RCTs)</td>
</tr>
</tbody>
</table>

BPD

<table>
<thead>
<tr>
<th>Studies: 8</th>
<th>Participants: 3003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis: 113 per 1000 (11.3%)</td>
<td>OR 1.39 (0.87 to 2.24) Network estimate</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Based on 279 participants (1 RCT)</td>
</tr>
</tbody>
</table>

All results are reported as OR with 95% credible intervals.

* These trials were all had some concerns or were at high risk of bias .
* There was significant heterogeneity.
* This is a surrogate outcome or was an indirect comparison.
* Less than 300 events in combined groups.
* There is evidence of publication bias.
* BPD, bronchopulmonary dysplasia; RaI, rate ratio; RCT, randomised controlled trial.

**Health-related quality of life**

No study assessed HRQOL.

**Quality of evidence**

The overall quality of the evidence was low or very low for all comparisons due to the high risk of bias, heterogeneity, indirectness, imprecision and publication bias.

**Heterogeneity**

Since there was no meaningful way in which to rank these studies, we were unable to perform the comparison-adjusted funnel plot to assess reporting bias. Due to paucity of data, we were unable...
to perform planned subgroup analyses based on gestation, type of ventilation or antenatal steroid use alone. To explore heterogeneity, a sensitivity analysis was carried out comparing studies using current best practice (over 60% antenatal steroid use and NCPAP for stabilisation).

**NCPAP and high antenatal steroid use**

A summary of findings is shown in table 6. Six studies met the criteria, including 2,554 infants. There was no statistically significant difference seen in mortality, BPD, pneumothorax or grade 3/4 IVH. There was an increased rate of major morbidity in the 60% threshold group—310 more per 1000 (95% CrI intervals 136 more to 572 more). ORs, DIC and variance for each comparison are provided in online supplemental tables 3 and 4. Each comparison had a very low quality of evidence.

**DISCUSSION**

Our primary outcome, mortality, showed no statistically significant differences between the thresholds of FiO₂ examined. Regarding the major morbidities of preterm birth, the 60% threshold showed a higher incidence of ROP on direct comparison with prophylaxis. Regarding surfactant doses received, there was significant differences between thresholds. The 60% threshold had the least doses, 30% threshold second, 50% threshold third and 40% threshold last. This may suggest that earlier selective treatment decreases the need for repeat doses, and that earlier use of surfactant may be appropriate as infants reaching this threshold will need more surfactant if treatment is delayed. However, this would be contradicted by the 60% threshold requiring least doses. Interpretation is complicated by differences in rescue dosing, dosing strategies between studies and total amount of doses allowed. The 30% threshold, despite having less doses of surfactant, had a higher incidence of prolonged respiratory support. This may relate to exposure to harmful effects of ventilation earlier, when the neonatal lung is more vulnerable.

A sensitivity analysis of infants treated with the current standard of care showed an increase in major morbidity in the 60% threshold group. While our analysis failed to identify an optimal threshold, it adds to scarce data. In the absence of evidence showing a benefit to treatment at 30%, 40% or 50% FiO₂, it warrants consideration of higher thresholds (except 60%)—decreasing invasive procedures, associated mechanical ventilation, surfactant use, sedation and associated side effects. The economic impact is likely to be significant.

Despite the common nature of this issue, there are little data to guide clinicians. A secondary analysis of prospectively collected data has been used to support lower thresholds. This study reviewed infants between 25 weeks and 32 weeks of gestation initially managed on NCPAP. Multivariate analysis showed
NCPAP failure was predicted by the highest FiO\textsubscript{2} in the first hours. This study was limited by several factors: its retrospective nature, the small numbers at each gestation and the low number primarily managed with NCPAP (50%). The authors concluded that NCPAP failure was predicted by an FiO\textsubscript{2} greater than 30% in the first hours and was associated with adverse outcomes. A review of the literature by Dani also evaluated this issue, primarily managed with NCPAP (50%). The authors concluded that the most effective threshold is unknown.

The European Consensus Guidelines on the management of RDS,\textsuperscript{2} based on the above paper by Dargaville et al.,\textsuperscript{5} suggests ‘early’ use of rescue surfactant outside of the delivery room at an FiO\textsubscript{2} of 30% or above. However, the guideline also recommends using 30%–40% FiO\textsubscript{2} for initial stabilisation despite advising against prophylactic surfactant.

Despite the common use of FiO\textsubscript{2} as a major criterion for provision of selective surfactant, there are limitations to its use, especially in isolation. A combination of pH, clinical assessment and FiO\textsubscript{2} will give a more accurate assessment. FiO\textsubscript{2} can be influenced by many factors including NCPAP interface, mode of non-invasive ventilation and level of positive end expiratory pressure and can be a measure of pathologies other than surfactant deficiency.

The strength of this review was the range of databases searched without restrictions. Two independent reviewers carried out article identification and data extraction. Analysis was performed using fixed-effect and random-effect models, with the most conservative reported. There were limitations. A scoping search revealed no studies directly comparing thresholds for provision of surfactant, and therefore, we relied on indirect comparisons. A paucity of data decreased confidence in results and precluded planned analyses.

There was a lack of long-term neurodevelopmental follow-up and assessment of quality of life. As survival rates of prematurity increase, long-term effects become increasingly important. Parental perspective is vital in this regard.

CONCLUSION

This network meta-analysis of 14 studies and 5290 infants suggests no statistically significant difference between a range of 30% to 50% FiO\textsubscript{2} for the provision of surfactant to preterm infants regarding mortality, respiratory outcomes or complications of prematurity. A 60% threshold may result in more major morbidities. Despite the low quality of evidence and limitations of indirect comparisons, this review provides the strongest evidence currently available, supporting more judicious use of surfactant in preterm infants.

Contributors JM contributed to the conception and design of the study idea and methodology, performed study selection and reviewed the manuscript. AB contributed to the conception and design of the study idea and methodology, performed study selection, data extraction and risk of bias assessment, contributed to the interpretation of the data and drafted the manuscript. KG contributed to the conception and design of the study idea and methodology and the interpretation of the data. IT performed data extraction and risk of bias assessment and contributed to the interpretation of the data. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript. JM is responsible for the overall content as the guarantor.

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