Does sustained lung inflation at resuscitation reduce lung injury in the preterm infant?

A E Harling, M W Beresford, G S Vince, M Bates, C W Yoxall

Background: Bronchopulmonary dysplasia (BPD) is a common outcome of preterm birth. Experimental animal work has shown that initial ventilation strategies injure the immature lung and may lead to BPD. Studies with asphyxiated babies have shown that, if tidal ventilation at birth is preceded by sustained lung inflation, larger inflation volumes can be achieved, which is thought to lead to clearance of lung fluid and formation of the functional residual capacity (FRC).

Objective: To see if sustained lung inflation at initial resuscitation of preterm babies would facilitate the removal of lung fluid, establish the FRC, and allow an even distribution of alveolar opening, permitting less aggressive ventilation, leading to a reduction in pulmonary inflammation and subsequent BPD.

Method: The outcomes of 52 babies of less than 31 weeks gestation, resuscitated at birth using either a sustained lung inflation of five seconds or a conventional lung inflation of two seconds for the first assisted breath of resuscitation, were examined. Evidence of pulmonary inflammation was determined by quantification of interleukins 6, 10, and 1β and tumour necrosis factor α in bronchoalveolar lavage fluid by enzyme linked immunosorbent assay.

Results: There were no significant differences in any of the cytokines. Death occurred in 3/26 babies in the conventional group and 6/26 babies in the sustained lung inflation group. Survival without BPD occurred in 13/26 and 14/26 respectively.

Conclusion: The use of sustained lung inflation at resuscitation did not reduce lung injury, as measured by inflammatory markers.

METHODS

The study was a randomised controlled trial with factorial design. The interventions compared were SLI of five seconds duration compared with conventional lung inflation (CLI) of two seconds duration for the first assisted breath of resuscitation at birth and is reported here. The second intervention investigated was the use of 100% oxygen compared with 50% oxygen for resuscitation at birth.

The primary outcome measure was evidence of pulmonary inflammation as determined by concentrations of the cytokines interleukin (IL)6, IL1β, IL10 and tumour necrosis factor α (TNFα) in bronchoalveolar lavage (BAL) fluid obtained at 12 hours of age. BAL fluid was also obtained immediately after intubation at birth from which we elicited baseline cytokine concentrations.

Secondary outcome measures included: the severity of initial lung disease, as determined by blood gas analyses and oxygen and ventilator requirements over the first 24 hours of postnatal life; death; BPD (oxygen requirement at 36 weeks postmenstrual age); major cranial ultrasound abnormality (post-haemorrhagic ventriculitis dilatation requiring treatment, post-haemorrhagic leukomalacia requiring treatment, severe cranial ultrasound abnormality); and necrotising enterocolitis (severity and duration of treatment for necrotising enterocolitis).

Abbreviations: BAL, bronchoalveolar lavage; BPD, bronchopulmonary dysplasia; CLI, conventional lung inflation; FRC, functional residual capacity; IL, interleukin; SLI, sustained lung inflation; TNFα, tumour necrosis factor α
Resuscitation of preterm infant

Table 1 Basic and clinical details of babies receiving conventional or sustained lung inflation, and cytokine concentrations at 0 hours in both inflations

<table>
<thead>
<tr>
<th></th>
<th>CLI (n = 26)</th>
<th>SU (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>1095 (560–1562)</td>
<td>885 (518–1460)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>28 (23–31)</td>
<td>27 (23–30)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>12/14</td>
<td>12/14</td>
</tr>
<tr>
<td>Age at 1 min</td>
<td>5 (2–10)</td>
<td>6 (1–10)</td>
</tr>
<tr>
<td>Age at 5 min</td>
<td>8 (2–10)</td>
<td>8 (3–10)</td>
</tr>
<tr>
<td>PROM (h)</td>
<td>1 (0–121)</td>
<td>0 (0–277)</td>
</tr>
<tr>
<td>Cord pH</td>
<td>7.33 (7–7.4)</td>
<td>7.31 (6.95–7.44)</td>
</tr>
<tr>
<td>Delivery mode (C/V)</td>
<td>12/14</td>
<td>10/16</td>
</tr>
<tr>
<td>IL6 at 0 h (pg/ml)</td>
<td>537 (0–19208)</td>
<td>1768 (16–29205)</td>
</tr>
<tr>
<td>IL1β at 0 h (pg/ml)</td>
<td>43 (0–2950)</td>
<td>29 (0–1972)</td>
</tr>
<tr>
<td>IL10 at 0 h (pg/ml)</td>
<td>514 (111–2330)</td>
<td>533 (10–1753)</td>
</tr>
<tr>
<td>TNFα at 0 h (pg/ml)</td>
<td>44 (8–662)</td>
<td>63 (13–449)</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or number.

Table 2 Cytokine concentrations in the babies resuscitated with conventional lung inflation compared with those resuscitated with sustained lung inflation

<table>
<thead>
<tr>
<th></th>
<th>CLI</th>
<th>SU</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>790 (104–19708)</td>
<td>1156 (42–15192)</td>
<td>0.69</td>
</tr>
<tr>
<td>IL1β</td>
<td>38 (5–2590)</td>
<td>43 (0–663)</td>
<td>0.86</td>
</tr>
<tr>
<td>IL10</td>
<td>652 (78–1993)</td>
<td>608 (0–1242)</td>
<td>0.67</td>
</tr>
<tr>
<td>TNFα</td>
<td>25 (0–1838)</td>
<td>21 (0–143)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Values are median (range) expressed as pg/ml bronchoalveolar lavage fluid.

Resuscitation

Resuscitation was performed if the baby was making little or no respiratory effort and was bradycardic despite having a clear airway. Babies were intubated if they did not sustain adequate respiration after face mask ventilation, did not respond to face mask ventilation, or required long term ventilation because of prematurity.

Resuscitation was conducted on a Vickers Resuscitator Radiant Warmer Pneumatic System (Air-Shields; Hill-Rom, Leicester, UK) which delivered ventilation via a diaphragm controlled adjustable pressure relief valve. The blow off valve was initially set at 25–30 cm H₂O and controlled adjustable pressure relief valve. The blow off valve was set to deliver ventilation via a diaphragm controlled adjustable pressure relief valve. The blow off valve was set to deliver ventilation via a diaphragm controlled adjustable pressure relief valve.

Parenchymal haemorrhage, or cystic periventricular leucomalacia; necrotising enterocolitis (pneumoperitoneum or pneumatosis on abdominal radiograph or confirmed at laparotomy or postmortem examination); retinopathy of prematurity leading to treatment in accordance with national guidelines or blindness; a patent ductus arteriosus requiring treatment; systemic infection proven by positive blood culture; pneumothorax requiring chest drain insertion.

Subjects

Babies of less than 31 completed weeks gestation and without life threatening malformations were recruited into the study; babies who did not require resuscitation at birth were excluded.

Cytokine quantification

An enzyme linked immunosorbent assay (R&D Systems Europe Ltd, Abingdon, Oxon, UK) was used to determine the concentrations of the cytokines in the supernatant. The cytokine concentrations are expressed as pg/ml BAL fluid in line with the current recommendations of the ERS task force.

Statistical analysis

No previously published data were available from which to generate a sample size calculation. We planned to use any differences observed between the groups of this pilot study to calculate a sample size for a later definitive study. To show a difference of one standard deviation in any of the continuous variables, we planned to randomise 20 ventilated babies into each group. The Mann-Whitney U test was used for the continuous data, and the χ² test for categorical data. Two tailed tests were used for all statistical comparisons, and p < 0.05 was considered significant. Statistical analyses were performed using SPSS for Windows 10.0.7. (SPSS, Chicago, Illinois, USA).

Ethical considerations

Informed parental consent was obtained in the antenatal period, and the study had the approval of the local paediatric research ethics committee.

Randomisation

Block randomisation using sealed envelopes was used. Although consent was obtained earlier, randomisation did not take place until delivery of the baby was imminent.

Figure 1 Median partial pressure of oxygen over first 24 hours in babies resuscitated with conventional lung inflation (CLI; two seconds) or sustained lung inflation (SU; five seconds).
RESULTS

Sixty three babies were recruited in the antenatal period and were then randomised into the inflation group at delivery. Of the 63 randomised babies, 11 did not require any resuscitation and were therefore not recruited into the study. Fifty two required some resuscitation and received the intervention via either the face mask or endotracheal tube. Forty two babies were intubated at birth, and four were intubated shortly after birth on the neonatal unit. BAL fluid samples were only collected from ventilated babies. To measure the primary outcome of BAL fluid inflammatory markers at 12 hours, randomisation continued until there were sufficient babies intubated. Clinical outcomes for all resuscitated babies are reported, including those in whom BAL was not performed. Thirty four samples collected at 0 hours and 40 collected at 12 hours were suitable for analysis. The volume of BAL fluid collected did not permit analysis of all four cytokines at each time point in every baby.

The babies in the SLI group were slightly more premature and had lower median birth weights than the CLI group (27 v 28 weeks gestation and 885 v 1095 g; table 1), otherwise the groups were well matched.

Cytokine concentrations

The interassay coefficient of variation and intra-assay coefficient of repeatability22 for each cytokine were as follows: IL6, 5.98% and 24.11%; IL1β, 1.76% and 19.80%; IL10 16.32% and 33.49%; TNFα 5.93% and 42%.

All four cytokines studied were present in the BAL fluid from immediately after birth and at 12 hours of postnatal life, although not all babies had detectable concentrations of each cytokine at each time point. The distribution of cytokine concentrations between each group did not show any significant difference at 12 hours of age (table 2).
Clinical outcomes
Although the SLI group was slightly more premature and had a lower median birth weight, there was no significant difference between the two groups in any of the long term clinical outcomes (table 3).

DISCUSSION
Research involving animal models has shown that the lung sustains mechanical damage when large tidal volume ventilation is used. The damage occurs in pulmonary capillary endothelium and the alveolar and airway epithelium, allowing fluid, protein, and blood to leak into the airspaces and lung interstitium. This begins a sequence of altered lung mechanics that promotes lung inflammation.23–27

In an effort to minimise the need for aggressive ventilation and subsequent lung injury after resuscitation at birth, we reproduced the sustained lung inflation described by Vyas et al.15 However, we were unable to show any detectable differences in lung injury between the inflation groups when assessed by BAL fluid cytokine concentrations (table 2).

There was a slight difference between our study groups in the ventilatory requirements during the first 24 hours. The SLI group required more respiratory support than the CLI group, but this appeared to be a consequence of the lower gestation and lower birth weight of the SLI group, rather than a treatment effect. These early differences did not translate into any difference in long term outcomes (table 3).

The observations made by Vyas et al were in more mature babies, with lungs rich in surfactant, rather than premature babies predisposed to the development of BPD. The injury that is described usually occurs at a time when premature lung development is in the canalicular or saccular phase. This means that, for the most premature babies, the lungs will only consist of terminal bronchioles, prospective respiratory bronchioles, and a few branched buds that will eventually develop into saccules. We have not been able to show a benefit of SLI during resuscitation of preterm babies in this study. This may be because developmentally the lung structure was immature and deficient in surfactant, and consequently the lungs were unable to respond to the inflation manoeuvre. We are unable to completely exclude a small benefit based on this study, however, as, with an incidence of death or BPD of 50% in our study population, a study of this size would only be able to detect a difference in death or BPD rate of 34% with a power of 80% and significance of 5%.

What is already known on this topic
- Low birthweight, low gestation preterm infants who require prolonged mechanical ventilation are more likely to develop BPD
- Studies of the effect of a sustained lung inflation at birth suggest that it may assist in fluid clearance and the formation of the FRC, facilitating a more homogeneous distribution of air through the lungs

What this study adds
- The use of a sustained lung inflation for the first assisted breath of resuscitation of the preterm baby did not prove to be of any benefit to this population

CONCLUSION
SLI at birth did not prove to be of any benefit to the very premature baby with respect to minimising the injury sustained by the lungs through mechanical ventilation.

RECOMMENDATIONS
We recommend that current resuscitation guidelines on initial lung inflation16 17 continue to be followed, and that we strive to find other means to reduce mechanical lung injury in our very premature population.

Authors' affiliations
A E Harling, M W Beresford, C W Yoxall, NICU, Liverpool Women’s Hospital, Liverpool L8 7SS, UK
G S Vince, M Bates, Immunology Department, University of Liverpool, Liverpool L69 3GA, UK

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