Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial

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ABSTRACT

Objective To evaluate if nebulised surfactant reduces intubation requirement in preterm infants with respiratory distress treated with nasal continuous positive airway pressure (nCPAP),

Design Double blind, parallel, stratified, randomised control trial.

Setting Sole tertiary neonatal unit in Western Australia.

Patients Preterm infants (29–33 weeks’ gestational age, GA) less than 4 hours of age requiring 22–30% supplemental oxygen, with informed parental written consent.

Interventions Infants were randomised within strata (29–31 and 32–33 weeks’ GA) to nCPAP or bubble nCPAP and nebulised surfactant (200 mg/kg: poractant alfa) using a customised vibrating membrane nebuliser (eFlow neonatal). Surfactant nebulisation (100 mg/kg) was repeated after 12 hours for persistent supplemental oxygen requirement.

Main outcome measures The primary outcomes were requirement for intubation and duration of mechanical ventilation at 72 hours. Data analysis followed the intention-to-treat principle.

Results 360 of 606 assessed infants were eligible; 64 of 360 infants were enrolled and randomised (n=32/group). Surfactant nebulisation reduced the requirement for intubation within 72 hours: 11 of 32 infants were intubated after continuous positive airway pressure (CPAP) and nebulised surfactant compared with 22 of 32 infants receiving CPAP alone (relative risk 95% CI 0.526 (0.292 to 0.950)). The reduced requirement for intubation was limited to the 32–33 weeks’ GA stratum. The median (range) duration of ventilation in the first 72 hours was not different between the intervention (0 (0–62) hours) and control (9 (0–64) hours; p=0.220) groups. There were no major adverse events.

Conclusions Early postnatal nebulised surfactant may reduce the need for intubation in the first 3 days of life compared with nCPAP alone in infants born at 29–33 weeks’ GA with mild respiratory distress syndrome. Confirmation requires further adequately powered studies.

Trial registration number ACTRN12610000857000.

What is already known on this topic?

- Surfactant replacement therapy reduces the severity of respiratory distress in preterm newborn infants.
- Until now, administration of exogenous surfactant has required instrumentation of the trachea, with bolus surfactant delivered via a laryngeal mask, tracheal tube, angiocath or feeding tube.

What this study adds?

- We provide the first evidence of a successful non-invasive nebulised surfactant replacement in preterm infants with respiratory distress syndrome or mild respiratory distress after 72 hours.
- Early postnatal nebulised surfactant may reduce the need for intubation in very and moderate preterm infants with mild RDS.
- These findings require confirmation in further adequately powered studies.

INTRODUCTION

Primary treatment of neonatal respiratory distress syndrome (RDS) with non-invasive nasal continuous positive airway pressure (nCPAP) is increasing. However, worsening of RDS may necessitate delayed intubation and bolus surfactant therapy. Delayed surfactant delivery may promote aetrauma due to alveolar collapse, with resultant increased respiratory disease severity and prolongation of mechanical support. Brief tracheal instrumentation for bolus delivery of surfactant may reduce aetrauma. However, tracheal instrumentation is associated with tube malposition or perforation, induces transient cardiovascular instability and a stress response, and is often accompanied by transient sedation and/or paralysis.

Surfactant nebulisation offers an alternative approach consistent with a non-invasive treatment. In animals with surfactant deficiency, nebulised surfactant reduces the frequency of adverse haemodynamic effects compared with bolus surfactant instillation, and improves homogeneity of surfactant distribution, lung compliance, ventilation efficiency index and oxygenation. Nebulised surfactant to reduce the severity of neonatal respiratory distress in unventilated human infants was described in 1964, via aerosol generated within an incubator. Three of four subsequent studies used jet nebulisation, which is highly commercial re-use. See rights and permissions. Published by BMJ.

inefficient due to air entrainment. Only one of these four studies was a randomised controlled trial; it showed no effect of nebulised surfactant on the requirement for mechanical ventilation, duration of nCPAP or ventilation, oxygenation requirements, or the incidence of bronchopulmonary dysplasia. A 2012 Cochrane review concludes there is insufficient evidence from randomised controlled trials to guide use of nebulised surfactant in preterm infants at risk of RDS.

New miniature vibrating membrane nebulisers do not require bias flow and are more efficient than the jet nebulisers, reducing nebulised surfactant wastage. However, surfactant delivery remains lower when nebulisation is via a mask or nasal prongs compared with a tracheal tube. A pilot non-randomised study using a vibrating membrane nebuliser noted lower nCPAP failure and (bolus) surfactant replacement therapy in very preterm infants compared with contemporaneously recorded infant data. While encouraging, this non-randomised pilot study does not permit definitive comment about the efficacy of nebulised surfactant during nCPAP for treatment of neonatal RDS.

We aimed to evaluate the clinical efficacy and feasibility of nebulised surfactant for the treatment of RDS in very preterm infants. We hypothesised that nebulised surfactant administered in the first 4 hours of life to newborn infants with clinical signs suggestive of evolving RDS would reduce the incidence of nCPAP failure without increasing the incidence of adverse clinical outcomes.

PATIENTS AND METHODS

We conducted a single-centre, blinded, pragmatic, randomised controlled trial to assess the feasibility, safety and short-term efficacy of nebulised surfactant for the treatment of evolving RDS in infants at 29\(^0\)–32\(^0\) weeks’ gestational age (GA).

Eligibility and recruitment

Inborn neonates were enrolled by the recruiting team (SM, CAB) between 14 October 2010 and 12 May 2012. The eligibility criteria for study inclusion were 29\(^0\)–33\(^0\) weeks’ GA, <4 hours’ age, and clinical signs suggestive of evolving mild to moderate RDS requiring treatment with nCPAP of 5–8 cmH\(_2\)O and supplemental fractional inspired oxygen (FiO\(_2\)) of 0.22–0.30 to maintain a peripheral oxygen saturation of 86%-94%. The exclusion criteria included prior intubation or surfactant treatment, known pneumothorax, cardiorespiratory instability, cardiothoracic malformation and obvious chromosomal aberrations.

Randomisation and masking

Eligible infants were randomised (SM, CAB) after obtaining written informed parental consent. Computer-generated randomisation sequences were generated with balanced block design for each GA strata (29\(^0\)–31\(^0\) weeks’ GA and 32\(^0\)–33\(^0\) weeks’ GA) and sealed in opaque, sequentially numbered envelopes. All infants remained behind an opaque screen with the treatment team for 20–30 min for either nebulised surfactant or sham nebulisation. Continuous positive airway pressure (CPAP) water chambers were emptied and refilled at the end of nebulisations to reduce the risk of unblinding clinicians to treatment assignment associated with surfactant deposition. The clinical team responsible for management were blinded to group assignment. nCPAP strategy was the same for both study groups: nCPAP commenced at 5 cmH\(_2\)O and increased up to 8 cmH\(_2\)O for increasing FiO\(_2\). nCPAP bias flow used 6–8 L/min as required to achieve active bubbling. Masked data were analysed by an investigator (JJPJJ) with minimal involvement in recruitment or treatment.

Intervention

The intervention group received 200 mg/kg body weight aerosolised surfactant (poractant alfa, Chiesi Farmaceutici SpA, Parma, Italy) via a customised vibrating membrane nebuliser (eFlow neonatal surfactant system, PARI Pharma, Starnberg) positioned between the mask and the bubble nCPAP circuit. Nebulisation commenced as soon as possible after randomisation. Repeat surfactant nebulisation (100 mg/kg) was given for persisting oxygen requirement and/or respiratory distress (persistent tachypnoea >60 breaths/min, sternal or intercostal muscle recession, or grunting) 12 hours after initial nebulisation.

nCPAP failure criteria

nCPAP therapy failure was defined as one or more of the following criteria:

1. FiO\(_2\) >0.35 over more than 30 min OR FiO\(_2\) >0.45 at anytime.
2. More than four apnoeas/hour OR two apnoeas requiring bag and mask ventilation.
3. Two capillary blood gas samples with a pH <7.2 and partial pressure of carbon dioxide >65 mm Hg (or partial pressure of carbon dioxide in arterial blood (PaCO\(_2\)) >60 mm Hg if arterial blood gas sample).
4. Intubation deemed necessary by the attending physician. Infants who failed nCPAP were intubated and received surfactant according to normal unit practice (200 mg/kg poractant alfa, with additional 100 mg/kg poractant alfa after 12 hours if required). Extubation criteria were not defined.

Outcomes

The primary dichotomous outcome was the need for intubation within the first 72 hours of life, and the primary continuous outcome was the mean duration of mechanical ventilation at 72 hours of age. The secondary outcomes included the number of infants that remained intubated at 24 hours, 72 hours and 7 days; time to intubation; total surfactant dose per kilogram; associated neonatal morbidities; and physiological stability following randomisation.

Sample size and statistical analysis

The intubation frequency of infants commenced on nCPAP after birth at 29\(^0\)–33\(^0\) weeks’ gestation in the preceding 12 months was 30%. A sample size of 70 patients (35 patients/group) would detect a reduction in intubation frequency from 30% to 9%, with a power of 80% and a significance level of α=0.05 (two-sided test).

Data were analysed for the whole group, and in the predefined GA strata on an intention-to-treat basis. The primary dichotomous outcomes were assessed using Pearson’s \(χ^2\) test and relative risk (RR) with Fisher’s exact test for low event rate as secondary outcomes. Continuous data were summarised as mean (SD) or median (range) for parametric and non-parametric data distributions, respectively. A t-test or Mann-Whitney U test was used to assess differences between groups in continuous data at 72 hours. Data analysed using Kaplan-Meier survival analysis included log-rank (Mantel-Cox) \(χ^2\) statistic for assessments of time-dependent differences. All reported \(p\) values are two-sided.
Supplemental O2 (protocol violation). One infant was intubated missed its second surfactant nebulisation despite remaining in study between 15 October 2010 and 14 May 2012. One infant

Figure 1 shows the Consolidated Standards of Reporting Trials diagram for study recruitment and treatment assignment. CPAP, continuous positive airway pressure; FiO2, fractional inspired oxygen; GA, gestational age.

RESULTS
Baseline demographics and clinical characteristics

Figure 1 shows the Consolidated Standards of Reporting Trials diagram for recruitment. Sixty-four infants were recruited to the study between 15 October 2010 and 14 May 2012. One infant missed its second surfactant nebulisation despite remaining in supplemental O2 (protocol violation). One infant was intubated immediately after randomisation prior to surfactant nebulisation. Both infants were included in the full analysis (intention-to-treat). The study was closed to recruitment after 19 months due to insufficient funding/personnel.

Only 64 of 360 eligible infants were enrolled, due primarily to non-availability of study personnel to ensure masking of the intervention. No differences were seen in baseline demographic and clinical characteristics of the recruited cohort (table 1). The proportion of male and caesarean section deliveries was higher in the study group versus eligible but not recruited cohort (online supplementary table 1), but no other selection bias was evident.

Table 1 Patient demographics

Primary outcome
Surfactant nebulisation reduced the requirement for intubation within 72 hours of birth: 11 of 32 infants were intubated in the intervention group compared with 22 out of 32 infants receiving CPAP alone (RR (95% CI)=0.526 (0.292 to 0.950)). The reduced risk for intubation was restricted to the 32.0–33.3 weeks’ GA group: 1 out of 11 infants receiving CPAP plus nebulised surfactant was intubated compared with 10 out of 13 infants receiving CPAP alone (RR (95% CI)=0.254 (0.089 to 0.727)). There was no difference in intubation risk in the 29.0–31.0 weeks’ GA group: 12 out of 21 infants receiving CPAP plus nebulised surfactant were intubated compared with 12 out of 19 infants receiving CPAP alone (RR (95% CI)=0.860 (0.389 to 1.90)). The duration of ventilation in the first 72 hours was not different between the groups: the median (range) was 0 (0–62) hour for the nebulisation group and 9 (0–64) hours for the control group (p=0.220).

Secondary outcomes
The secondary outcomes are shown in table 2. There was no difference between the groups in the total duration of any mechanical support (mechanical ventilation+CPAP) or in the duration of supplemental O2. Surfactant nebulisation did not alter the proportion of infants remaining intubated after 24 hours, 72 hours or 7 days. The duration of mechanical ventilation in infants intubated because they met the nCPAP failure criteria was marginally longer in the nebulised surfactant group compared with those in the nCPAP-only group. However, this finding is skewed by the differences in the GA of infants failing CPAP in each group: within the 29.0–31.0 weeks’ GA substrata, the median (IQR) duration of ventilation was not different between the nebulised (25.5 (13.9–82) hours) and the control (19.2 (13.6–46.7) hours) groups (U=58.0, p=0.436). The total surfactant dose did not differ between the groups. Nine infants received a second nebulised surfactant dose after 12 hours due to persisting FiO2 requirement or clinical signs of respiratory distress. The mean (95% CI) difference in bolus surfactant use after intubation was 9.2 (−14.5 to 32.9) mg/kg for the intervention versus the control.

The time dependencies of the requirement for intubation (as the estimated probability of remaining on nCPAP) are displayed as Kaplan-Meier survival curves for the whole cohort and the two substrata in figure 2. For the subgroup of infants failing nCPAP, the time to meet the nCPAP failure criteria was significantly longer after nebulised surfactant (table 2). The median delay (95% CI) in time to intubation for the nebulisation group was 4.5 (−0.18 to 7.17) hours compared with the control group. While not significant, 29.0–31.0 weeks infants receiving nebulised surfactant tended to meet the criteria after a more prolonged initial nCPAP course (figure 2B).

Nebulisation was associated with a transient increase in transcutaneous partial pressure of carbon dioxide (TcPCO2) in some infants, which resolved immediately following face mask removal. One infant developed apnoea necessitating a brief procedural pause. No other significant change in heart rate or clinical desaturation occurred during nebulisation. The incidence of neonatal morbidities was not different between the groups. Two infants from the control group developed pneumothorax.

The main reasons for failure were exceeding the modest maximum FiO2 failure criteria or due to clinician assessment of significant respiratory distress (table 3). Clinical indicators of respiratory distress did not differ between the groups for infants requiring intubation (table 4).

Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Control (n=32)</th>
<th>Nebulised surfactant (n=32)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (weeks)</td>
<td>31.4 (1.4)</td>
<td>31.4 (1.4)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1645 (409)</td>
<td>1562 (399)</td>
</tr>
<tr>
<td>Birth weight Z score</td>
<td>0.00 (0.81)</td>
<td>−0.29 (0.69)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>26 (81.3)</td>
<td>22 (68.8)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>Any steroids, n (%)</td>
<td>29 (90.6)</td>
</tr>
<tr>
<td>Complete course, n(%)</td>
<td>16 (50.0)</td>
<td>21 (65.6)</td>
</tr>
<tr>
<td>Caesarean section, n (%)</td>
<td>23 (71.9)</td>
<td>26 (81.3)</td>
</tr>
<tr>
<td>Apgar 1 min</td>
<td>7 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Apgar 5 min</td>
<td>8 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Age at first nebulisation (min)</td>
<td>–</td>
<td>178 (52)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
DISCUSSION
We report a preliminary, blinded, randomised controlled trial to evaluate the efficacy of nebulised surfactant in the first 4 hours of life for non-invasive clinical management of moderately preterm and very preterm neonates with evolving mild to moderate RDS. The non-invasive combination of nebulised surfactant and nCPAP is consistent with recent trends in neonatal respiratory care. Our finding of reduced risk for intubation after surfactant nebulisation with a vibrating membrane nebuliser contrasts with the only other clinical trial of nebulised surfactant nebulisation with a vibrating membrane nebuliser published to date.9 Our finding of prolonged nCPAP duration, with a median of 6 hours of nCPAP duration after intubation, is consistent with the only other clinical trial investigating nebulised surfactant in the delivery room.1 The median time to meet failure criteria in the nebulised surfactant group reached the CPAP failure criteria later than the infants in the nCPAP-only control group. The longer time lapse before meeting the CPAP failure criteria in the nebulisation group was not associated with more severe lung disease at the time of intubation as the FiO2 and PaCO2 tended to be lower rather than higher than the corresponding measurements at the time of nCPAP failure in the control group. The longer time to meet failure criteria in the more immature infants implies some physiological benefit of nebulised surfactant was achieved, despite the absence of a difference in intubation risk for more immature infants. Surfactant redosing before 12 hours may be indicated for nebulised surfactant therapy given the mean time to failure was just less than 12 hours in the nebulised group.

The duration of mechanical ventilation did not differ between the two groups. The marginally longer median duration of mechanical ventilation in nebulised and subsequently ventilated infants compared with the intubated infants in the control group should be interpreted with considerable caution as extubation criteria were not mandated for this preliminary trial. Further, the failures in the nebulised group were skewed to the more immature infants, which may influence the duration of ventilation as evidenced by the absence of difference in the duration of ventilation in infants failing nCPAP in the 29th–31st gestational age stratum. Importantly, there were also no differences between the study groups in the number of infants still intubated at 24, 72 or 168 hours.

For those infants that required intubation, infants in the nebulised surfactant group reached the CPAP failure criteria later than the infants in the nCPAP-only control group. The longer time lapse before meeting the CPAP failure criteria in the nebulisation group was not associated with more severe lung disease at the time of intubation as the FiO2 and PaCO2 tended to be lower rather than higher than the corresponding measurements at the time of nCPAP failure in the control group. The longer time to meet failure criteria in the more immature infants implies some physiological benefit of nebulised surfactant was achieved, despite the absence of a difference in intubation risk for more immature infants. Surfactant redosing before 12 hours may be indicated for nebulised surfactant therapy given the mean time to failure was just less than 12 hours in the nebulised group.

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The failure rate for CPAP was substantially higher in this group than anticipated from historical data. We believe this outcome is likely a consequence of the time required for the separate recruiting team to arrive to consent and randomise, during which time many infants on CPAP were weaned to air and became ineligible for the study. Additionally, the blinded treating clinician group reserved the right to intubate infants with perceived significant respiratory distress in the absence of elevated FiO2 or PaCO2 when they considered early bolus surfactant therapy would be beneficial. This early surfactant approach requirement. However, these findings require verification in a future, adequately powered clinical trial, as this study was not powered to detect subgroup differences.
Table 3  Reason for failure of nCPAP

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Nebulised surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.0–31.6</td>
<td>32.0–33.6</td>
<td>29.0–31.6</td>
</tr>
<tr>
<td>↑FiO₂&gt;0.35</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Apnoea/Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>↓pH or ↑PaCO₂</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Both ↑FiO₂ and ↑PaCO₂</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Clinician decision</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

FiO₂, fractional inspired oxygen; nCPAP, nasal continuous positive airway pressure; PaCO₂, partial pressure of carbon dioxide in arterial blood.

Table 4  Clinical variables at failure of CPAP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Nebulised surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO₂</td>
<td>0.36 (0.13)</td>
<td>0.32 (0.05)</td>
</tr>
<tr>
<td>pH</td>
<td>7.24 (1.0)</td>
<td>7.31 (0.6)</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>58.9 (20.5)</td>
<td>44.7 (12.5)</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>63 (17)</td>
<td>70 (18)</td>
</tr>
<tr>
<td>nCPAP, cmH₂O</td>
<td>6.3 (0.6)</td>
<td>6.3 (0.6)</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).
CPAP, continuous positive airway pressure; FiO₂, fractional inspired oxygen; nCPAP, nasal continuous positive airway pressure; PaCO₂, partial pressure of carbon dioxide in arterial blood.

Figure 2  Kaplan-Meier survival curves illustrating the temporal relation between the treatment assignment and the probability of remaining on nCPAP all infants (top); 29.0–31.6 w gestation stratum (middle); and c) 32.0–33.6 w gestation stratum (bottom). Solid circles: nCPAP only; open triangles: nCPAP+nebulised surfactant. Infants were more likely to remain on CPAP if they received nebulised surfactant. Stratified analysis indicated a significant benefit of nebulised surfactant was restricted to the more mature gestational age group. CPAP, continuous positive airway pressure; GA, gestational age; nCPAP, nasal continuous positive airway pressure.
CONCLUSION
Nebulised surfactant administered in the first 4 hours of life to very and moderately preterm infants with mild RDS may promote successful establishment of non-invasive respiratory support. These findings require confirmation in a subsequent, adequately powered randomised controlled trial evaluating the benefits of nebulised surfactant in infants with mild to moderate respiratory distress. Future trials should target evaluation of the patient interface for nebulisation, and consider enrolling infants receiving contemporary ‘less-invasive’ surfactant delivery methods as a comparator group.

REFERENCES
10 Herting E. Less invasive surfactant administration (USA) - ways to deliver surfactant in spontaneously breathing infants. Early Hum Dev 2013;89:875–80.


Correction: Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial

The authors of this paper (Arch Dis Child Fetal Neonatal Ed 2019;104:F313–19) were alerted by a reader of the journal to errors in the reporting of their primary outcome for this trial. The errors in the manuscript are as follows:

1. The flow chart (figure 1, pF315, incorrectly reports the outcomes of the 29<sup>−</sup>31<sup>w</sup> GA subgroup randomised to CPAP and nebulised surfactant as 8 requiring only CPAP and 13 requiring intubation. The correct numbers are 9 requiring only CPAP and 12 requiring intubation. Please note that the number requiring intubation in that subgroup is reported correctly in the main text for this group.

2. The abstract and the text (page F315) incorrectly report that 11/32 infants in the intervention group required intubation in the first 72 hours (primary endpoint), when the correct number is 13/32 infants resulting in a RR (95% CI) of 0.567 (0.342, 0.940). The error does not change the conclusion of the study.

3. Absolute numbers reported in the text for the gestational age strata are correct for the dichotomous primary outcome of requirement for intubation in the first 72 hours. However, the reported relative risks are incorrect, due to erroneous arrangement of the 2 x 2 table used in statistical analysis. The authors have detailed the correct primary dichotomous outcomes for both the full cohort and each of the gestational age groups in the table below.

All other data and figures reported are correct, including figure 2, which has the correct number of infants in each group for both the total and the stratified survival curves. The authors confirm that they used an intention to treat analysis as described in the statistical section.

The revised statistical data do not change the outcome of the study as the intervention remains significant. All original case report forms are available for audit and review.

Table 1  The correct primary dichotomous outcomes for both the full cohort and each of the gestational age groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPAP+Nebulised surfactant</th>
<th>CPAP</th>
<th>χ²</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Cohort</td>
<td>Intubated</td>
<td>13</td>
<td>22</td>
<td>5.107</td>
<td>0.567</td>
</tr>
<tr>
<td></td>
<td>Not Intubated</td>
<td>19</td>
<td>10</td>
<td></td>
<td>0.342, 0.940</td>
</tr>
<tr>
<td>29&lt;sup&gt;−&lt;/sup&gt;31&lt;sup&gt;w&lt;/sup&gt; GA</td>
<td>Intubated</td>
<td>12</td>
<td>12</td>
<td>0.150</td>
<td>0.889</td>
</tr>
<tr>
<td></td>
<td>Not Intubated</td>
<td>9</td>
<td>7</td>
<td></td>
<td>0.493, 1.602</td>
</tr>
<tr>
<td>32&lt;sup&gt;−&lt;/sup&gt;33&lt;sup&gt;w&lt;/sup&gt; GA</td>
<td>Intubated</td>
<td>1</td>
<td>10</td>
<td>11.043</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>Not Intubated</td>
<td>10</td>
<td>3</td>
<td></td>
<td>0.018, 0.784</td>
</tr>
</tbody>
</table>

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