Prospective Randomized Controlled Trial Comparing the use of Biphasic Positive Airway Pressure (BiPAP) with Nasal Continuous Positive Airway Pressure (n-CPAP) Following Extubation of Preterm Babies

Chikkanayakanahalli M Manjunatha1*, Sridhar Kalyanasundaram2, Samuel E Ibhanesebhor3, Denise Vigni4 and Christopher Robertson5

1Consultant Neonatologist, Wishaw General Hospital, Wishaw, Lanarkshire, UK
2Zulekha Hospital, Al Qusais, Dubai, United Arab Emirates
3Consultant Neonatologist, Royale Hayat Hospital, Hawally, Kuwait
4Research Nurse, Wishaw General Hospital, Wishaw, Lanarkshire, UK
5Professor of Statistics, Strathclyde University, Glasgow, UK

*Corresponding Author: Chikkanayakanahalli M Manjunatha, Consultant Neonatologist, Wishaw General Hospital, Wishaw, Lanarkshire, UK.

Received: April 25, 2019; Published: May 29, 2019

Abstract

Objective: To compare the efficacy of nasal Biphasic Positive Airway Pressure (BiPAP) in reducing the incidence of failed extubation compared to nasal Continuous Positive Airway Pressure (n-CPAP) in preterm babies born at or below 30 weeks gestation.

Design, Settings and Patients: Prospective randomized controlled trial of Preterm babies born at or less than 30 weeks of gestation at the maternity unit in Wishaw General Hospital, Wishaw.

Primary Outcome: Successful extubation defined as not meeting extubation failure criteria for the first 72 hours following extubation.

Secondary Outcome: Total duration of ventilatory support (mechanical ventilation including non-invasive ventilation), incidence of BPD, death, pneumothorax, incidence and severity of IVH, feeding intolerance, NEC and time to achieve full enteral feeds.

Results: 122 babies were recruited to the study, 2 were withdrawn and one baby died. There were 60 babies in CPAP group and 59 babies in BiPAP group. There was no statistically significant difference in the primary outcome (P value 0.395, Confidence interval: 0.64-4.82) and secondary outcomes between the two groups.

Conclusions: In this study, BiPAP when compared to n-CPAP did not reduce extubation failure in babies born at or less than 30 weeks of gestation during 72 hours following extubation.

Keywords: n-CPAP: Nasal-Continuous Positive Airway Pressure; n-BiPAP: Nasal Biphasic Positive Airway Pressure; PIP: Peak Inspiratory Pressure; HFNC: High Flow Nasal Cannula; BPD: Bronchopulmonary Dysplasia; NEC: Necrotizing Enterocolitis

What is known on this subject?

BiPAP and n-CPAP are used as the modes of noninvasive respiratory support in preterm babies following extubation from mechanical ventilation. There are limited published studies which compare the efficacy of BiPAP with n-CPAP in preterm babies following extubation.

What this study adds

BiPAP when compared to n-CPAP did not reduce extubation failure in babies born at or less than 30 weeks of gestation during 72 hours following extubation.

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Introduction
Respiratory distress syndrome remains a significant problem in preterm babies. These babies may require mechanical ventilation in the immediate postnatal period of life. One of the critical periods for these babies is after extubation. Cochrane review of n-CPAP after extubation concluded that n-CPAP is effective in preventing extubation failure [2]. The literature reports a re-intubation rate of 30% - 40%, when preterm babies are extubated to nasal continuous positive airway pressure [1,2]. Any intervention which reduce re-intubation rate will be beneficial by reducing the untoward effects like local trauma, stress and hemodynamic compromise. Recently, n-BiPAP is increasingly used as an alternative to n-CPAP. Migliori., et al. [3] reported significant improvement of gas exchange during BiPAP. Lista., et al. [4] reported that n-CPAP and BiPAP induce same changes in cytokine levels but babies in the CPAP group required longer respiratory support and oxygen. However, there were not many published studies which compare its efficacy in reducing re-intubation when compared with n-CPAP. Therefore, this study was conducted to address this issue.

Methods

Single centre study conducted at the Neonatal unit, Wishaw General Hospital, NHS Lanarkshire, Scotland, UK.

Study period
April 2012 to August 2014 initially but extended to June 2017. Extension to the study period was obtained from the Ethics committee as the recruitment was slow due to reduced number of deliveries in the eligible gestational age. The study was completed within the extension period.

Study population
Preterm babies born at or less than 30 weeks of gestation at the maternity unit in Wishaw General Hospital, Wishaw, Scotland, UK.

Study design
Prospective Randomized controlled trial (unblinded) to compare the efficacy of BiPAP in reducing the incidences of failed extubation when compared with n-CPAP following extubation of preterm babies born at or below 30 weeks gestation.

Primary outcome
Extubation failure was defined as the need for re-intubation and mechanical ventilation/additional respiratory support after extubation based on the presence of any one of the following criteria (after trial on maximal support on BiPAP or n-CPAP): PaCO₂ > 9 KPa in arterial sample or > 10 KPa in capillary sample or one or more of the following: episodes of apnea requiring positive pressure ventilation, frequent (> 3/hours) apnea/bradycardia spells (cessation of respiration for > 15s and associated with a heart rate of < 100/min) not responding to standard management measures, persisting increase in FiO₂ > 0.5 and clinical evidence of exhaustion. Successful extubation was defined as not meeting extubation failure criteria for the first 72 hours following extubation.

Secondary outcomes
Total duration of ventilatory support (mechanical ventilation and noninvasive respiratory support), incidence of Broncho pulmonary dysplasia, death, pneumothorax, incidence and severity of intra-ventricular haemorrhage, necrotizing enterocolitis and time to achieve full enteral feeds.

Inclusion criteria
Babies born between 23 weeks and 0 days and 30 weeks and 6 days gestation who were ventilated for at least 6 hours in the first 28 days of life (first episode of ventilation only).

Exclusion criteria
Hypoxic ischemic encephalopathy stage 2 - 3, major congenital malformations or neuromuscular problems evident from the initial period.

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Consenting process

Informed consent was obtained after the baby was delivered. In exceptional circumstances when parents were unavailable, recruitment and randomisation was permitted pending retrospective consent. However, this option was not exercised during the study.

Randomisation

Babies were stratified to three groups based on gestational age: < 25 weeks (group 1), 26 - 27 weeks (group 2) and 28 - 30 weeks (group 3) to ensure equal distribution at randomisation. Randomization was carried out in accordance with guidelines suggested by Doig and Simpson [5] to ensure equal recruitment into both arms of the study. The envelope was kept at the bedside and opened just prior to extubation.

Criteria for extubation

Babies were extubated when clinically felt appropriate (minimal ventilation requirements, good respiratory effort with haematocrit > 0.35). All the babies were given a loading dose of Caffeine citrate prior to extubation followed by maintenance dose as per the local protocol. After extubation, babies were allocated to the appropriate randomization mode. In the event of unplanned (accidental) extubation, if the baby was felt to be suitable for non-invasive respiratory support, the baby was started on randomised mode and loading dose of Caffeine citrate was administered.

CPAP and BiPAP settings

BiPAP was provided by SIPAP machines (Viasys medicals, Cardinal healthcare) whereas n-CPAP was provided by Infant flow advance or a SIPAP machine. Standard circuits, humidifiers, nasal prongs and nasal masks were used to deliver the flow. Babies on n-CPAP were started on pressures of 5 - 8 cm of H₂O. For babies on BiPAP, CPAP of 5 - 8 cm H₂O, PIP of 8 - 11 cm H₂O, rate of 30 - 40 breaths per minute and inspiratory time of 0.3 - 0.5 seconds was used. Initial settings and subsequent alterations within the range, triggered or non-triggered BiPAP were permitted as felt appropriate. Although attempts were made to maintain the set pressure in all the babies, it was accepted that the variation in delivered pressure is expected for any baby on non-invasive support. A blood gas analysis was carried out one hour after extubation, every eight hours for next 24 hours and every 12 hours for next 48 hours. Additional blood gases were performed as required.

BiPAP/n-CPAP was administered by a team of experienced nursing staff who closely monitored all the vital parameters. Feeding was as per the unit policy. Oro-gastric tubes were inserted for all the babies and left open in between feeds. Adherence to the study protocol was monitored by the medical team.

If a baby required re-intubation within the first 30 minutes post extubation, it was considered a reflection of the underlying condition requiring endotracheal tube change and the baby continued in the same randomized mode after next planned extubation.

In the first 72 hours following extubation, depending on the clinical condition, the infant in the n-CPAP group was changed to High Flow Nasal Cannula device, low flow nasal cannula oxygen or room air. In the BiPAP group, the mean airway pressure was initially reduced before changing on to n-CPAP, HFNC, nasal cannula oxygen or room air as appropriate.

If the baby required additional support within the first 72 hours post extubation following weaning, the baby was restarted on the randomized mode. Study allowed the baby on n-CPAP to cross over to the BiPAP mode as was the practice in the unit, provided the extubation failure criteria for the study is met-the baby would be considered to have failed extubation on N-CPAP, and would be analyzed as having failed the primary outcome.

Data collection

Data on participants’ clinical condition was collected until the time of discharge or death by a trained neonatal research nurse. The analysis was on intention to treat basis.

Sample size and power calculations

In a similar group of babies (< 1000g birth weight), Stefanescu., et al. [1] found an extubation failure rate (< 7 days post extubation) of close to 40%. In the paper by Barrington., et al. [6] (<1250g birth weight) extubation failure rate (< 72 hours post extubation) in the n-CPAP limb was 44% and in the NIPPV limb was 14%. Our study population and extubation failure criteria (< 72 hours) are similar to the
Barrington study. Using a predicted reduction in rate of re-intubation from 44% (as in the Barrington study in n-CPAP group) to 20% in the BiPAP group (slightly higher level than the 14% they found in the NIPPV group) with alpha error of 0.05 and power of 80%, each arm of the study required 60 babies in each group.

Statistical analysis was performed with SPSS for Windows (SPSS, Inc., Chicago, IL). Biphasic and n-CPAP groups were compared with the use of student's t test, x², or Mann-Whitney U analyses, as appropriate. Logistic regression analysis was used to examine factors that influence successful extubation. P value < 0.05 was considered statistically significant. The entire analysis was carried out in discussion with statistician. Analysis of the primary endpoint was on intention to treat basis for babies not completing the study for any reason. Babies with missing data on duration and age at enteral feeds were not included in the analyses of these secondary endpoints.

The primary analysis of differences in the proportions of babies experiencing extubation failure was accomplished using exact logistic regression adjusting for the stratification into the three gestational age groups and using p values derived from 10,000 bootstrap simulations. The main secondary analysis factors which were based upon binary responses were analyzed in the same way. Differences in the duration of use of n-CPAP/BiPAP and age at enteral feeds were tested using linear regression models for the logarithm of duration or age, both measured in days, and again adjusting for the stratification into the three gestational age groups.

Results

This study recruited 122 babies, 2 babies were withdrawn at parental request and one baby died leaving 119 babies in the study against the proposed 120 babies. 60 babies were in n-CPAP group and 59 babies in BiPAP group (Figure 1). Although the study allowed recruiting babies ventilated for the first time during the neonatal period, all the babies were ventilated in the first 24 hours of life.

Ten babies in n-CPAP and twelve babies in n-BiPAP group were medically treated for PDA. Two babies in n-CPAP group and three babies in BiPAP group required PDA ligation subsequent to failed medical management. 56 mothers in n-CPAP and 53 mothers in the BiPAP group received antenatal steroids.

All the babies in both arms received at least one dose of surfactant (this was due to our inclusion criteria of babies needing mechanical ventilation). There was no statistically significant difference in the demographic characteristics, antenatal steroids and surfactant administration as detailed in the table 1a and 1b.

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<table>
<thead>
<tr>
<th>Gender</th>
<th>Gestation</th>
<th>CPAP (60 babies)</th>
<th>BiPAP (59 babies)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>23 - 25 weeks</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>26 - 27 weeks</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>28 - 30 weeks</td>
<td>20</td>
<td>12</td>
<td>25</td>
<td>8</td>
</tr>
</tbody>
</table>

Birth Weight

<table>
<thead>
<tr>
<th>Gestation</th>
<th>CPAP group (60 babies)</th>
<th>BiPAP group (59 babies)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 - 25 weeks</td>
<td>765 (550 - 870 grams)</td>
<td>709 (480 - 1035 grams)</td>
<td>0.87</td>
</tr>
<tr>
<td>26 - 27 weeks</td>
<td>973 (638 - 1375 grams)</td>
<td>882 (465 - 1130 grams)</td>
<td></td>
</tr>
<tr>
<td>28 - 30 weeks</td>
<td>1376 (795 - 1750 grams)</td>
<td>1286 (540 - 1755 grams)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1a: Gender and birth weight.

Surfactant (all babies received surfactant)

<table>
<thead>
<tr>
<th>Gestation</th>
<th>CPAP group (59)</th>
<th>BiPAP group (60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 - 25 weeks</td>
<td>29 received 2 doses, 3 babies received 3 doses</td>
<td>31 received 2 doses, 4 babies received 3 doses</td>
<td>0.67</td>
</tr>
<tr>
<td>26 - 27 weeks</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>28 - 30 weeks</td>
<td>32</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Antenatal steroid administration

<table>
<thead>
<tr>
<th>Gestation</th>
<th>CPAP group (59)</th>
<th>BiPAP group (60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 - 25 weeks</td>
<td>35 received 2 doses</td>
<td>33 received 2 doses</td>
<td>0.59</td>
</tr>
<tr>
<td>26 - 27 weeks</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>28 - 30 weeks</td>
<td>16</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>56 (50 received within 7 days of delivery)</td>
<td>53 (45 received within 7 days of delivery)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1b: Surfactant administration and antenatal steroids.

Overall 35% of babies in the n-CPAP group and 24% babies in the BiPAP group failed extubation p value: 0.395 (Table 2). 19 babies out of 21 babies in n-CPAP group who failed extubation, were switched to BiPAP, three of them were subsequently re-intubated.

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Extubation failure</th>
<th>Odd Ratio (CPAP Vs BiPAP)</th>
<th>Lower Confidence Limit</th>
<th>Upper Confidence Limit</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-CPAP</td>
<td>60</td>
<td>21 (35%)</td>
<td>1.64</td>
<td>0.64</td>
<td>4.82</td>
<td>0.395</td>
</tr>
<tr>
<td>BiPAP</td>
<td>59</td>
<td>14 (24%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Primary outcome - extubation failure within 72 hours of extubation.

There were no statistically significant difference in any of secondary outcome measures (Table 3).

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Discussion

In this single center randomized controlled trial comparing the BiPAP and n-CPAP in babies born at or below 30 weeks of gestation, 35% of babies in the CPAP group and 24% in BiPAP group failed the extubation within 72 hours following extubation but with no statistically significant difference between two groups (Table 2). We observed that the incidence of extubation failure in the CPAP limb of this study is below that described by Barrington, et al. which was used for the power calculation in this study and we speculate that this may be related to various other advances in Neonatology, including better nursing proficiency in non-invasive ventilation.

Zhi-Hui Rong, et al. reported that bi-level positive airway pressure compared with CPAP reduced the need for re-intubation within first 72 hours of age in babies born between 26 and < 33 weeks of gestation in their retrospective cohort study [7]. O’Brien, et al. [8] compared n-CPAP with BiPAP in babies with birth weight < 1250 grams and found no difference in the primary outcome of sustained extubation for 7 days. Suresh Victor, et al. reported that nasal biphasic positive airway pressure confers no significant benefit in preventing extubation failure.

Table 3: Secondary outcomes.

<table>
<thead>
<tr>
<th>Measures</th>
<th>CPAP group (n = 60)</th>
<th>BiPAP group (n = 59)</th>
<th>Odd ratio CPAP Vs BiPAP</th>
<th>Lower Confidence Limit</th>
<th>Upper Confidence Limit</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broncho pulmonary dysplasia (oxygen requirement at 36 weeks)</td>
<td>44</td>
<td>47</td>
<td>0.64</td>
<td>0.18</td>
<td>1.76</td>
<td>0.515</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>1</td>
<td>4</td>
<td>0.15</td>
<td>0.00</td>
<td>2.26</td>
<td>0.199</td>
</tr>
<tr>
<td>Time to full enteral feeds (Proportional change CPAP Vs BiPAP)</td>
<td>20.9</td>
<td>25.0</td>
<td>0.92</td>
<td>0.77</td>
<td>1.09</td>
<td>0.329</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (any grade)</td>
<td>19</td>
<td>21</td>
<td>0.82</td>
<td>0.34</td>
<td>1.92</td>
<td>0.835</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
<td>2</td>
<td>1.15</td>
<td>0.08</td>
<td>16.91</td>
<td>1.000</td>
</tr>
<tr>
<td>Total duration of ventilation and noninvasive respiratory support</td>
<td>16.8 days</td>
<td>23.9 days</td>
<td>0.78</td>
<td>0.52</td>
<td>1.17</td>
<td>0.223</td>
</tr>
<tr>
<td>(Proportional change CPAP Vs BiPAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
<td>1</td>
<td>1.03</td>
<td>0.01</td>
<td>79.39</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Figure 2: Days on CPAP or BiPAP in 3 subgroups.

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failure at equivalent mean air way pressure in preterm infants born before 30 weeks of gestation within first 48 hours of extubation [9]. Our study looked at the extubation failure within 72 hours of extubation and included the babies born at or before 30 weeks of gestation.

This pragmatic study allowed the clinician to choose the initial and subsequent settings within acceptable parameters. Therefore, higher mean airway pressure was tried before declaring an extubation failure and there was no comparison of equivalent mean airway pressure unlike the extubation trial by Suresh Vector., et al [9]. This may be seen as weakness as well as the strength of this study which reflects what happens in day to day clinical practice. This study allowed the babies who failed n-CPAP to be switched to BiPAP as per the prevailing practice in the unit. Nineteen babies in the n-CPAP group were changed to BiPAP after meeting the criteria for extubation and only three of them required re-intubation. It is difficult to explain this finding, but we speculate that escalating the respiratory support from CPAP to BiPAP rather than starting on BiPAP initially may reduce the need for re-intubation. This will need further studies.

There was no statistically significant difference in secondary outcomes (Table 3). The results of secondary outcome may have been influenced by the crossover of the babies who failed n-CPAP to BiPAP. The study by Kirpalani., et al. [10] comparing NIPPV with n-CPAP found no difference in the primary outcome of rate of survival to 36 weeks of postmenstrual age without bronchopulmonary dysplasia and secondary outcomes similar to this study.

This study found that babies in CPAP group achieved full enteral feeds relatively earlier (8% reduction in age to full feeds compared to BiPAP) but it was not statistically significant. Also, there was no difference in the time to achieving full enteral feeds in all the three gestational age groups; P value for the interaction was 0.6561.

The duration of ventilation prior to extubation in n-CPAP group was 22% less but was not statistically significant. Subgroup analysis did not show any statistically significant difference in the duration of ventilation prior to extubation in the three gestational age groups (P value: 0.9092). The duration of respiratory support (ventilation and noninvasive respiratory support) between the n-CPAP and BiPAP groups was also not statistically significant. Again, this might have been affected by the crossover of babies who failed n-CPAP to BiPAP.

Based on the results of this study, we are unable to recommend BiPAP over n-CPAP or vice versa as the mode of choice for post extubation respiratory support in preterm babies. Therefore, an individualized approach could be considered wherein the clinician decides to start BiPAP after extubation either directly based on clinical condition or after a period on CPAP when work of breathing is noted to be increasing [11].

**Conclusion**

This trial did not show any evidence that BiPAP was more effective than n-CPAP in preventing extubation failure within 72 hours in babies born at or below 30 weeks of gestation. This study does not address whether BiPAP offer any advantage over n-CPAP in other clinical circumstances.

**Acknowledgements**

We would like to thank all the parents who enrolled their babies into this study, nursing and medical staff at the Neonatal Unit, Wishaw General Hospital, Lanarkshire for their help in successfully completing this study. We are grateful to Mr Raymond Hamill, research and Development Department manager, NHS Lanarkshire for sponsoring the study.

**Author Contributor Ship**

Dr Kalyanasundaram conceived the study, prepared the protocol, and obtained ethical approval and was the chief investigator at the start of the study. Dr Manjunatha, contributed to preparation of protocol, recruiting the participants and was the chief investigator subsequently. Dr Ibhanesebhor contributed to the initial planning and writing the protocol. Denise Vigni contributed to the recruitment of the patients and collection of data. Professor Robertson contributed to the analysis of the data and preparation of the article. All the authors contributed to the preparation of the article.

**Competing Interest**

None.

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Ethical Approval

This study was conducted with the approval of West of Scotland Research Ethics Committee (REC reference no.10/S0703/9, IRAS project ID: 32249, ISRCTN 94116457).

Bibliography


