Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial

Claus Klingenberg,1,2 Marit Pettersen,1 Elin A Hansen,1 Linn J Gustavsen,1 Ingvild A Dahl,1 Arild Leknessund,1 Per I Kaaresen,1,2 Marianne Nordhov1,2

ABSTRACT

Objective To compare patient comfort in preterm infants treated with heated humidified high flow nasal cannulae (HHHFNC) versus nasal continuous positive airway pressure (NCPAP).

Design Randomised cross-over trial (2x24 h).

Setting Single tertiary neonatal unit.

Patients 20 infants less than 34 weeks postmenstrual age treated with NCPAP due to mild respiratory illness.

Interventions After parental consent, infants were randomised to 24 h of treatment with NCPAP or HHHFNC followed by 24 h of the alternate therapy.

Main outcome measures Primary outcome was patient comfort assessed by the EDIN (neonatal pain and discomfort) scale. Secondary outcomes were respiratory parameters (respiratory rate, FiO2, SpO2, TcPCO2), ambient noise, salivary cortisol and parental assessments of their child.

Results We found no differences between HHHFNC and NCPAP in mean cumulative EDIN score (10.7 vs 11.1, p=0.25) or ambient noise (70 vs 74 dBa, p=0.18). Parents assessed HHHFNC treatment as significantly better in the three domains, 1) child satisfied, 2) parental contact and interaction and 3) possibility to take part in care. Mean respiratory rate over 24 h was lower during HHHFNC than CPAP (41 vs 46, p=0.001). Other respiratory parameters were similar.

Conclusions Using EDIN scale, we found no difference in patient comfort with HHHFNC versus NCPAP. However, parents preferred HHHFNC, and during HHHFNC respiratory rate was lower than during NCPAP.

ClinicalTrials.gov number NCT01526226.

INTRODUCTION

The use of heated humidified high flow nasal cannulae (HHHFNC) as a non-invasive mode of respiratory support for preterm neonates has rapidly expanded.1 Two clinical trials that included preterm infants found HHHFNC comparable with nasal continuous positive airway pressure (NCPAP) in avoiding need for mechanical ventilation and safety.2 3 The physiological effect of HHHFNC is mediated in part through positive pressure support of the airways, similar to NCPAP, as well as lowering the inspiratory resistance, improvements in conductance and pulmonary compliance and reducing energy expenditure for gas conditioning.4 The high gas flow, in combination with gas leak around the nostrils, also contributes with dead space washout of CO2.1 5

NCPAP-interaces, prongs or masks, are strapped tightly to the nose and are often ‘bulky’. This may contribute to nasal trauma and impair visual interaction with the child.

Potential benefits of HHHFNC compared with NCPAP include reduced nasal trauma, improved parent interaction1 6 and reduced ambient noise.7 8 However, except from a reduction in nasal trauma,2 3 evidence from clinical trials supporting these benefits is limited.9 We performed a randomised cross-over trial to test the hypothesis that comfort, defined as absence of prolonged pain, in preterm infants with mild respiratory illness was greater during support with HHHFNC than NCPAP.

METHODS

This study was conducted in the neonatal unit at the University Hospital of North Norway in Tromsø.10 Infants were eligible for the study if they were less than 34 weeks postmenstrual age (PMA) and had mild respiratory illness defined as treatment with CPAP for at least 72 h if PMA <29 weeks and at least 24 h if 29 weeks to 33 weeks PMA; FiO2 <0.30; and last (venous/arterial/capillary) PCO2 <8 kPa before study enrolment. Infants were
excluded if they were 34 weeks or more PMA, had congenital anomalies, required higher concentrations of supplemental oxygen, or were considered to be in need of frequent blood samples due to infection, hypoglycaemia or other intercurrent conditions. After parental consent, the patients were randomised to continue with NCPAP for 24 h and then switch to HHHFNC for the next 24 h, or to immediately switch to HHHFNC for 24 h and then back to NCPAP for 24 h. After the 48 h study period (2×24 h epochs) further respiratory support was at the discretion of the clinical team.

Equipment

The HHHFNC was administered with the Fisher & Paykel RT329 system (Fisher & Paykel Healthcare, Auckland, New Zealand) using 2.4-mm external diameter nasal cannulae. Gas flow was set at 6 L/min for infants weighing >1500 g and at 5 L/min if <1500 g. The NCPAP was administered using the Infant Flow or SiPAP (CareFusion, San Diego, California, USA) variable flow driver. The nasal interface was either a mask or binaural prongs at the discretion of the nurse. We aimed for a NCPAP of 4–5 cm H2O. Failure criteria of either HHHFNC or NCPAP during the 48 h study period were a respiratory deterioration with an increase in 1) respiratory rate over first 8 h (>20%), 2) FiO2 (>0.1) or 3) transcutaneous pCO2 (>2 kPa), respectively.

Primary and secondary outcomes

The primary outcome was patient comfort, defined as a state free of prolonged pain. Secondary outcomes were respiratory parameters, ambient noise, salivary cortisol and parental assessments of their child.

Patient comfort

This was assessed by a validated neonatal pain and discomfort scale (EDIN scale) that has been in use in our unit since 2007. The EDIN scale is a unidimensional scale using five behavioural indicators (facial activity, body movements, quality of sleep, quality of contact with nurses and consolability) to identify and quantify well-being or prolonged pain in preterm infants. The EDIN score was an assessment over the entire 70 h epoch in order to assess whether each of the interventions had an impact of CO2 removal. FiO2 values were recorded hourly from the CPAP device or from the oxygen blender for HHHFNC. Target SpO2 was per unit protocol 90–94% for infants receiving supplemental oxygen.

Ambient noise

Sound levels, expressed in dBA, were measured with a handheld audiometer (Bruel & Kjaer, Instr.no: 1648127, Copenhagen, Denmark). The microphone was held approximately 15 cm above the infants face and sound levels were measured twice a day for 10 min during a quiet period in the morning and in the evening. Average sound levels were reported.

Salivary cortisol

Saliva was collected by placing a cotton bud in the patient’s mouth for approximately 10 min. Saliva was collected in the morning and evening for each 24 h epoch. We aimed to collect saliva when patients were quiet, fed and comfortable. After collection, the saliva was centrifuged, frozen at ~20°C and stored at ~70°C. The saliva samples were later analysed with a radioimmunoassay to measure the cortisol concentrations.

Parental assessment

Immediately after each 24 h epoch we administered three questions (box 1) to the parents and asked to respond on a visual analogue scale from 1 to 10. Parents returned the first questionnaire before entering their response for the next 24 h epoch.

Sample size and randomisation

Based on previous observations in our unit we estimated that mean (SD) cumulative EDIN score in infants on NCPAP would be 16 (3). We considered a 25% reduction in the cumulative EDIN score to be clinically relevant. To find this difference with 80% power and a type 1 error of 80%, sample size of 20 infants was required. Infants were block (blocks of 4) randomised, using sealed opaque envelopes, to start with either HHHFNC or CPAP.

Data analysis and statistics

Data were analysed using IBM SPSS (V20.0) statistical software. Descriptive results are expressed as mean (SD) or median (IQR), as appropriate. Paired t test was used to compare continuous data and proportions were compared using χ2 test. A p < 0.05 was considered statistically significant.

Ethics and trial registration

The study was approved by the committee for human medical research ethics, Region North in Norway. The study was registered with ClinicalTrials.gov (NCT01526226). Written informed consent was obtained from parents before any infant was enrolled in this study.

Results

Forty-six infants with gestational age (GA) <34 weeks were admitted during the study period (February 2012–April 2013). Twenty-one did not meet the inclusion criteria, either due to severe illness or not needing respiratory support. One family withdrew from the study after 24 h HHHFNC not wanting their child back on CPAP. In three infants technical problems led...
**DISCUSSION**

In our randomised cross-over trial of preterm infants with mild respiratory illness, patient comfort assessed by bedside nurses using the EDIN scale was comparable on HHHFNC versus NCPAP. There was no significant statistical difference in noise with HHHFNC versus NCPAP. Despite our best efforts, we only managed to collect enough saliva for cortisol measurement in 11 out of 80 attempts. Data on cortisol are therefore omitted from statistical comparisons. The parents preferred HHHFNC as respiratory support for their infants. During the 24 h HHHFNC-epoch patients had significantly lower respiratory rate than during the 24 h NCPAP-epoch. All other respiratory parameters were similar. During NCPAP most infants used nasal masks, but some alternated and used masks and prongs during the 24 h epoch. None of the infants met the failure criteria during the study period.

### Table 1: Study population (n=20), baseline data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HHHFNC</th>
<th>NCPAP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, mean (SD)</td>
<td>29.3 (1.7) weeks</td>
<td>29.4 (1.9) weeks</td>
<td>0.95</td>
</tr>
<tr>
<td>Birth weight, mean (SD)</td>
<td>1234 (353) grams</td>
<td>1240 (380) grams</td>
<td>0.55</td>
</tr>
<tr>
<td>Postnatal age at study entry, median (IQR)</td>
<td>6 (4–10) days</td>
<td>6 (4–10) days</td>
<td>1.00</td>
</tr>
<tr>
<td>Last pCO₂ prior to study enrolment*</td>
<td>5.6 (0.9) kPa</td>
<td>5.5 (1.0) kPa</td>
<td>0.24</td>
</tr>
<tr>
<td>Mechanical ventilation prior to study enrolment*</td>
<td>6/20 (30%)</td>
<td>6/20 (30%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Male/ Female</td>
<td>13/7</td>
<td>13/7</td>
<td>1.00</td>
</tr>
<tr>
<td>Randomised to start with HHHFNC/NCPAP</td>
<td>9/11</td>
<td>9/11</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Blood gas obtained during routine clinical care within 96 h prior to study enrolment. No additional blood gases were obtained for study purpose.
HHHFNC, heated humidified high flow nasal cannulae; NCPAP, nasal continuous positive airway pressure.

**Table 2: Primary and secondary outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HHHFNC</th>
<th>NCPAP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDIN score, cumulative*</td>
<td>10.7 (3.3)</td>
<td>11.1 (3.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Noise, dBA</td>
<td>70 (10)</td>
<td>74 (10)</td>
<td>0.18</td>
</tr>
<tr>
<td>Parental assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Child satisfied</td>
<td>8.6 (1.1)</td>
<td>6.9 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. Contact and interaction</td>
<td>9.0 (1.1)</td>
<td>6.7 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. Possibility to take part in care</td>
<td>9.1 (1.2)</td>
<td>8.0 (1.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>TcPCO₂ (mean 2 h) kPa</td>
<td>5.5 (1.1)</td>
<td>5.5 (1.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Respiratory rate (mean 24 h)</td>
<td>41 (7)</td>
<td>46 (9)</td>
<td>0.001</td>
</tr>
<tr>
<td>FiO₂ (mean 24 h)</td>
<td>21.8 (1.6)</td>
<td>21.5 (1.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>SpO₂ (mean 24 h)</td>
<td>95 (2)</td>
<td>95 (2)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

All data are mean (SD).
*Cumulative score based on assessment over three nursing shifts (day, evening, night).
HHHFNC, heated humidified high flow nasal cannulae; NCPAP, nasal continuous positive airway pressure.

Our study has several limitations. First, we used our previous observations of EDIN scores in infants on CPAP to estimate our sample size. During the present trial, (average) EDIN scores were substantially lower. Thus, our sample size may have been too small to demonstrate a difference in the two modes of respiratory support. A second limitation is that the EDIN scale, designed to assess pain (high scores), may not be appropriate to assess comfort (low scores). However, in an observational study in preterm infants, type of respiratory support was found to affect the EDIN scale. A third limitation is that in many of our subjects, CPAP was applied using masks rather than nasal prongs. It is possible that masks might be more comfortable than prongs, although we did not record sufficiently detailed data to test that hypothesis. Finally, our study was unblinded and thus subject to potential bias. Although the nurses were asked not to express a preference for either mode of support, it is possible that a positive attitude could be transmitted to the parents. However, the fact that the nurses recorded no difference in the EDIN scale supports our observation that parents independently preferred HHHFNC compared with CPAP.

**CONCLUSION**

In this unblinded, randomised, cross-over trial of infants with relatively mild respiratory illness we found no difference in patient comfort with HHHFNC versus NCPAP using the EDIN scale.
scale. However, parents reported a preference for HHHFNC, and during HHHFNC respiratory rate was significantly lower than during NCPAP.

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Contributors CK conceived the study, reviewed the literature, wrote a first draft and submitted the manuscript. All authors participated in study design, collection of patient data and editing of the manuscript. All authors have read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

Ethics approval The study was approved by the committee for human medical research ethics, Region North in Norway.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data from this study, stored in a SPSS file, will be made accessible to other researchers who are interested.

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