Comparison of Nasal Continuous Positive Airway Pressure Therapy with and without Prophylactic Surfactant in Preterm Neonates

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ABSTRACT

Background: Preterm labor is at risk for respiratory distress syndrome (RDS) and sometimes requires to mechanical ventilation (MV) and surfactant therapy. Continuous positive airway pressure (CPAP) and Nasal Continuous positive airway pressure (NCPAP) are the methods of respiratory support especially for using in RDS of neonates. In other method surfactant is administered to babies via tracheal instillation. The aim of study was comparing nasal continuous positive airway pressure (NCPAP) with and without prophylactic surfactant therapy in preterm neonates’ RDS.

Methods: This is a randomized clinical trial study that performed on eighty newborns (28-34 weeks) who were born in Ali-Ebne-Abitaleb Hospital of Zahedan University of Medical Sciences from October 2008 to September 2010. Subjects were randomly classified in two groups whom received nasal CPAP alone or with surfactant (40 patients in each group). The Including criteria for entrance to research were approved suggested RDS, gestational age less than 34 weeks and neonates 72 hours after delivery. The data collected through direct observation and questionnaire contained fourteen items. Groups received either surfactant (Curosurf, Parma, Italy) with NCPAP or NCPAP alone. The data analyzed were conducted through SPSS 17.00 version and followed by Crosstab (Pearson Chi-square).

Results: Results revealed that six neonates who received only NCPAP and four patients who received NCPAP plus surfactant required to mechanical ventilation (MV) therapy. After a week, 33 neonates who received only NCPAP and 36 patients who received CPAP plus prophylactic surfactant remained alive. There was no significant difference between the groups regarding adverse outcomes (P=0.518).

Conclusion: According to the results of this study, NCPAP is affordable as a safe protocol for RDS in preterm neonates. Further research especially with control or placebo groups is required to clarify and validate our findings.

Keywords: RDS, Preterm, Neonate, CPAP.

Introduction

Respiratory distress syndrome (RDS) as a condition of pulmonary insufficiency is the single most important cause of mortality and morbidity in preterm infants despite significant technologic and pharmacologic advances during the past 30 years (Simpson and Creehan, 2012). During the last 50 years, significant efforts have been made in the understanding of the etiology and pathology of this syndrome as well as treatment, meanwhile the optimal treatment regimen is still controversial and challenging (Harrison, 2011). If untreated, this will result in epithelial injury and pulmonary oedema which further interfere with surfactant function, producing the clinical picture of RDS (Bohlin, 2012). There is some conflicting data about its treatment efficacy (Harrison, 2011).

Preterm neonates that affected with severe RDS will be requiring to mechanical ventilation (MV) for living. Of course oxygen tension should be restricted (Saugstad, 2001) and also should be carefully monitored (Askie et al., 2003). However, mechanical ventilation (MV) maybe induce varying degree of lung damage, with epithelial disruption followed by fluid leakage and inflammatory response that can inactivate surfactant (Dreyfuss and Saumon, 1998; Parker, Hernandez and peevy, 1998). Furthermore, mechanical ventilation (MV) has been implicated as the single most important risk factor for the later development of Broncho pulmonary dysplasia (BPD) (Bohlin et al., 2009). The efforts had made to decrease the utilization of mechanical ventilation (MV) at the first days of life to prevent...
barotraumas and to reduce the severity of BPD. The important factors to be considered for reducing of its complications include minimal use of oxygen saturation and tension, early establishment of NCPAP and, if necessary, early surfactant therapy (Verder, 2010). The results of Verder et al. (1994) The randomized controlled trial of surfactant instillation during NCPAP demonstrated that in newborns with moderate-to-severe RDS, the need for subsequent mechanical ventilation (MV) could be reduced by 50% after a single dose of surfactant. The introducing of NCPAP improved the treatment and reduced the mortality rate due to RDS (Dunn, 1984; Gregory et al., 1971; Rhodes & Hall, 1973). NCPAP is pressure, flow and oxygen delivered continuously to the airway to maintain expansion of the alveoli and promote oxygen (Harrison, 2010). This method is the first line of therapy especially for very low-birth-weight newborns and the other infants as well that can be successfully managed without mechanical ventilation (MV) (Kamper, Wulff, Larsen, Lindquist, 1993; Papadakos, Apdakos, Lachmann, 2008). The administration of exogenous surfactants improves oxygenation and decreases neonatal mortality rates among affected newborn infants (Soll & Özek, 2010; Soll, 2000). The effectiveness of combined treatment of NCPAP plus surfactant has been demonstrated (Verder et al., 1999; Verder et al., 1994). Surfactant therapy combined with mechanical ventilation (MV) has been used in babies with RDS since around 1980. Surfactant therapy has been shown to improve mortality and reduce air leak in babies with RDS (Foulain and Clements, 1995). Hence, there is a hypothesis that CPAP and surfactant mixed would be better than CPAP alone (Adeela, Shalabh and Sunil, 2011). CPAP in newborn infants with RDS has proven the benefits include no need for intubation or sedative and paralytic agents’ therefore less long-term respiratory morbidity. It is a selective therapy in spontaneously breathing infants and so far there is no clear weight or gestational cut-off at which CPAP is more effective and it can improve by coexistent administration of surfactant (Gupta, Sinha, Donn, 2009; De Paoli, Davis, Faber, 2008). The Scandinavian treatment strategy which now is spreading, the treatment begins all spontaneously breathing preterm neonates on mask- or NCPAP at delivery room immediately after birth (Verder, 2010). In spite of significant progress on understanding of the etiology and pathophysiology of the RDS as well as its treatment, but the optimal treatment is still under debate. Therefore, in present study, we decided to compare NCPAP therapy with and without prophylactic surfactant in preterm neonates.

**Material and Method**

This is a randomized clinical trial study which was performed on eighty preterm infants (28-34 weeks) at Ali-ebn-Abitalbe Hospital of Zahedan University of Medical Sciences, from October 2008 to September 2010. The sample size was computed based on results of previous studies e.g Gregory et al. (1971) who performed their studies with 20 infants and Verder (1994) carried out their study with eleven neonates. By using these information and results, the sample size was calculated 27 neonates for each group but the researchers allocated 40 neonates for each one to gain more valid and reliable data. Informed consents were obtained from all the parents. This study was approved by Ethical Committee of Zahedan University of Medical Sciences (Zahedan, Iran). The subjects were randomly assigned in two groups to receive NCPAP alone and NCPAP associated surfactant. All newborns’ mothers had received corticosteroids during the last week before delivery. The combined prophylaxis with prenatal steroids and early postnatal treatment with intubation surfactant has shown to decrease the severity and mortality of RDS and BPD compared to treatment with mechanical ventilation (MV) and surfactant (Verder, 2010). The including criteria were approved RDS, gestational age less than 34 weeks, neonates with 72 hours age after delivery. The excluding criteria were, the neonates with APGAR score less than 3 at five minutes after birth, those whom mothers had rupture of the membrane for more than three weeks, severe malformations, chromosomal anomalies such as trisomy of 13, 18 and 21, pneumonia and pneumothorax. The data collected through direct and closed observation as well as questionnaire containing of fourteen items about demographic and clinical characteristics. One group received surfactant (Curosurf; Chiesi Farmaceutici,Parma,Italy) at 100mg.kg.24hours or 4ml.kg.24hours with NCPAP and the other NCPAP alone in the delivery room immediately after birth. Curosurf Vials were prepared and reserved between +2 and +8 degree of centigrade. Before using, the Curosurf vials warmed gradually to 37 degree of centigrade without any shaking and administered into trachea via a F5 catheter on all positions. Manual ventilation was given after each dose of Curosurf for 2-5minutes. If assessment during ten minutes showed appropriate oxygen.
saturation and spontaneously breathing, the neonates would be extubated.

All newborns were observed for seven days for the need for mechanical ventilation, adverse outcomes and death. Meanwhile, pneumothorax, brain hemorrhage, lung hemorrhage, icterus, Patent Ducts Arteriosus (PDA) and disseminated intravascular coagulopathy (DIC) were determined. The indications for mechanical ventilation were severe attacks of apnea, PH<7.20 due to respiratory acidosis and to decrease in the oxygen tension ratio to less than 0.15.

Median system (Germany) was used for NCPAP. On the other hand Positive end-expiratory pressure (PEEP) was set between 4 to 6 cmH2o and FiO2<60%. Prophylaxis with theophylline was done for those neonates who did not need mechanical ventilation. The data analysis were conducted through the Statistical Package for Social Sciences (SPSS) 17.0 and followed by Crosstab (Pearson Chi-square) and independent sample t-test and differences between groups less than 0.05 considered significant. The odds ratio (OR) and 95% confidence intervals (95% CI) were also estimated.

Results

Eighty preterm neonates were enrolled in the study, forty newborn in the NCPAP therapy group and the same number in the NCPAP therapy with prophylactic surfactant group. As shown in table 1, the groups were similar in demographic and clinical characteristics at baseline. The outcome of the subjects after 7 days was shown in table 2. Our findings revealed that six patients of CPAP group and four patients who received surfactant had undergone mechanical ventilation therapy. Although the number of patients who undergone mechanical ventilation was higher in only CPAP than CPAP accompanied surfactant, but there was no statistically significant difference (0.737).

After observation of the patients for a week, 33 out of 40 patients of the group who received CPAP without surfactant and 36 out of 40 patients of the group who received CPAP with surfactant were stayed alive. There was no statistically significant difference between the groups (p=0.518). In addition, two groups showed no significant difference between the groups regarding pneumothorax, brain hemorrhage, lung hemorrhage, icterus, PDA and DIC.

Discussion

Preterm babies are at risk of RDS and sometimes need for mechanical ventilation (MV) to keep them alive. However, there are some complications associated with mechanical ventilation (MV) which are mostly iatrogenic. Of these, ventilator-induced lung injury (Dunn, 1984) has long been recognized contributor to the development of Broncho pulmonary dysplasia (BPD) or chronic lung disease (CLD). There has been increased tendency to CPAP as a primary therapy, gentler mode of respiratory support in RDS to improve mortality and reduce the occurrence of long-term respiratory morbidity.

Mechanical ventilation (MV) has been shown to be potentially harmful to the lung tissue due to the risk of barotraumas. However, the incidence of BPD remain high with Ventilator-Induced Lung Injury (VLLI) being a major factor. Ventilation, also, involves insertion of an endotracheal tube which can have associated long term complications such as subglottic stenosis and respiratory infections. In the present study we evaluated Nasal Continuous Positive Airway Pressure (NCPAP) therapy with and without prophylactic surfactant in preterm infants. Our findings showed no significant difference between the groups regarding adverse outcomes. In preterm infants, surfactant deficiency as well as incomplete lung development doesn’t have sufficient alveoli independently to perform gas exchange. The use of CPAP keeps the alveoli open, improves the functional residual capacity, stents the airway and diaphragm, and reduces the work of breathing (Aly et al., 2004). It has been reported that NCPAP is a safe treatment procedure with no increasing in short (Aly et al., 2004; De Klerk & De Klerk, 2001; Finer et al., 2004; Morley et al., 2008) and long- term (Dahl & Kamper, 2006; Hansen et al., 2004) morbidity. Several small studies have indicated improving respiratory outcomes when surfactant administration has been followed by extubation and toward CPAP treatment at birth (Blennow et al., 1999; Verder et al., 1999). In spite of some advances in perinatal management of neonatal RDS, controversies still exists. The combination of surfactant and mechanical ventilation was introduced in 1980. Verder et al (1999) had shown that NCPAP in combination with early treatment with surfactant significantly improved oxygenation and reduced the need for subsequent ventilation in infants less than 30 weeks’ gestational age with RDS. While Ho JJ, Henderson, Davis (2002) showed the early use of...
CPAP decreased the use of subsequent positive pressure ventilation. There is growing evidence indicates that early CPAP from birth is feasible and safe in preterm infants. NCPAP improves oxygenation in the few hours of the life. The use of CPAP was able to help in the establishment and maintenance of functional residual capacity (Gregory et al. 1971). Although, many infants will develop RDS and require surfactant treatment (Bohlin, 2012).

Ammari et al. (2005) reported that 78% of spontaneously breathing preterm babies with RDS and birth weight <1240 g could be managed with CPAP alone. As respiratory insufficiency may be a component of multiorgan dysfunction, preterm and term infants receiving surfactant-replacement therapy should be managed in facilities with technical and clinical expertise to administer surfactant and provide multisystem support.

The finding of Khosravi and Mohagheghi (2008) did not support the routine use of intubation solely to administer surfactant in large preterm infants with mild to moderate RDS.

Conclusion

In the present study, researchers found that the adverse outcomes and death were not statistically different between CPAP therapies alone and accompanied with prophylactic surfactant in preterm infant. Regarding the cost and expertise for surfactant administration, it entails great expenditure particularly in developing countries. NCPAP can be used as a safe prophylactic procedure and may be defensive in absentia or inaccessible of surfactant for preterm neonates affected with RDS.

Booth et al. (2006) showed the use of early CPAP led to a decrease in the need for mechanical ventilation (MV) (Because mechanical ventilation (MV) especially in the first few days of life to considerably increase the risk for BPD. Because surfactant therapy needs to intubation and mechanical ventilation (MV). In our practice if we administer early NCPAP, therefore we won’t have the effects of intubation and barotraumas. Further research especially with control or placebo groups is required to clarify and validate our findings. Of course, as well as we need waiting for multicenter results about this promotion with diversity in the selection of population by considering include gestational age, weight, time of prophylactic interventions for RDS.

Acknowledgement

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Conflict of interest

There is no conflict of interest.

References

**Table 1.** Demographic and clinical characteristics of the population study

<table>
<thead>
<tr>
<th></th>
<th>NCPAP without surfactant</th>
<th>NCPAP with surfactant</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>31± 2.0</td>
<td>30.4 ± 1.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex (F.M)</td>
<td>15.25</td>
<td>15.25</td>
<td>1.000</td>
</tr>
<tr>
<td>APGAR score</td>
<td>7</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1345± 542</td>
<td>1357±395</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antenatal Steroids (%)</td>
<td>69</td>
<td>67</td>
<td>0.48</td>
</tr>
<tr>
<td>Delivery (c.s-VD)</td>
<td>21.19</td>
<td>15.25</td>
<td>0.261</td>
</tr>
<tr>
<td><strong>RDS severity (%) base on</strong></td>
<td><strong>32.5 42.5 25.0</strong></td>
<td><strong>37.5 35.0 27.5</strong></td>
<td>0.786</td>
</tr>
</tbody>
</table>

**CXR (severe.moderate.mild)**

F: female, M: male, C.S: Cesarean Section, VD: Vaginal delivery

**Table 2.** Clinical outcomes in the patient's receiving NCPAP with and without surfactant after following for a week

<table>
<thead>
<tr>
<th></th>
<th>NCPAP without surfactant</th>
<th>NCPAP with surfactant</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7 (17.5%)</td>
<td>4 (10%)</td>
<td>0.517</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6 (15%)</td>
<td>4 (10%)</td>
<td>0.737</td>
</tr>
<tr>
<td>Icterus</td>
<td>6 (15.0%)</td>
<td>3 (7.5%)</td>
<td>0.481</td>
</tr>
<tr>
<td>Brain hemorrhage</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>PDA</td>
<td>6 (15.0%)</td>
<td>2 (5.0%)</td>
<td>0.263</td>
</tr>
<tr>
<td>Lung hemorrhage</td>
<td>3 (7.5%)</td>
<td>3 (7.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2 (5.0%)</td>
<td>2 (5.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>DIC</strong></td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

PDA: Patent Ductus Arteriosus; DIC: disseminated intravascular coagulation