

## Comparison of Nasal Continuous Positive Airway Pressure Therapy With and Without Prophylactic Surfactant in Preterm Neonates

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**Abstract:** Preterm babies are at risk of respiratory distress syndrome (RDS) and require mechanical ventilation (MV) and surfactant for living. A method of MV is continuous positive airway pressure (CPAP) especially for neonates is Nasal CPAP in which surfactant is administered to them via tracheal instillation. The aim of present study was comparing nasal continuous positive airway pressure NCPAP therapy with and without prophylactic surfactant in preterm neonates. This is a randomized clinical trial study performed on eighty newborns (28-34 weeks) whom were born in Ali-ebne-Abitaleb hospital affiliated to Zahedan University of Medical Sciences from October 2008 to September 2010. Subjects were randomly classified into groups whom received nasal CPAP with or without surfactant (40 patients in each group). Factors for entrance to research were including approved RDS, gestational age less than 34 weeks and neonates 72 hours after delivery. The data collected through direct observation and 14 purposeful items by researcher. Both groups received surfactant (Curosurf, Parma, Italy) at 100mg/kg/24hours or 4ml/kg/24hours with NCPAP and NCPAP alone. The data analysis were conducted through the Statistical Package for Social Sciences (SPSS) 17.00 and followed by Crosstab (Pearson Chi-square). Results revealed that six neonates who received only NCPAP and four patients who received NCAPA and surfactant underwent MV. After a week follow up, 33 neonates who received only NCPAP and 36 patients who received CPAP and prophylactic surfactant remained alive. There was no significant difference between the groups regarding adverse outcomes ( $P=0.518$ ). According to the results of this study, NCPAP is indictable as a safe protocol for RDS in preterm neonates. Further research is required to clarify and validate our findings.

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### Introduction

Respiratory distress syndrome (RDS) is the single most important cause of mortality and morbidity in preterm infant. During the last 50 years significant and conclusive progress has been made in the understanding of the etiology and pathology of this syndrome as well as treatment, while the optimal treatment regimen is still controversial and under discussion. (Reference). Preterm neonates with RDS which is a condition of pulmonary insufficiency, require MV for living. Oxygen should be restricted (Saugstad, 2001) and the oxygen tension should be carefully monitored (Askie *et al.*, 2003). However, MV in itself may induce varying degree of lung injury, with epithelial disruption followed by fluid leakage and inflammatory response that can inactivate surfactant (Dreyfuss and Sauon, 1998; Parker, Hernandez and peevy, 1993). Furthermore, MV has been implicated as the single most important risk factor for the later development of bronchopulmonary dysplasia (BPD) (Bohlin *et al.*, 2007). Efforts had to

made to decrease the utilization of MV at the first days of life to prevent barotraumas and to reduce the severity of BPD. The important factors to be considered are 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) randomized controlled trial of surfactant instillation during NCPAP demonstrated that in newborns with moderate-to-severe RDS, the need for subsequent MV could be reduced by 50% after a single dose of surfactant. The introduction of NCPAP improved the treatment and reduced the mortality rate due to RDS (Dunn, 1974; Gregory *et al.*, 1971; Rhodes & Hall, 1973) because it is the first line of therapy for very low-birth-weight newborns and many infants can be successfully managed without MV (kamper, Wulff, Larsen, Lindequist, 1993; Jonsson *et al.*, 1997). The administration of exogenous surfactants improves oxygenation and decreases neonatal mortality rates among affected newborn infants (Soll & Ozek, 2010;

Soll, 2000). The effectiveness of combined treatment of NCPAP and surfactant has been demonstrated (Verder *et al.*, 1999; Verder *et al.*, 1994). Surfactant therapy combined with 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 (Poulain 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 benefits: no need for intubation or sedative and paralytic agents and 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 be improved by concomitant administration of surfactant (De Paoli, Cooke, Gupta, 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 progresses 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.

### Materials and methods

This is a randomized clinical trial study which was performed on 80 preterm infants (28-34 weeks) at Ali- ebn- Abitaleb Hospital Affiliated to Zahedan University of Medical Sciences, at Zahedan City from October 2008 to September 2010. Zahedan is the center of Sistan and Balouchestan Province in the southeast of Iran, which located on the North of Oman Sea and has a common long border with Pakistan and Afghanistan in the east. The sample size was computed based on results of a previous studies e.g Gregory *et al.*(1971) performed their studies with 20 infants and Verder, 1994 did his study with eleven neonates. Using these information and results, the research sample was calculated 27 neonates for each group but the researchers allocated 40 neonates for each one to gain more valid and reliable data. The subjects were randomly assigned into groups to receive NCPAP alone and with surfactant. The entire 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 MV and surfactant (Verder, 2010). The criteria included: 1/approved RDS, 2/gestational age less than 34 weeks, 3/ neonates

72 hours after delivery. The excluding criteria were: neonates with APGAR score <3, 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 observation and 14 purposeful items by researcher. Both groups received surfactant (Curosurf; Chiesi Farmaceutici, Parma, Italy) at 100mg/kg/24hours or 4ml/kg/24hours with NCPAP and NCPAP alone in the delivery room immediately after birth. Curosurf Vials were prepared products 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 catheter F5 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 followed for seven days up and the need for mechanical ventilation, death and adverse outcomes. Pneumothorax, brain hemorrhage, lung hemorrhage, icter, patent ductus 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 a decrease in the oxygen tension ratio to less than 0.15. Median system (Germany) were used for NCPAP. Positive end-expiratory pressure (PEEP) was set between 4 to 6 cmH<sub>2</sub>O and FiO<sub>2</sub><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) 17.00 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. Informed consents were obtained from all the parents. This study was approved by Ethical Committee of Zahedan University of Medical Sciences (Zahedan, Iran).

### Results

Eighty preterm neonates were enrolled in the study; 40 in the NCPAP therapy group and 40 in 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 6 patients of CPAP group and 4 patients who received surfactant had undergone mechanical ventilation. Although the

number of patients who undergone mechanical ventilation was higher in CPAP without surfactant than CPAP with surfactant, but statistically no significant (0.737).

After following 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 alive. There was no statistically significant difference between the groups ( $p=0.518$ ). In addition the results showed no significant difference between the groups regarding pneumothorax, brain hemorrhage, lung hemorrhage, icter, PDA and DIC.

Table 1: demographic and clinical characteristics of the study population.

	NCPAP without surfactant	NCPAP with surfactant	P-value
Gestational age (weeks)	31± 2.0	30.4 ± 1.8	<0.01
Sex (F/M)	15.25	15.25	1.000
APGAR score	7	8	-
Birth weight (g)	1345± 542	1357±395	<0.01
Antenatal Steroids(%)	69	67	0.48
Delivery (c/s-VD)	21.19	15.25	0.261
RDS severity (%) base on CXR (severe/moderate/mild)	32.5/42.5/25.0	37.5/35.0/27.5	0.786

F:female, M:male,C/S:cesarean section, VD: vaginal delivery

Table2: Clinical outcomes in the patient's receiving NCPAP with and without surfactant after following for a week.

	NCPAP without surfactant n=40	NCPAP with surfactant n=40	P-value
Death	7 (17.5%)	4 (10%)	0.517
Mechanical ventilation	6 (15%)	4 (10%)	0.737
Icter	6 (15.0%)	3 (7.5%)	0.481
Brain hemorrhage	1 (2.5%)	0 (0.0%)	1.000
PDA	6 (15.0%)	2 (5.0%)	0.263
Lung hemorrhage	3 (7.5%)	3 (7.5%)	1.000
Pneumothorax	2 (5.0%)	2 (5.0%)	1.000
DIC	1 (2.5%)	1 (2.5%)	1.000

PDA: Patent ductus arteriosus; DIC: disseminated intravascular coagulation

## Discussion

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

endotracheal tube which can have associated complications such as subglottic stenosis and respiratory infections. In the present study we evaluated nasal continuous positive airway pressure (CPAP) therapy with and without prophylactic surfactant in preterm infant in Zahedan, Iran. Our findings showed no significant difference between the groups regarding adverse outcomes. In preterm infants, surfactant deficiency as well as premature lungs does not have sufficient alveoli to independently 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 that NCPAP is a safe treatment procedure with no increase in short-term (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) morbidities. Several small studies have indicated improved respiratory outcomes when surfactant administration has been followed by extubation to CPAP at birth (Blennow *et al.*, 1999; Verder *et al.*, 1999). In spite of some advances in perinatal management of neonatal RDS, controversies still exist. 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 <30 weeks' gestational age with RDS.

There is growing evidence indicating that early CPAP from birth is feasible and safe in preterm infants. Though, many infants will develop RDS and require surfactant treatment (Bohlin, 2012).

Ammari *et al.* (Ammari *et al.*, 2005) reported that 76% of spontaneously breathing preterm babies with RDS with birth weight <1250 g could be managed with CPAP alone. Because 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 did not support the routine use of intubation solely to administer surfactant in large preterm infants with mild to moderate RDS (Khosravi and Mohagheghi, 2008).

In conclusion, in the present study, researchers found that the adverse outcomes and death were not statistically different between CPAP therapy with and without prophylactic surfactant in preterm infant. Regarding the cost and experts for surfactant administering, NCPAP can be used as a safe prophylactic procedure for preterm neonates with RDS particularly in developing countries. Larger studies are required to validate our findings.

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