



Factors Influencing the Success of Using Nasal Continuous Positive Airway Pressure in Neonates 28-34 Weeks' Gestation with Respiratory Distress Syndrome

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Abstract: *Premature babies are a serious problem worldwide, with 15 million births annually and more than one million dying from premature complications. Respiratory distress syndrome (RDS) is the most common cause of morbidity and mortality in neonates (44%), almost >70% require a breathing apparatus. Nasal Continuous positive airway pressure (NCPAP) is the recommended breathing apparatus for the management of RDS, but not all of them are successfully treated with NCPAP. This study aims to determine the factors that influence the success of using NCPAP in infants aged 28-34 weeks with RDS. This study is an analytical observational study with a prospective design in infants born at Hasan Sadikin Hospital Bandung in August to November 2018 with a gestational age of 28-34 weeks and experiencing RDS. Subjects who met the inclusion and exclusion criteria had NCPAP installed and evaluated. A total of 83 research subjects found the NCPAP success rate was 45.8%. Respiratory distress syndrome was more common in male infants 57.8%. Maximum baby weight 1500 grams 53 (63.9%), mean gestational age 32 weeks. Gestational age, antenatal steroid administration and grade of RDS based on chest X-ray were factors that significantly influenced the success of using NCPAP ($p < 0.05$). After controlling for gestational age, administration of antenatal steroids and the degree of RDS, there was a significant relationship between the success of NCPAP and the administration of antenatal steroids OR_{adj} 4.67 ($p = 0.043$) and the degree of RDS with the success of NCPAP OR_{adj} 21.25 ($p = 0.001$). The degree of RDS based on chest X-ray and antenatal steroid administration were factors that significantly affected the success of NCPAP.*

Keywords: RDS; NCPAP; success

I. Introduction

Premature babies are a serious problem worldwide because they are the biggest cause of morbidity and mortality in this vulnerable group. According to the World Health Organization (WHO) in 2015 the most deaths of children under 5 years were neonates, namely 46% and an increase from 40% in 1990 with the main cause of death being complications from premature birth. WHO data in 2015 found that the number of premature births in Indonesia was 15.5% of live births, ranked 5th out of 11 countries in the world with a preterm birth rate above 15% (Biro Pusat Statistika, 2015).

Respiratory distress syndrome (RDS) is a respiratory disorder disease that occurs due to surfactant deficiency which functions to lower the surface pressure of the alveoli and keep the alveoli from collapsing (Schmolzer, GM, 2013; Wright, CJ, 2018). Respiratory distress syndrome (RDS) is the most common complication in premature infants, which is about 50% (WHO, 2014). Respiratory distress syndrome is the most common cause of morbidity and mortality in premature infants. Data from Hasan Sadikin Hospital in Bandung in 2017 found that the neonatal mortality rate was 7.8% of live births,

6.9% of live births were premature neonates, 14% of neonates experienced respiratory distress. This number increased in 2018 due to the 2012 RI Minister of Health regulation concerning tiered referrals,

Respiratory distress syndrome occurs 60%-80% in infants less than 28 weeks' gestation, 15%-20% at 32 to 36 weeks' gestation. Every year 40,000 infants suffer from RDS in the United States and almost 20% cause death. The incidence of RDS is also strongly influenced by gestational age and body weight. Data from the United States that the incidence of RDS in body weight between 501 grams to 750 grams 86%, body weight 751 grams to 1000 grams 79%, body weight 1001 grams to 1250 grams 48%, body weight 1251 grams to 1500 grams 27% (WHO, 2014; Morris, 1, 2012). Risk factors for RDS increase in young pregnant women, mothers who smoke, consume alcohol and drugs, low socioeconomic status, poor nutrition during pregnancy, irregular antenatal care, pregnant women with diabetes, multiple pregnancies, cesarean delivery, as well as infant asphyxia, and hypothermia (WHO, 2014; Morris, 2012; Reuter, S, 2014). Birth by cesarean section is one of the risk factors for RDS because in the delivery process perv. There is an increase in surfactant production and fluid expulsion from the alveoli with the formation of β -adrenergic, prostaglandins and chest compressions in the first stage of labor, and this stage is not found in the process of cesarean delivery. Increasing gestational age causes an increase in the concentration of surfactants and endogenous glucocorticoids which can reduce the risk of RDS (Wright, CJ, 2018).

Respiratory distress syndrome is managed with exogenous surfactant administration and mechanical ventilation, but surfactant administration has limitations, especially in developing countries because of the high cost, the administration may have to be repeated, and the technique of administration requires special skills (Kamath, BD, 2011; Murki, S, 2014). The use of mechanical ventilation with high oxygen concentrations causes the release of proinflammatory cytokines that impair surfactant function, lung overdistention causes lung damage and progresses to bronchopulmonary dysplasia (BPD) (Bohlin, K. 2012). As a result of this, a strategy is needed in the management of RDS to minimize lung damage with a non-invasive method in the form of Continuous positive airway pressure (CPAP) (WHO, 2014; Dargaville, PA, 2016).

Continuous positive airway pressure is a non-invasive method of respiratory ventilation that provides constant positive pressure in the airways throughout the spontaneous breathing cycle. The positive pressure that CPAP exerts on the lungs during expiration will improve the recruitment of alveolar stability so as to prevent alveoli from collapsing, improve functional residual capacity and improve oxygenation. The use of CPAP can also artificially increase pulmonary pressure in the expiratory phase of spontaneously breathing infants. Spontaneous breathing with positive pressure maintained throughout the respiratory cycle is termed continuous positive airway pressure (CPAP) (Dargaville, PA, 2014; Pillai, M, 2011).

Not all RDS patients were successfully treated with CPAP. Research in New Zealand by Dargaville and colleagues found a success rate of using CPAP 57% (25-28 weeks) and 75% (29-32 weeks). which is incomplete. The severity of RDS was based on a chest X-ray. This study divided into two groups, namely the group that was successfully treated with CPAP and the group that failed to use CPAP within 72 hours after birth (Dargaville, PA, 2016).

Pillai and colleagues conducted a study in New Delhi in 2007 to find predictors of CPAP failure, and produced a clinical scoring system for CPAP success consisting of several variables, namely: gestational age, premature rupture of membranes, use of antenatal steroids and initial setting of CPAP in the form of PEEP and FIO₂ (Pillai, M,

2011). A study by Rastogi in New York found that weight and gestational age were factors that greatly influenced the success of CPAP weaning. Prevention of chorio amnitis, identification and prevention of maternal anemia are factors that influence the duration of CPAP use (Rastogi, S, 2012). Research in India by Ballaji and colleagues found that CPAP in newborns with RDS reduced mortality from 33% to 14.9%, but another study stated that newborns with RDS even though CPAP was given could still cause death. Various factors that play a role in this are infant factors such as birth weight, incidence of infection, prematurity, time to start giving CPAP > 5 hours after birth. The degree of RDS, asphyxia also contributes to the risk factors for infants. Other influencing factors are antenatal steroid administration and surfactant administration (Balaji RVJ, 2015). Research in Thailand by Sahussarungsi (2017) found risk factors that were predictors of successful use of CPAP in the form of gestational age, birth weight, sex, use of antenatal steroids, the degree of RDS based on chest X-ray and infection. Based on the above background, this study aims to determine the risk factors that influence the successful use of CPAP in premature infants aged 28-34 weeks with respiratory distress syndrome. The multidimensionality of stress, according to Yakubu in Orji, (2020), is evidence by the fact that it takes different forms and it concern different fields, for example, Clinical and Applied Psychology, Anthropology, Sociology, Psychosomatic Medicine, Industrial Relations and Epidemiology.

II. Research Methods

This study is an analytical observational study with a prospective cohort design carried out from August to November 2018 in infants born at Hasan Sadikin Hospital, Bandung at 28-34 weeks of gestation experiencing respiratory distress syndrome and using CPAP. Patients with major congenital abnormalities were not included in the study, the selection of subjects was done without randomization. In the research subjects, nasal CPAP was installed using a nasal prong interface that was suitable for the size of the baby, routine blood laboratory examinations and chest X-ray examinations were carried out. Then the research subjects were treated according to the applicable management procedures in dr. Hasan Sadikin. After that, the risk factors that influence the success of using CPAP in infants with RDS were evaluated. The research began after obtaining approval from the Health Research Ethics Committee, Faculty of Medicine, Padjadjaran University RS. Dr. Hasan Sadikin Bandung.

III. Results and Discussion

3.1 Results

During the study period, there were 192 babies born with gestational age 28-34 weeks 6 days, 87 patients with respiratory distress syndrome were found according to the inclusion criteria, using a breathing apparatus in the form of NCPAP, 2 study subjects were included in the exclusion criteria with multiple congenital anomalies.. Subjects were followed from birth to 72 hours of age and observed whether the subjects managed to escape NCPAP based on improvement in clinical symptoms and ability to breathe without using NCPAP, which were then categorized into the NCPAP successful group. Subjects who were still using NCPAP for more than 72 hours or had worsening symptoms before 72 hours and had to use mechanical ventilation were categorized into the NCPAP failure group.

Table 1. Characteristics of Premature Infants with RGS 28-34 Weeks Gestation

Characteristics	n=83 (%)
Preterm Infants	
Gender, n (%)	
Man	48 (57.8)
Woman	35 (42.2)
Mode of delivery, n (%)	
Pervaginal	32 (38.6)
Forceps extraction	2 (2,4)
Sectio caesarean	49 (59.0)
Birth weight (g)	
<1000	5 (6.0)
1000-<1500	25 (30.1)
≥ 1500	53 (63.9)
Average (SD): 1610.2 (385.3)	
Range: 900-2300	
Gestational Age (weeks)	
28-32	47 (56.6)
33-34	36, (43,4)
Average (SD): 32.0 (1.9)	
Range: 28-34	
Antenatal Steroids	
Complete 4x	16 (19.3)
Incomplete (<4x)	10 (12)
There is not any	57 (68.7)
RGS degree	
I	64 (76.3)
II	19 (23.7)
III	-
IV	-
Down Score	
4	34 (40.9)
5	38 (45.8)
6	11 (13.3)

Table 2. Relationship of Various Factors with Success CPAP

Characteristics	CPAP success		p value*
	Successful n (%)	Not successful n (%)	
Gender			
Man	25 (52)	23 (48)	0.177
Woman	13 (37)	22(63)	
How to give birth			
Peraginam	15 (47)	17 (53)	0.421
Forcep Extraction	0	2 (100)	
Sectio Carea	23 (47)	26 (53)	
Birth weight (g)			
<1000	1 (20)	4 (80)	0.084
1000-<1500	8 (32)	17 (68)	
1500	29 (55)	24 (45)	
Average (SD)	1733,2(361,9)	1506.4 (377.4)	
Range	900-2300	900-2130	
Gestational Age (weeks)	17 (36)	30 (64)	0.045

28-32	21 (58)	15 (42)	
33-34	32.4 (1.8)	31.6 (1.9)	
Average (SD)	28-34	28-34	
Range			
Antenatal Steroids			
Complete 4x	12 (75)	4 (25)	0.046
Incomplete (<4x)	5 (50)	5 (50)	
There is not any	20 (35)	37 (65)	
RGS degree			
I	39 (59)	25 (41)	<0.001
II	2 (10)	17 (90)	

Note: *) Based on Chi-Square Test; means if p<0.5

The table above shows that the risk factors that influence the success of NCPAP are gestational age, antenatal steroid administration and the degree of RDS based on a chest X-ray, with Chi-square test $P < 0.05$ while gender, mode of delivery and birth weight do not affect the success of using NCPAP. P value > 0.05 . Antenatal steroid administration and the degree of respiratory distress syndrome based on chest X-ray greatly affect the success rate of NCPAP. In this study, 16 (19.3%) subjects received complete antenatal steroids, namely steroids 4 times before parturition with a success rate of 12 (75%) NCPAP and 10 (12.0%) incomplete steroid subjects < 4 times with success rates. NCPAP 5 (50%) and 57 (68.7%) study subjects did not receive steroids and the NCPAP success rate was 20 (35%).

Table 3. Multivariable Analysis of Factors that Influence CPAP Outcomes

Variables	Coefficient (B)	SE (B)	p	Adjusted OR (95%CI)
Early Models:				
Gender:				
Man	0.220	0.586	0.707	1,246 (0.395-3.928)
Weight (g)				
< 1500	0.487	1.395	0.727	1.627 (0.1062-5.065)
> 1500	0.298	1.463	0.839	1.347 (0.077-23.691)
Gestational Age:				
33-34 weeks	0.753	0.658	0.253	2.124 (0.584-7.719)
Antenatal Steroids:				
Incomplete (<4x)	-1,220	0.953	0.201	0.295 0.046-1.912)
Complete (4X)	1,937	0.970	0.046	6,941 (1,037-46,467)
RGS degree				
Degree I	2,771	0.944	0.003	15,971 (2,509-101,671)
Final Model:				
Antenatal Steroids:				
Incomplete (<4x)	-1,435	0.887	0.106	0.238 (0.042-1.354)
Complete (4x)	1,536	0.893	0.043	4,647(1.00-26,721)
RGS degree				
Degree I	3.069	0.898	0.001	21.526 (3.706-125.039)

Information: ROadj (95 %): Adjusted Odds ratio and 95% confidence interval

Table 3 shows multiple logistic regression analysis of 6 variables that have a p value < 0.25 based on bivariable analysis (table 4.2 and table 4.3), obtained two variables that are simultaneously associated with the success of NCPAP, namely steroid use and the degree of RDS based on x-rays. From the table above, it can be concluded that the use of complete steroids (4x) has NCPAP success of 4,627 times when compared to using incomplete steroids. For grade I RDS based on X-ray results, the success is 21.52 times compared to grade II RDS.

This study found that patients who experienced RDS were more male than female as many as 48 (57.8%), this is in accordance with previous research by Anadkat js, et al in 2012 that male infants more often experience RDS caused by hormonal differences that regulate lung maturation (Anadkat, JS, 2012).

Respiratory distress syndrome (RDS) is one of the complications of preterm birth due to surfactant deficiency, and is the most common cause of mortality and morbidity. The incidence and severity of RDS generally increase with advancing gestational age (Whitsett JA, 2016; Weinert DM, 2015).

In this study, gestational age was categorized into two groups, namely 28-32 weeks and 33-34 weeks based on WHO criteria with an average value of 32 weeks and it was found that the most experienced RDS was the 28–32-week gestational age group, which was 56.6%. These results are in accordance with research by Halliday HI et al, in Philadelphia (2010) that the younger the gestational age, the higher the incidence of RDS. The incidence of RDS in a row is 90% at 26 weeks' gestation, 80% at 28 weeks' gestation, 70% at 30 weeks' gestation, 55% at 32 weeks' gestation, 25% at 34 weeks' gestation and 12% at 36 weeks' gestation. week. The success rate of CPAP based on gestational age in this study was 17 subjects (36%) for 28-32 weeks' gestation and 21 subjects (58%) for 33-34 weeks' gestation and it was found that there was a significant difference in the success of using CPAP in RDS based on age. gestational age with $P < 0.05$, but after multivariate analysis it was found that gestational age did not affect the success of using NCPAP in RDS with $p = 0.25$. The results of the above study are in accordance with Dargaville, et al in 2016 that the success rate for NCPAP is greater at higher gestational ages, namely at 32-33 weeks of gestation with a success rate of 79% (Dargaville PA, 2016). Tod et al also found similar results for the high success rate of NCPAP in the 31.9 age group The results of the above study are in accordance with Dargaville, et al in 2016 that the success rate for NCPAP is greater at higher gestational ages, namely at 32-33 weeks of gestation with a success rate of 79% (Dargaville PA, 2016). Tod et al also found similar results for the high success rate of NCPAP in the 31.9 age group The results of the above study are in accordance with Dargaville, et al in 2016 that the success rate for NCPAP is greater at higher gestational ages, namely at 32-33 weeks of gestation with a success rate of 79% (Dargaville PA, 2016). Tod et al also found similar results for the high success rate of NCPAP in the 31.9 age group ± 0.1 weeks, as well as an RCT study by Rastogi et al in 2013 that the NCPAP success rate was highest at 33.8 gestational age ± 2.6 weeks (Todd, DA, 2012; Respiratory Management, 2013).

Surfactants contain phospholipids which are needed to lower the surface tension of the alveoli and prevent alveolar collapse. One of the phospholipid contents is lecithin whose secretion in the fetal lung increases after 32-33 weeks' gestation (Clair, C, 2008). The increase in lecithin is able to reduce the incidence of RDS by increasing the surface tension of the alveoli, thereby increasing the success rate of using NCPAP in RDS. Research by Dargaville in 2013 also found the same thing as the study above that there was an increase in the duration of NCPAP use in premature infants with gestational age. ≤ 32 weeks (Dargaville PA, 2016). The incidence of RDS is not only influenced by gestational age but also by the baby's birth weight. A study in the United States in 2004 found that the incidence of RDS was 86% at birth weight 501-750 grams, 79% at birth weight 751-1000 grams, 48% at birth weight 1001-1250 grams and 27% for birth weight 1251-1500 grams (Intensive care nursery house staff manual, 2004).

This study found that the average birth weight of infants with RGS was 1610 grams, because the highest birth weight of premature babies in RSHS was 1500 grams. During the study period the number of subjects who experienced RGS based on body weight was for birth weight 1500 grams by 53 (63.9%), birth weight 1000 - < 1500 grams 25 subjects (30.1), birth weight <1000 grams (6%). The baby's birth weight clinically has an important role in the success of using NCPAP as well as gestational age, the smaller the baby's birth weight, the success rate of using NCPAP is also getting smaller, but in this study statistically it did not affect the success rate of CPAP with $P = 0.084$, this is This is

because in this study it was found that birth weight was not normally distributed. The results of this study differ from those of Pillai et al., 2011 which stated that premature infants with very low birth weight had a high risk of developing respiratory distress syndrome immediately after birth which required intubation and mechanical ventilation.

Scientifically giving antenatal steroids in addition to reducing the incidence of respiratory distress syndrome also reduces other complications of prematurity such as intraventricular haemorrhage (IVH). Cochrane analyzed 21 studies that found that pregnant women with a risk of premature birth if given a single dose of antenatal steroids could reduce the risk of death by 31%, the risk of RDS by 44% and the risk of IVH by 46%. Antenatal steroid administration also reduces the incidence of enterocolitan necrotization, reduces the use of breathing apparatus, and reduces the incidence of infection in the first 24 hours (Dargaville PA, 2013; Heljic, S, 2009). This study divided the administration of complete steroids (if given four times) before the baby was born, and incomplete (if given less than four times). Most of the research subjects did not receive steroids at all, as many as 68.6%, This is because the Hasan Sadikin Hospital in Bandung is a tertiary referral center in West Java so that pregnant women who come in emergency situations such as fetal distress, eclampsia, ante partum bleeding must take immediate action to save the mother and baby, and do not have the opportunity to give antenatal steroids. Research subjects who received incomplete steroids were 12.2% and complete steroids 19.2%.

The most common cause of premature infant death is RDS, which is caused by immaturity of the fetal lung, both in the form of immature lung structure and function. The immaturity of the fetal lung causes a decrease in surfactant production by type II alveolar cells leading to surfactant deficiency and the baby is born with RDS. Surfactants consist of 90% fat and 10% protein. Antenatal steroids used are betamethasone and dexamethasone.

It is a long-acting glucocorticoid with a different chemical structure and both can cross the placenta in their active form and are equally effective because they have a low affinity for maternal cortisol binding globulin, and only a small amount is eliminated by placental enzymes (Mercer, BM, 2009; Bannerman, CG, 2016; Faizah, RN, 2015). Betamethasone exists in two forms. namely betamethasone sodium phosphate with a half-life of 36-72 and betamethasone acetate suspension with a longer half-life. Injectable betamethasone in Indonesia is difficult to find and expensive, so dexamethasone is used for antenatal steroids at a dose of 6 mg given four times every 12 hours, to mimic endogenous corticosteroid exposure that occurs during pregnancy where the induction of endogenous cortisol in the mother occurs within 48 hours (Kamath, BD, 2011).

Neonates born by cesarean section, especially if there are no signs of labor, do not benefit from expulsion of lung fluid and compression of the chest and thus experience more persistent respiratory distress. Fetal chest compression in the second stage of labor pushes fluid out of the respiratory tract. The birth process by sectio secarea triggers the release of stress hormones in the mother which is the key to the maturation of the baby's lungs. The relatively large pressure generated by chest compressions during vaginal delivery is capable of pushing fluid into the fetal lungs equal to one-fourth of the functional residual capacity of the lungs. The thoracic compression that accompanies vaginal delivery and expansion of delivery are factors in favor of the initiation of respiration (Mwansa-JK, 2010; Brownfoot, FC, 2013; Wambach, JA, 2015).

3.2 Discussion

This study found that the rate of delivery by cesarean section of 49 (59%) is the most common type of delivery, vaginal 32 (38.6%) and delivery with the help of forceps extraction of 2 (2.4%). Statistically, the type of delivery was not associated with the

success rate of using NCPAP ($P=0.421$), multivariate analysis was not performed for this variable because the P value >0.25 . This study is in accordance with research by Sahusssarungsi, 2017 at Thammasat University Hospital that there is no significant relationship between the type of cesarean delivery and the success rate of NCPAP.

The results of this study are different from research by Reuter S, in 2014 which found that cesarean delivery increased the incidence of RDS in premature infants (Schuller RC, 2014). The difference in the results of this study may be due to the small number of samples in our study and the samples were not normally distributed, meaning that there was a large difference between the types of delivery of premature babies with respiratory distress syndrome at Hasan Sadikin Hospital, Bandung.

Radiologic features of RDS are highly variable and can represent the severity of RDS. Radiologically, it is characterized by the presence of atelectasis, air bronchograms and diffuse reticulogranular infiltration which may become severe with bilateral opacity called “white-out” (Whitsett JA, 2016; Weinert, DM, 2015). The typical radiographic appearance of RDS shows uniform alveolar collapse including a fine granular or ground-glass appearance with reduced lung volume. Radiological changes in RDS can occur immediately after birth, but can also occur in the first 6-12 hours of life, in uncomplicated cases, radiological abnormalities will improve in 3-4 days or faster when given surfactant. The results of the chest X-ray on the RDS show the severity of RDS (Weinert, DM, 2015). In this study, getting RDS grade I 65 (76, 3%) and RDS grade II of 19 (23.7%). The results were then performed bivariate analysis and found a significant difference between the severity of RDS based on chest X-ray on the success of using CPAP with $P<0.001$. These variables were then analysed multivariately and found that the severity of RDS based on chest X-ray greatly influenced the success rate of CPAP with $P=0.001$.

The results in this study are in accordance with a study conducted by Sahusssarungsi, 2017 at Thammasat University Hospital which found that the severity of RDS based on a chest X-ray significantly affected the success rate of CPAP in premature infants with RDS. The type of CPAP also plays a role in influencing the success of Weaning. A study by Shadkam et al in 2017 found that the duration of mechanical ventilation was shorter in patients using bubble CPAP compared to CPAP ventilators, but there was no significant difference in the complications caused in the two groups. a study by Gupta et al in 2015 comparing the effectiveness and safety of using bubble CPAP with infant flow driver CPAP in preterm infants after extubation found that the duration of CPAP use was significantly lower in the group using bubble CPAP (Grupta, N, 2015).

IV. Conclusion

Factors that greatly influence the success rate of using CPAP in premature infants aged 28-34 weeks with RDS are the use of antenatal steroids and the degree of RDS based on chest radiographs.

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