PEDIATRIC SCIENCES JOURNAL
The Official Journal of the Pediatric Department, Faculty of Medicine, Cairo University, Egypt

Original Article

Clinical Predictors for Outcome of Continuous Positive Airway Pressure in Respiratory Distress Syndrome in Preterms: Single Center Study

Amira M. Sabry*, Rana Saber Bastawy, Dalia Ahmed Khairy Abdullatif, Amira Abdel Fattah Edris, Mohamed S. El-Baz

Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt; ranasaber90.rs@gmail.com, dalkhairy@yahoo.com, amira_edris@yahoo.com, mbaz72@hotmail.com
* Correspondence: amirasabryelshafie@kasralainy.edu.eg,
Received: 24/10/2022; Accepted: 5/12/2022; Published online: 6/12/2022

Abstract:
Background: Applying mechanical ventilation (MV) to premature lungs carries many risks, up to lung injury and bronchopulmonary dysplasia. Stabilization with continuous positive airway pressure (CPAP) avoids intubation and invasiveness.
Aim of work: To evaluate the predictors of outcome of nasal CPAP on preterms with respiratory distress syndrome (RDS).
Material and Methods: This prospective observational study included all preterms with RDS that necessitated CPAP introduction (according to the European Consensus Guidelines on the Management of RDS), who were admitted to the Neonatal Intensive Care Unit (NICU) of Department of Pediatrics, Cairo University Hospitals, from February to July 2019. CPAP was initiated in the first 2 hours of life. Respiratory compromise was assessed using Silverman score. Hematological scoring system (HSS) was studied as a predictor of outcome. Those who did not need subsequent intubation were labeled CPAP success group and were compared to the group where CPAP failed.
Results: Over 6-months, 508 preterm with gestational age (GA) 27-33 weeks with RDS were admitted to our NICU, of them 61 (mean GA± SD of 32.08 ± 1.98 weeks) were included in the study. Of them 35 (57.4%) were males and 26 (42.6 %) females. CPAP was successful in 37 (60.7%) and Silverman score improved 2 hours after CPAP. Their initial median (IQR) of Silverman score was 5 (range 3-6) and improved to 1 (range 1-2) 2 hours after CPAP, while in the failure group, it was 6 (range 5-7) initially and worsened to 8 (range 7.5-9) (p=0.026). Antenatal steroids administration was highly protective (p= 0.000) but not GA p=0.086) or gender (p=0.521). Initial severe RDS in chest X-ray at birth was present in 1 (2.7 %) preterm in the CPAP success group and 10 (41.7 %) in the failure group (p=0.000). The systolic blood pressure ≤ 66, HSS, chest X-ray before CPAP, non-improvement of chest X-ray after CPAP and apnea were the important predictors for CPAP failure (p= 0.023), (p= 0.090), (p= 0.025), (p= 0.011) and (p= 0.049) respectively.
Conclusion: Trials of CPAP for preterms with severe RDS with hemodynamic stability are effective in obviating the need for more invasive MV. Factors including hypercarbia, apnea, poor respiratory efforts, systemic hypotension, higher Silverman score and HSS ≥5 were the most significant associations of failed CPAP.

Level of Evidence of Study: IIA (*1*)**.**
Keywords: nasal continuous positive airway pressure; CPAP; preterm; Respiratory distress syndrome.
Abbreviations: BPD: Bronchopulmonary dysplasia; CPAP: Continuous positive airway pressure; CPAP: nasal continuous positive airway pressure; FiO_2: fraction of inspired oxygen; GA: Gestational age; HSS: Hematological scoring system; MV: Mechanical ventilation; NICU: Neonatal intensive care unit; NRP: Neonatal resuscitation program; LMIC: low and middle income countries; PDA: patent ductus arteriosus; PPV: Positive pressure ventilation; RDS: Respiratory distress syndrome; RD: Respiratory distress; RSS: Respiratory scoring system; SLI: Sustained lung inflation; SBP: systolic blood pressure; SpO_2: Oxygen saturation.

Introduction

Respiratory distress syndrome (RDS) is the most common cause of admission in neonatal intensive care units (NICUs). Initial stabilization of preterms through management of the airway, breathing and circulation should be properly achieved (*2*). Support of newborn's respiratory system in delivery room is crucial according to Golden Hour principles (*3*). Neonatal Resuscitation Program (NRP) guidelines modified the use of oxygen and sustained lung inflation (SLI) in the delivery room, use of pulse oximetry and oxygen saturation targets to reduce lung injury and bronchopulmonary dysplasia (*4*). Continuous positive airway pressure (CPAP) is useful in preterms with RDS who are spontaneously breathing and its usage extends both in the early acute and late weaning/recovery phases of RDS. Frequency of atelectasis is reduced, owing to the reduction in the continuous distending pressure applied to the lungs, thus improving oxygenation and ventilation-perfusion matching (*5*). Nasal CPAP is the intervention of choice for preterms with RDS versus the combined regimen of endotracheal intubation, surfactant therapy and mechanical ventilation. Side effects of CPAP include pulmonary air leaks, abdominal insufflation, impaired cardiac output and pain (*6*). Successful use of CPAP on the first day of life is associated with lower risk of bronchopulmonary dysplasia (BPD) or death in very low birth weight infants, in addition to reduction in the risk of severe intraventricular hemorrhage, patent ductus arteriosus (PDA) requiring surgical ligation, days on mechanical ventilation with its associated complications like pneumothorax, pulmonary interstitial emphysema and ventilation acquired pneumonia (*7*). We aimed to evaluate the use of CPAP in preterms of 27- 33 weeks gestational age (GA) with RDS and to study the predictors associated with success/failure of CPAP.

Subjects and Methods

This prospective observational cohort study was conducted over a 6-months-duration (from February to July 2019), it included all preterm neonates who were admitted to the NICU of Department of Pediatrics, Cairo University Hospitals, and necessitated CPAP according to the European consensus guidelines for management of RDS in preterms (*8*). Our NICU is a tertiary referral center in Egypt. The NICU admits inborn preterms and neonates from the obstetrics department which averages 25,000 deliveries per year with a capacity of 45 incubators with a nurse: patient ratio of 1:3. An informed consent was taken from patients' guardians before enrollment with explanation of type of study. The study design conformed to the requirements of Revised Helsinki Declaration of Bioethics (2013) (*9*). The study was approved by The Scientific Committee of Pediatrics Department, Faculty of Medicine, Cairo University and Higher Studies Research Committee of Faculty of Medicine. Data were documented in the patients' files. Confidentiality on handling the database was guaranteed and privacy of participants was ensured.

Participants

Sixty one preterms were consecutively enrolled in the study. All the preterms included in the study were subjected to full history taking from their parents or caregivers including maternal history. GA, birth weight and APGAR scores at 1, 5 and 10 minutes were recorded. All preterms were subjected to the standard clinical evaluation. Recorded data included that of prescribed medications, feeding protocol, blood cultures and associated early complications of prematurity as early sepsis, intracranial hemorrhage, presence of patent ductus arteriosus (PDA) by echocardiography, and others.

Methods

The enrollment criteria were: 1) preterms with RDS not necessitating mechanical ventilation (MV). 2) CPAP started in first 2 hours after birth. 3) GA 27-33 weeks (calculated from date of last menstruation and early obstetric ultrasonography). The following preterms were excluded: full term neonates, neonates with RDS put initially on MV, meconium aspiration and any congenital anomalies affecting respiratory functions (e.g. diaphragmatic hernia and tracheoesophageal fistula). Preterms were categorized into 2 groups: Group (1): CPAP success group with successful CPAP treatment in the first 72 hours of life and Group (2) CPAP failure group who failed CPAP treatment and needed endotracheal intubation and MV within 72 hours of life with initial CPAP settings PEEP 5-7 cm H_2O, flow 6-8 L /min and 21-60% fraction of inspired oxygen (FiO_2).

Respiratory compromise was assessed using Silverman Andersen respiratory severity score (RSS) score for preterms. It evaluates five parameters of work of breathing and assigns an overall score, score 0= no respiratory distress (RD), 1-3= mild RD, 4-6 = moderate RD, >6 = impending respiratory failure and score 10= severe RD (*10*).

Oxygen saturation (SpO_2) targets after 10 minutes of age were 90-95%, we considered oxygen saturation 90% as a cutoff in comparing the 2 groups (*11*). SpO_2 readings were recorded continuously and non-invasively by using a pulse oximetry monitor (TFT Used Philips MP50 Patient Monitor LCD, Amsterdam, Netherlands).

Applying SLI Resuscitator: Neopuff (Fisher & Paykel Healthcare, New Zealand) SLI was employed in resuscitation of preterms < 32 weeks according to its availability and function at time of birth. A pressure-controlled (25 cmH_2O) inflation was sustained for 15 seconds after oropharyngeal and nasal suctioning, followed by the delivery of 6 cmH_2O CPAP via a neonatal mask and a T-piece ventilator (*12*).

Surfactant was administered via INSURE technique (intubate-surfactant-extubate), only according to the severity of RDS in chest X-ray.

Respiratory support protocol: CPAP was delivered using short binasal prongs with conventional ventilators SLE2000, UK (*13*) or via bubble CPAP Fisher & Paykel Healthcare bubble CPAP, New Zealand.

We used initial pressure of 4-5 cm H_2O and FiO_2 of 0.4-0.5. We targeted to maintain the oxygen saturation between 90-95% using the pressure and FIO_2, by increments of 1 cmH_2O up to a maximum of 7cm H_2O and increments in FiO_2 of 0.5 up to a maximum of 0.6. Adequacy of CPAP was monitored by Silverman score, chest expansion, oxygen saturation and radiologically by assessment of lung volume in chest X-ray.

The cut-off time of the study: We maintained strict monitoring of the preterms enrolled during the 72 hours after birth to detect our primary outcome which is CPAP failure, transfer to MV, to identify different risk factors and early complications of prematurity that can influence CPAP failure. Follow up was completed till 1 week of life to assess successful weaning from CPAP. Mortalities and total hospital stay were obtained from the records of the unit. Criteria of weaning from CPAP were: absence of RD and SpO_2 >90% and/or PaO_2 >7.6Kpa (which is equivalent to 57.01 mmHg), while on FiO_2 <0.25 (*14*).

CPAP Success: It was considered when clinical and radiological improvement occurs within 72 hours.

Failure of CPAP Weaning: if after 72 hours and success of CPAP, when weaning the preterms from the CPAP starts, if any of the following presented up to 7 days after CPAP removal, preterms will return back to CPAP: persistent tachypnea (>60/min for >2 hours) and marked retractions; apnea associated with bradycardia or cyanosis with >2 episodes in 12 hours or >3 in 24 hours necessitated bag and mask ventilation; increased O_2 requirement >0.21 to maintain the SpO2 >90% and abnormal blood gases with low pH <7.2, PaO_2 <50 mmHg and $PaCO_2$ >65 mmHg repeated twice (*15*).

CPAP Failure was considered: if the need of intubation and MV arises within the first 72 hours of life according to the following guidelines: Hypoxia (partial pressure of oxygen (PaO_2) <50mmHg; SpO_2 <85%), prolonged apnea (>20seconds) or recurrent apnea (> 2 episodes in 24hours), persistent/worsening RD (Silverman score >4), hypercarbia ($PaCO_2$ >65mmHg) and/or acidosis (pH <7.2) despite maximum CPAP pressure of 7cm H_2O, FiO_2 of 0.6 and systemic hypotension requiring vasopressors (*16*).

Laboratory studies: Capillary blood gases before and 2 hours after CPAP, complete blood count with differential count and blood cultures, and hematological scoring system (HSS) for sepsis of Rodwell was calculated for all the preterms enrolled in the study (*17*).

Imaging studies: Chest x-ray at birth, bedside echocardiography and cranial ultrasound were performed to all the preterms in the 1st 72 hours of life. According to chest X-ray findings 4 grades of RDS where identified according to classification for RDS (*18*). Hemodynamically significant PDA was considered if ≥3 of the following criteria were existing: blood pressure <3rd centile for GA, wide pulse pressure >25 mmHg, pulmonary edema or cardiomegaly evident in chest X-ray, serum lactate > 4 mg/dl and ductal size 3mm and left atrial-to-aortic root ratio >1.5 in echocardiography (*19*).

Statistical Analysis

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing 2 groups when normally distributed and Mann Whitney *U* test for independent samples when not normally distributed. For comparing categorical data, Chi square (x^2) test was performed. Exact test was used instead when the expected frequency is less than 5. *P*-values less than 0.05 were considered statistically significant. All statistical analyses were done using Statistical Package for the Social Science (SPSS); (SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

Over the 6-months duration of the study, 508 preterm with GA 27-33 weeks with RDS (various degrees) were admitted in NICU of Department of Pediatrics, Cairo University Hospitals. Of them 227 received MV in the delivery room or shortly after birth, 113 preterms were put on CPAP, and 168 preterms received high flow nasal cannula or nasal oxygen. The 113 preterms who received CPAP as an initial treatment were eligible to participate in the study, but 28 were excluded due to presence of congenital anomalies detected during the first week of life and 24 were subsequently excluded, 15 of them due to death in the first 24 hours of life and 9 preterms due to transfer to another unit, leaving a final sample size of 61. (Figure 1)

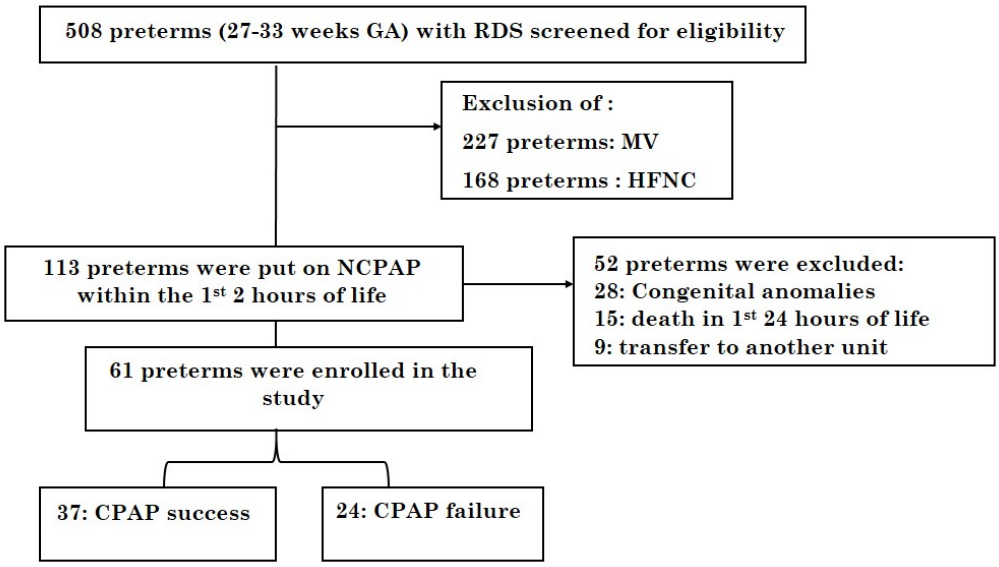

Figure 1. CONSORT flow diagram

RDS: respiratory distress syndrome; MV: mechanical ventilation; HFNC: high flow nasal cannula; CPAP: continuous nasal positive airway pressure

This prospective cohort study was conducted on a total of 61 preterms with RDS, where CPAP was initiated within 2 hours after birth in the NICU of department of Pediatrics, Cairo University Hospitals. The mean ± SD GA was 32.08 ± 1.98 weeks, and the mean (± SD) was birth weight (BW) was 1.73 ± 0.47 kg. Of them 35 preterms (57.4%) were males. 23 preterms (37.7%) were resuscitated by tactile stimulation, 35 (57.3%) using oxygen and only 3 preterms (4.9%) were resuscitated by positive pressure ventilation (PPV). SLI at resuscitation was performed to 9 preterms (14.8%). The median (IQR) Apgar score at 1 min was 6 (6-7) and 8 (8-9) at 5 min. CPAP was administrated through conventional ventilators in 57 (93.44%) preterms, and bubble CPAP was administrated in 4 (6.5%) preterms only.

The mean maternal age was 28.54 ± 5.11 years, 6.6% of mothers had diabetes mellitus, 27.9% had hypertension, 6.6% had antepartum hemorrhage and 52.5% of mothers received antenatal steroids. Only 19 (31.1%) preterms had hemodynamically significant PDA detected on bedside echocardiography and 5 preterms (8.1%) had grade I or II intracranial hemorrhage.

The mean ± SD GA in CPAP success group was 32.43 ± 1.79 weeks, while in CPAP failed group was 31.54 ± 2.17 weeks (p=0.086). Apgar scores at 1, 5 and 10 minutes were not of statistical difference between both groups. Usage of SLI at birth was not positively correlated to CPAP success. Also gender and birth weight were similar in both groups. Perinatal data is shown in table 1.

The 61 neonates were further divided into 2 groups, group (1) CPAP success group where CPAP was weaned successfully in the first 72 hours of life, included 37(60.6%) preterms and group (2) CPAP failure group that failed CPAP treatment and required endotracheal intubation and MV within 72 hours of life, it included 24 (39.3%) preterms. In failed CPAP group (24 preterms), the cause of intubation and transfer to MV was due to hypercarbia in blood gases in 5 preterms (20.8%), frequent apneas in 6 (25.0%), poor respiratory efforts in 11 preterms (45.8%) and tension pneumothorax in 2 preterms (8%). (Figure 2), (table 1). The antenatal history and maternal diseases was not different between the 2 groups except for the administration of antenatal steroids. Mothers of 27 preterms (73%) in the CPAP success group received antenatal steroids, while only 5(20.8%) in the CPAP failure group with a highly significant correlation (p= 0.0001).

Table 1. Perinatal Data in both groups

		Group 1 (CPAP Success) (Number= 37)	**Group 2** (CPAP Failure) (Number = 24)	**P-value**
GA in weeks (mean ± SD)		32.43 ± 1.79	31.54 ± 2.17	0.086
Birth weight in kg (mean ± SD)		1.76 ± 0.43	1.68 ± 0.54	0.521
Gender	Males	19 (51.4%)	16 (66.7%)	0.237
	Females	18 (48.6%)	8 (33.3%)	
Silverman score Median (IQR)		5 (3 – 6)	6 (5 – 7)	0.026
SLI at resuscitation		4 (10.8%)	5 (20.8%)	0.281
Apgar Scores Median (IQR)				
Apgar score at 1 minute		4 (3 – 5)	3.5 (3 – 4.5)	0.187
Apgar score at 5 minutes		6 (6 – 7)	6 (5.5 – 7)	0.589
Apgar score at 10 minutes		8 (8 – 9)	8 (7 – 8)	0.069

BW: birth weight; CPAP: continuous positive airway pressure; GA: gestational age; SLI: sustained lung inflation.

At time of CPAP application, the means ± SD of heart rate and initial capillary refill did not show a statistical significant difference between the 2 groups with p-values of 0.082, and 0.211 respectively, but the diastolic blood pressure was lower in the CPAP failure group, where its mean was 45.27± 9.01 in CPAP success group and 39.92 ± 10.57 in CPAP failure group (p= 0.038). The systolic blood pressure was significantly lower in the CPAP failure group with a p-value 0.001. Before CPAP initiation, only 1 preterm (2.7%) had oxygen saturation ≤ 90% in CPAP success group, while 7 preterms (29.9%) in CPAP failure group (p= 0.000). Severe RDS in chest x-ray at birth was detected in 1 (2.7 %) preterm in the CPAP success group and 10 (41.7 %) in the CPAP failure group before CPAP (p= 0.000). Surfactant therapy was administered to 13 preterms (54.2%) in the CPAP failure, however it did not show advantage and only 3 preterms (8.1%) in CPAP success group received surfactant. HSS for sepsis ≥ 5 was detected in 3 preterms (8.1%) in CPAP success group and in 7 preterms (29.2%) in CPAP failure group (p= 0.030). Positive blood cultures were encountered in 3 preterms in CPAP success group and 4 in CPAP failure group (p= 0.151). Presence of hemodynamically significant PDA detected by bedside echocardiography was present in 14 neonates (58.3%) in the failed group, compared to 5 neonates (13.5%) in the success group (p= 0.000). Initial FiO_2 was not different between the 2 groups, but 2 hours after CPAP, we had to increase the FiO_2 to improve the targeted oxygen saturation, so it showed a statistical higher significant levels in the CPAP failure group. All the parameters were demonstrated in Table 2. The FIO_2 threshold was increased in CPAP failure group 2 hours after applying CPAP, where the mean ±SD FIO_2 after 2 hours was 22.73 ± 3.6 in CPAP success group and 35.92 ± 6.83 in CPAP failure group (p= 0.000). (Figure 3). Among our primary outcomes, median Silverman score before CPAP was 5 in CPAP success group and 6 in CPAP failure group (p= 0.026) and preterms in CPAP failure group got worse after 2 hours, and accordingly their Silverman score worsened till became 8 in CPAP failure group and improved in CPAP success group (p= 0.000). (Figure 3).

Table 2. Parameters of Capillary blood gases and CPAP

	Group (1) CPAP Success (No.=37)	**Group (2)** CPAP Failure (No.=24)	**P value**
Blood gases parameters (mean± SD)			
Initial PH before CPAP	7.27 ± 0.09	7.26 ± 0.1	0.709
Initial HCO_3 before CPAP	17.78 ± 3.15	20.14 ± 4.26	0.016
Initial PCO_2	39.49 ± 12.26	43.8 ± 8.5	0.138
PH after 2 hours	7.35 ± 0.06	7.27 ± 0.08	0.000
HCO_3 after 2 hours	19.32 ± 3.03	19.9 ± 3.3	0.488
PCO_2 after 2 hours	34.57 ± 6.37	45 ± 12.39	0.000
CPAP Parameters			
Initial FiO_2	37.16 ± 4.94	38.42 ± 3.45	0.283
Initial PEEP	6.05 ± 0.52	6.17 ± 0.38	0.368
Initial flow	5.35 ± 0.72	6.08 ± 0.78	0.000
FIO_2 after 2 hours	22.73 ± 3.6	35.92 ± 6.83	0.000
PEEP after 2 hours	5.08 ± 0.36	6.04 ± 0.69	0.000
Flow after 2 hours	3.24 ± 1.42	5.56 ± 1.35	0.000

CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; PEEP: positive end expiratory pressure

Table 3. Causes of Transfer to mechanical ventilation

	Failure (No. = 24)	**Success (No. = 37)**	**P-value**
Hypoxia	1 (4.2%)	0 (0.0%)	0.211
Hypercarbia	6 (25.0%)	0 (0.0%)	0.001
Prolonged capillary refill time	10 (41.7%)	1 (2.7%)	0.000
Apnea	6 (25.0%)	1 (2.7%)	0.008
Systemic hypotension requiring vasopressors	11 (45.8%)	2 (5.4%)	0.000
Poor respiratory efforts	20 (83.3%)	3 (8.1%)	0.000
Pneumothorax	2 (8.3%)	0 (0.0%)	0.074
Pneumonia	0 (0.0%)	1 (2.7%)	0.417

MV: mechanical ventilation

The median (IQR) of duration of NICU stay was 11 (9 -15) days in CPAP success group and 15 (6.5 – 20.5) days in CPAP failure group (p= 0.024). Only 1(2.7 %) preterm died in CPAP success group, while 9 (37.5 %) preterms died in CPAP failure group (p= 0.000). The univariate logistic regression analysis showed that there was statistically significant association between CPAP failure and all parameters entered to the model. Also the multivariate analysis shows that the chest X ray after CPAP, SBP ≤ 66, chest X-ray before CPAP and apnea were the important predictors for CPAP failure with odds ratio and 95% CI of 0.099 (0.017 – 0.587), 52.689 (1.715 – 161.995), 10.678 (1.340 – 85.105) and 4.427 (1.033 – 18.458), respectively. (Table 3).

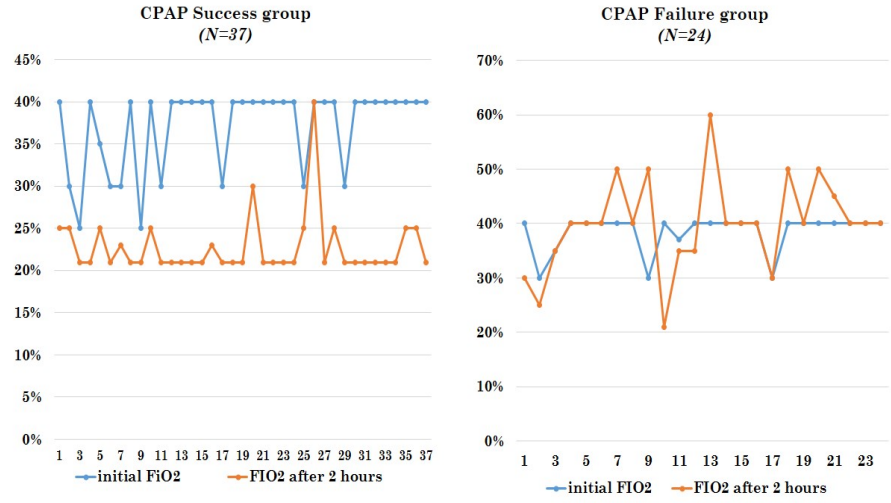

Figure 2. Initial fraction index of oxygenation (FiO_2) and after 2 hours in both groups

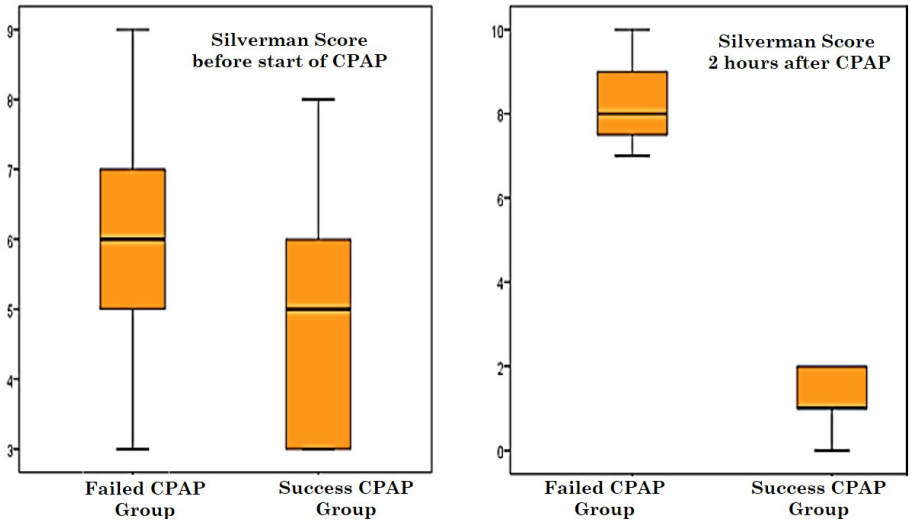

Figure 3. Silverman scores in both studied groups.

Table 3. Univariate and multivariate analysis for predictors of CPAP failure.

	Univariate analysis		Multivariate analysis	
	P value	**OR** (95% C.I. for OR)	**P value**	**OR** (95% C.I. for OR)
Systolic BP ≤ 66	0.000	8.571(2.629 – 27.950)	0.023	52.689 (1.715 – 161.995)
Oxygen saturation ≤ 90% before CPAP	0.000	0.284 (0.156 – 0.518)	0.011	0.099 (0.017 – 0.587)
Silverman score before CPAP > 5	0.023	3.562 (1.188 – 10.678)	0.276	0.073 (0.001 – 8.119)
HSS ≥ 5	0.040	4.667 (1.070 – 20.347)	0.090	10.856 (0.689 – 170.946)
Significant PDA	0.001	8.960 (2.583 – 31.078)	0.056	95.014 (0.892 – 101.158)
Severe RDS in chest X-ray before CPAP	0.001	3.828 (1.751 – 8.370)	0.025	10.678 (1.340 – 85.105)
Frequent apneas	0.026	12.000 (1.341 – 107.363)	0.049	4.427 (1.033 – 18.457)

CPAP: continuous positive airway pressure

Discussion

Mechanical ventilation or CPAP may be used for early respiratory support in preterm infants. Similar rates of BPD or mortality were documented with both modalities. CPAP may help initially to avoid MV, however some preterms will end by needing subsequent intubation and surfactant therapy (*20*). CPAP delivered nasally was effective in obviating the need for MV in 60% of the studied cohort. Hence, it reduced the hospital stay, the known complications of MV as ventilator associated pneumonia, pulmonary interstitial emphysema (PIE) and higher incidence of BPD (*21*, *22*), and allowed the newborn to be discharged home promptly. We confronted some complications from the application of CPAP, but they were all handled easily, as obstruction of prongs from secretions, skin irritation from securing tapes to the face and around nostrils due to strapping and positioning.

Defining the factors that were associated with favorable response to CPAP among preterms with RDS were crucial to improve outcome and reduce complications. Of these factors the antenatal steroids were found to be associated with successful response to CPAP (p= 0.000). Our finding supports the previous published works (*23*). Steroids are given to pregnant women at risk of early labour, typically as 2 injections, sometimes given before planned preterm birth and in some cases repeated courses can be administrated (*23*, *24*). This intervention is responsible for acceleration of the fetal lungs maturation. More effort is needed to implement this practice among pregnant women at risk of early labour. It is to be noted, however that other maternal factors as age, diseases (diabetes mellitus and hypertension), or antepartum hemorrhage did not influence response to CPAP. These factors seem to be responsible for the preterm delivery (*25*). A larger scale study is needed to verify the true influence of these factors on RDS in the newborn and its outcome.

Surfactant therapy is another very well-recognized factor that helps fetal lungs maturation, and RDS outcome (*26*). It was not found to be a predictor of response to CPAP in our studied

cohort. Its role is undeniable, yet it seems that the outcome relies in multiple factors and not a single one. Contrary to others, in our study only nine preterms in both groups were resuscitated by sustained lung inflation (SLI) in the delivery room, 5 (20.8%) in the CPAP success group and 4 (10.8%) in the CPAP failure group (p= 0.281). Despite not being a predictor of response to CPAP its effect on outcome of RDS remains to be studied(*27*).

The severity of the RDS dictated the response to CPAP. The Silverman-Andersen Score used to assess severity of respiratory distress in preterm infants proved to be valuable in defining response to CPAP. Silverman score at birth and after 2 hours of CPAP was predictive of failure (p=0.026) and (p= 0.000). We found the Silverman-Andersen Score very useful in our study. Larger studies to validate its sensitivity and specificity as a predictor of outcome and as an indicator for initial CPAP or initial MV is awaited.

Mild and moderate degrees of RDS responded to CPAP better than severe RDS. Hemodynamically significant patent ductus arteriosus was associated with poor response, as well as the HSS > 5 for sepsis, and severe RDS in chest X-ray. Hemodynamic stability is an important factor that needs prompt diagnosis and management by a skilled clinician. The chest X-ray findings proved very valuable as a guide and predictor of response to CPAP. This highlights the importance of bedside echocardiography, chest X-ray and other imaging modalities in NICU.

Attention to oxygenation, settings of CPAP and acid base balance are paramount as our study revealed that the response to CPAP was not related to the initial FiO_2 requirement but to the increase in the FiO_2 during the next 2 hours after CPAP was initiated. Those with failed CPAP required more initial flow, more FiO_2, PEEP. Initial HCO_3 before CPAP, pH after 2 hours, and PCO_2 after 2 hours were also of significant value in failure group than success one (p =0.0.16), (p=0.000), (p=0.000). It seems that those with persistent acidosis within 2 hours of CPAP need to be studied as a predictor for termination of CPAP and initiation of MV in a larger cohort.

Results of our studied preterms, adds to the controversy about APGAR score. APGAR score at 1, 5 and 10 minutes, need for resuscitation, mode of delivery and used anesthesia during delivery had non-significant correlations with the CPAP success or failure contrary to other studies (*28*, *29*). In the current study, the mean GA, mean birth weight, were lower in the CPAP failure group, but all did not show a statistical significance among both groups contrary to others (*30*, *31*). Gender also had no influence on response to CPAP.

The concept of "golden hour" has been introduced recently in field of neonatology, highlighting the extreme importance of neonatal care in the first 60 minutes of postnatal life. The first several hours to days are critical as well (*32*). We provided nasal CPAP in the first 2 hours of life as an inclusion criteria, as we considered some time delay because of the logistics of the unit for NICU admission, while, other studies used more strict enrollment criteria, where they considered 15 minutes as the time criterion for early CPAP(*33*). That delay in CPAP initiation, may be the reason for worsening of blood gases parameters after 2 hours and increasing the failure rates, so earlier CPAP administration is necessary.

We acknowledge some limitations of our study, the small number of enrolled cases, further studies on larger scales are recommended. We also faced missing of some recorded data. We did not include the results for a longer duration to determine long term complications of prematurity as retinopathy of prematurity, necrotizing enterocolitis and BPD. Also, we administrated CPAP through conventional ventilators in the majority of the studied preterms, and bubble CPAP was used in only 4 preterms, so, additional research addressing some of these limitations will be needed to validate our findings.

Conclusion

Antenatal steroids was found to be associated with successful response to CPAP. A threshold FiO_2 0.35, hypercarbia, apnea, poor respiratory efforts, systemic hypotension, increase in Silverman score, hemodynamically significant PDA, HSS ≥5 and poor control of acidosis within initial 2 hours were the most significant causes for failed CPAP. Modification of these risk factors can decrease the incidence of CPAP failure. Severe RDS in chest X-ray seems to be a constant predictor for CPAP failure, giving a trial of CPAP for preterms with severe RDS requires very close monitoring, a good oxygen saturation, perfusion and acceptable blood gases as CPAP has high failure rate in severe RDS.

Author Contributions:

Professor Dr. Amira Edris, Professor Dr. Dalia Khairy: conception and design of the work, revising all data and revising the article. Dr. Rana Saber: patient data collection, data analysis and interpretation. Dr. Amira Sabry: drafting the article, critical revision of the article and final approval of the version to be published. and Dr. Mohamed Saad El-Baz: drafting the article, critical revision of the article and final approval of the version to be published. All authors have read and agreed to the published version of the manuscript.

FUNDING

Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References

1. S. Tenny, M. Varacallo, *Evidence Based Medicine.* (StatPearls Publishing; Treasure Island (FL), 2020; https://www.ncbi.nlm.nih.gov/books/NBK470182/).
2. J. J. Ho, P. Subramaniam, P. G. Davis, Continuous distending pressure for respiratory distress in preterm infants. *Cochrane Database of Systematic Reviews* (2015), doi:10.1002/14651858.CD002271.pub2.
3. M. H. Wyckoff, Initial resuscitation and stabilization of the periviable neonate: The Golden-Hour approach. *Seminars in Perinatology*. **38**, 12–16 (2014).
4. Weiner GM, Zaichkin J., *Textbook of Neonatal Resuscitation (NRP)* (American Academy of Pediatrics, American Heart Association, 7th Edition., 2016).
5. X.-W. Zhu, J.-N. Zhao, S.-F. Tang, J. Yan, Y. Shi, Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: A preliminary report. *Pediatr Pulmonol*. **52**, 1038–1042 (2017).
6. N. Gupta, S. S. Saini, S. Murki, P. Kumar, A. Deorari, Continuous positive airway pressure in preterm neonates: An update of current evidence and implications for developing countries. *Indian Pediatr*. **52**, 319–328 (2015).
7. D. Flannery, E. O'Donnell, M. Kornhauser, K. Dysart, J. Greenspan, Z. Aghai, Continuous Positive Airway Pressure versus Mechanical Ventilation on the First Day of Life in Very Low-Birth-Weight Infants. *Amer J Perinatol*. **33**, 939–944 (2016).
8. D. G. Sweet, V. Carnielli, G. Greisen, M. Hallman, E. Ozek, A. te Pas, R. Plavka, C. C. Roehr, O. D. Saugstad, U. Simeoni, C. P. Speer, M. Vento, G. H. A. Visser, H. L. Halliday, European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2019 Update. *Neonatology*. **115**, 432–450 (2019).
9. World Medical Association, WMA Declaration of Helsinki- Ethical Principles for Medical Research Involving Human Subjects (2013), (available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/2013/).
10. A. B. Hedstrom, N. E. Gove, D. E. Mayock, M. Batra, Performance of the Silverman Andersen Respiratory Severity Score in predicting PCO2 and respiratory support in newborns: a prospective cohort study. *J Perinatol*. **38**, 505–511 (2018).
11. V. Manja, O. D. Saugstad, S. Lakshminrusimha, Oxygen Saturation Targets in Preterm Infants and Outcomes at 18–24 Months: A Systematic Review. *Pediatrics*. **139**, e20161609 (2017).
12. G. Lista, L. Boni, F. Scopesi, F. Mosca, D. Trevisanuto, H. Messner, G. Vento, R. Magaldi, A. Del Vecchio, M. Agosti, C. Gizzi, F. Sandri, P. Biban, M. Bellettato, D. Gazzolo, A. Boldrini, C. Dani, for the SLI Trial Investigators, Sustained Lung Inflation at Birth for Preterm Infants: A Randomized Clinical Trial. *Pediatrics*. **135**, e457–e464 (2015).
13. S. Amatya, D. Rastogi, A. Bhutada, S. Rastogi, Weaning of nasal CPAP in preterm infants: who, when and how? a systematic review of the literature. *World J Pediatr*. **11**, 7–13 (2015).
14. D. A. Todd, A. Wright, M. Broom, M. Chauhan, S. Meskell, C. Cameron, A. M. Perdomi, M. Rochefort, L. Jardine, A. Stewart, B. Shadbolt, Methods of weaning preterm babies <30

weeks gestation off CPAP: a multicentre randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. **97**, F236–F240 (2012).
15. Queensland Clinical Guideline, *Respiratory distress and CPAP*. (Queensland government, 2020; www.health.qld.gov.au/qcg).
16. C. F. Jensen, A. Sellmer, F. Ebbesen, R. Cipliene, A. Johansen, R. M. Hansen, J. P. Nielsen, O. H. Nikitina, J. P. Petersen, T. B. Henriksen, Sudden vs Pressure Wean From Nasal Continuous Positive Airway Pressure in Infants Born Before 32 Weeks of Gestation: A Randomized Clinical Trial. *JAMA Pediatr*. **172**, 824 (2018).
17. R. L. Rodwell, A. L. Leslie, D. I. Tudehope, Early diagnosis of neonatal sepsis using a hematologic scoring system. *The Journal of Pediatrics*. **112**, 761–767 (1988).
18. M. Hiles, A.-M. Culpan, C. Watts, T. Munyombwe, S. Wolstenhulme, Neonatal respiratory distress syndrome: Chest X-ray or lung ultrasound? A systematic review. *Ultrasound*. **25**, 80–91 (2017).
19. I. Zonnenberg, K. de Waal, The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review: The definition of a haemodynamic significant duct in randomized controlled trials. *Acta Paediatrica*. **101**, 247–251 (2012).
20. P. A. Dargaville, A. Gerber, S. Johansson, A. G. De Paoli, C. O. F. Kamlin, F. Orsini, P. G. Davis, for the Australian and New Zealand Neonatal Network, Incidence and Outcome of CPAP Failure in Preterm Infants. *Pediatrics*. **138**, e20153985 (2016).
21. A. Apisarnthanarak, G. Holzmann-Pazgal, A. Hamvas, M. A. Olsen, V. J. Fraser, Ventilator-Associated Pneumonia in Extremely Preterm Neonates in a Neonatal Intensive Care Unit: Characteristics, Risk Factors, and Outcomes. *Pediatrics*. **112**, 1283–1289 (2003).
22. M. A. Attar, S. M. Donn, Mechanisms of ventilator-induced lung injury in premature infants. *Seminars in Neonatology*. **7**, 353–360 (2002).
23. D. Roberts, J. Brown, N. Medley, S. R. Dalziel, Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* (2017), doi:10.1002/14651858.CD004454.pub3.
24. M. Mirzamoradi, F. Hasani Nejhad, R. Jamali, Z. Heidar, M. Bakhtiyari, Evaluation of the effect of antenatal betamethasone on neonatal respiratory morbidities in late preterm deliveries (34–37 weeks). *The Journal of Maternal-Fetal & Neonatal Medicine*. **33**, 2533–2540 (2020).
25. H. Dahman, Risk factors associated with preterm birth: a retrospective study in Mukalla Maternity and Childhood Hospital, Hadhramout Coast/Yemen. *Sudan J Paed*, 99–110 (2020).
26. N. Singh, H. L. Halliday, T. P. Stevens, G. Suresh, R. Soll, M. X. Rojas-Reyes, Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database of Systematic Reviews*. **2015** (2015), doi:10.1002/14651858.CD010249.pub2.
27. E. E. Foglia, A. B. te Pas, H. Kirpalani, P. G. Davis, L. S. Owen, A. H. van Kaam, W. Onland, M. Keszler, G. M. Schmölzer, H. Hummler, G. Lista, C. Dani, P. Bastrenta, R. Localio, S. J. Ratcliffe, Sustained Inflation vs Standard Resuscitation for Preterm Infants: A Systematic Review and Meta-analysis. *JAMA Pediatr*. **174**, e195897 (2020).
28. W. I. Permatahati, A. Setyati, E. L. Haksari, Predictor Factors of Continuous Positive Airway Pressure Failure in Preterm Infants with Respiratory Distress. *Global Pediatric Health*. **8**, 2333794X2110074 (2021).
29. M. S. Pillai, M. J. Sankar, K. Mani, R. Agarwal, V. K. Paul, A. K. Deorari, Clinical Prediction Score for Nasal CPAP Failure in Pre-term VLBW Neonates with Early Onset Respiratory Distress. *Journal of Tropical Pediatrics*. **57**, 274–279 (2011).
30. T. Isayama, H. Iwami, S. McDonald, J. Beyene, Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. *JAMA*. **316**, 611 (2016).
31. V. Dell'Orto, S. Nobile, A. Correani, P. Marchionni, I. Giretti, C. Rondina, I. Burattini, M. L. Palazzi, V. P. Carnielli, Early nasal continuous positive airway pressure failure prediction in preterm infants less than 32 weeks gestational age suffering from respiratory distress syndrome. *Pediatric Pulmonology*. **56**, 3879–3886 (2021).
32. S. E. W. Croop, S. M. Thoyre, S. Aliaga, M. J. McCaffrey, S. Peter-Wohl, The Golden Hour: a quality improvement initiative for extremely premature infants in the neonatal intensive care unit. *J Perinatol*. **40**, 530–539 (2020).

33. E. Gulczyńska, T. Szczapa, R. Hożejowski, M. K. Borszewska-Kornacka, M. Rutkowska, Fraction of Inspired Oxygen as a Predictor of CPAP Failure in Preterm Infants with Respiratory Distress Syndrome: A Prospective Multicenter Study. *Neonatology*. **116**, 171–178 (2019).