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Optimal Initial PEEP in Management of Preterm Infant with Respiratory Distress Syndrome: A Prospective Study at Newborn Unit of Moi Teaching and Referral Hospital

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Abstract

Background: Respiratory distress syndrome remains an important cause of neonatal mortality and morbidity worldwide. Early initiation of continuous positive airway pressure is a standard of care for preterm infants with respiratory distress syndrome. Positive end-expiratory pressure reduces the

need for invasive ventilation and prevents chronic lung disease. However, the optimum positive end expiratory pressure level to effectively treat respiratory distress syndrome in preterm infants remains unknown.

Objective: To determine the optimal initial positive end expiratory pressure level in management of preterm infants with respiratory distress syndrome.

Methods: This prospective descriptive study was conducted from July 2023 to January 2024 in the newborn unit of Moi Teaching and Referral Hospital. A total of 204 preterm infants (28-34 weeks gestational age) with respiratory distress syndrome who required Continuous Positive Airway Pressure treatment were recruited. Data on the maternal and neonatal characteristics, low and high positive end expiratory pressure levels, and outcomes at 72 hours were collected and analysed. Descriptive statistics were used for continuous variables, and frequencies were used for categorical data. A p value less than 0.05 was considered statistically significant at the 95% confidence interval. Receiver operating characteristic curves were used to determine the optimal positive end expiratory pressure level.

Results: A total of 45 and 159 preterm infants were started on low and high positive end expiratory pressure levels, respectively. Among 159 (77.9%) of the preterm infants started on high positive end expiratory pressure levels, majority (135, 66.2%) were initiated at a positive end expiratory pressure level of 6 cmH₂O. The Area under the curve for low positive end expiratory

pressure levels was 0.5757 and the one for high positive end expiratory pressure levels was 0.5405. DeLong's test for two ROC curves $D = 0.82979$, $df = 120.8$, $p \text{ value} = 0.4083$. The area under the curve of both low and high positive end expiratory pressure levels were close and not significantly different ($p=0.4083$).

Conclusion: In this study, low positive end expiratory pressure was associated with low failure rate and complications. However low and high positive end expiratory pressure levels were not significantly different to determine the optimal initial PEEP. Further research are needed to determine optimal PEEP for continuous positive airway pressure initiation in preterm infants with respiratory distress syndrome.

Keywords: High positive end expiratory pressure level, Low positive end expiratory pressure levels, Nasal continuous positive airway pressure, Preterm infant, Respiratory distress syndrome, optimal positive end expiratory pressure level.

Background

Every year, there are approximately 4 million infant deaths worldwide. Among these infants, more than 1 million die from respiratory failure (1,2). The majority of these deaths occur in low and middle -income countries (LMICs). In these countries, neonates account for 47% of under-five deaths (3), and most of those deaths are due to prematurity - related complications. Respiratory distress syndrome, which is the major complication of

prematurity, accounts for half of all preterm infant deaths (14). The 2019 Lancet global health report estimated that approximately 15 million babies are born preterm every year. Approximately half of the deaths among are related to respiratory distress syndrome (RDS) (13, 4). More than 60% of preterm births occur in sub-Saharan Africa and South Asia, but preterm birth is truly a global problem. Approximately one decade ago, twelve premature births occurred per hundred live births according to Kenya demographic and Health survey. A recent study conducted by Irimu G et al. in Kenya revealed that the neonatal mortality rate in newborn units is high and varies across hospitals and neonatal characteristics. In their study, Irimu G and colleagues reported that respiratory distress syndrome is one of the complications of prematurity and a common cause of admission to the newborn care unit across hospitals (5).

Noninvasive respiratory support has been used in the intensive care unit for decades, and it has reduced complications caused by invasive mechanical ventilation (6). Nasal Continuous Positive Airway Pressure (CPAP) is a type of noninvasive respiratory support that has been used for over 50 years in high-resource environments (2). The use of a CPAP machine has resulted in a 66% reduction in the mortality rate (13). Based on the effectiveness of CPAP machines, the World Health Organization (WHO) has recommended their use for the management of RDS in both term and preterm neonates (1).

Positive End Expiratory Pressure (PEEP) improves alveolar recruitment, reduces the impact of lung stress and strain, and reduces injury from atelectrauma. The aim of PEEP is to keep the alveoli open (19). According to Dagarville P et al., the optimum PEEP level is the PEEP level at which oxygenation and compliance with at least possible pressure are achieved during ventilation. This PEEP level will ensure that the lungs are well inflated, are recruited and have good compliance and is associated with minimal overdistension (18)

Low PEEP levels can lead to atelectrauma through alveolar collapse with impaired gas exchange. However, a high PEEP levels increase the risk of alveolar distension (barotrauma biotrauma) and elevated intrathoracic pressure decreases venous return, increasing right ventricular afterload and hypotension (16,17).

The prevention of lung injury is an important principle in the management of preterm infants with Respiratory distress syndrome. Although, there is wide variation in PEEP levels, compared with the clinical setting under which CPAP is applied, the optimal PEEP level remains unestablished(11)

The initial PEEP setting still depends on hospital guidelines and ranges from 5-9 CmH₂O. Even the latest European guidelines on the management of RDS (2023) recommended the initiation CPAP level of 6 cmH₂O. However, there is no strong evidence to recommend any particular level of pressure (23, 24). Due to the lack of consensus of levels on the PEEP level needed to initiate CPAP, this study aimed to investigate outcomes among

preterm infants with RDS who received low or high PEEP via a CPAP machine and provide guidance on the PEEP level for the management of RDS in preterm infants.

Methods

Study design and study site

This was a prospective observational study. A prospective study was chosen as the study design because this is a student study without fund. However, an RCT would have been the more appropriate design, as it could have helped minimize discrepancies in the number of participants in each study arm.

This study was carried out at Moi Teaching and Referral Hospital (MTRH) which is the second largest National Teaching and Referral Hospital (level 6 Public Hospital) after Kenyatta National Hospital. Annually, the Neonatal Intensive Care Unit (NICU) admits inborn preterm and neonates from the obstetrics department which averages 14000 deliveries, 600 preterms infants with RDS are admitted at MTRH neonatal unit.

The Newborn unit (NBU) has a 60-bed capacity with occupancy of 150-200% and consists of a 15 bed neonatal intensive care unit (NICU) which has 19 variables flow CPAP machines for the management of RDS and 3 bubble CPAP machines. The unit can also provide mechanical ventilation to 10 babies at any given time. The unit has acute preterm, stable preterm, high care (surgical, asphyxia, neurological), stable term, and Kangaroo

Mother Care sections. The neonatal Intensive care Unit and other dependency area are managed by 3 neonatologist, 1 fellow in neonatology, 2 pediatricians, 3 medical officer, resident in general paediatrics and 59 nurses. Data was collected from July 2023 to January 2024. Preterms infants admitted with RDS were screened for eligibility. Those who met inclusion criteria were reviewed by a trained research assistant. The enrollment criteria were: 1) Preterm infants with gestational age ranging from 28 to 34 weeks presenting with RDS symptoms. 2) Preterm infant between 28 and 34 weeks gestation who developed RDS during their hospitalization within 24 hours of life and for whom nasal CPAP was initiated. The following preterms were excluded: Preterm infants with RDS put initially on Nasal Intermittent Positive pressure Ventilation (NIPPV), Mechanical ventilation (MV), preterm infant resuscitated at birth and had an APGAR score ≤ 5 at 5 minutes of life, any congenital anomalies affecting respiratory functions (e.g. diaphragmatic hernia and tracheoesophageal fistula).

Diagnostic criteria

The diagnosis of RDS was made clinically by the medical doctor based on meeting one or more of the following diagnostic criteria: respiratory rate > 60 bpm, grunting, sternal or intercostal recessions, lower chest indrawing, and cyanosis. Gestational age for preterm with RDS was determined by using the new modified Ballard score which is based on neurological and

physical maturity assessment of the newborn between 30 minutes and 96 hours.

Preterm infants who are born at < 30 weeks are started on prophylactic CPAP(initiated for preterm infants between 28 and 30 weeks as soon as possible even in the absence of clinical signs of RDS) , whereas those born at > 30 weeks gestation are started on treatment with rescue CPAP(those > 30 weeks with signs of RDS). The initial PEEP setting depend on the medical doctor's decision with a maximum of 8 CmH₂O because of the absence of clear guidelines and a consensus on who should receive low or high PEEP levels.

Study population

Preterm infants born between 28 and 34 weeks gestational age started on CPAP within the first 24 h of life for RDS were enrolled. Neonates with multiple congenital abnormalities, those started on NIPPV, MV before enrollment and those in whom CPAP were initiated after 24 hours were excluded.

Study variables

Independent variables assessed in our study included gestational age, birth weight, 5 min APGAR score, Need of surfactant, mode of delivery, maternal antenatal steroids, maternal comorbidity, time to start CPAP therapy and degree of respiratory distress. The short-term outcome variable was PEEP failure, survival, or death within 72 hours of initiation of nCPAP. Low PEEP

failure was defined as need for high PEEP, NIPPV, and MV while High PEEP failure was defined as need for NIPPV, MV. Complications were defined as pneumothorax, IVH within 72hours of CPAP initiation. Optimal PEEP level was defined as a PEEP level with less failure rate and complication.

Sample size estimation

The sample size was calculated using Blume's formula (20). The Area Under the Curve (AUC) of the the predictor of CPAP failure was estimated to be 0.86 for preterm infants as reported from a study by Dell'Orto (21). This gave a sample size of 185 and assuming 10% for the loss to follow up, a total sample size of 204 was computed. In this study, we used a consecutive sampling technique.

Study procedure

Participants were recruited from the NBU by the principal investigator or a trained research assistant (RA) after the diagnosis of RDS and allocation to PEEP made by the medical doctor (at admission).

Preterm infants who were born between 28 and 34 weeks of gestation (using ballard score done by the medical doctor confirmed by the research assistant or the principal investigator) and diagnosed with RDS made clinically by the medical doctor were screened for eligibility.

Those who met inclusion criteria were reviewed by a trained research assistants (RA). RA were trained in gestational age estimation using the new

Ballard score (7) respiratory distress score using Downes score (22), how to obtain the consent from the parent and how to fill in the data sheet. Downes score was used by the medical doctor and researcher team to assess the severity of respiratory distress. A score of 0-3 was considered as mild respiratory distress, 4-7 as moderate respiratory distress and > 7 as severe respiratory distress. Informed consent was obtained by an RA or the principal investigator after allocation to PEEP by the doctor at admission. Baseline information such as maternal age, place, mode of delivery, comorbidities, infections, any dose of antenatal steroids and patient-specific data that included neonatal gestational age, birth weight, sex, initial oxygen saturation and the severity of RDS. The diagnosis of RDS was made by the primary clinician via physical examination, considering both the Downes score and pulse oximeter readings. After the decision to provide PEEP via CPAP by the primary doctor based on the CPAP criteria, the Principal Investigator (PI) or RA documented the initial PEEP level as either high or low PEEP. Preterm infants were categorized into 2 groups: Group (1): Low PEEP group (≤ 5 CmH₂O) and Group (2) High PEEP group (≥ 6 CmH₂O). The observation period started immediately after the initiation of PEEP for a period of 72 hours. During the observation period, data on the outcomes of interest and complication were collected. Chest X-ray was performed for patients who presented symptoms of pneumothorax (cyanosis, tachypnoea, grunting, irritability, restlessness, and retraction) with positive transillumination within 72 hours. Cranial ultrasound was performed at 72

hours as a routine screening method for intraventricular haemorrhage (IVH) in preterm infants. These outcomes were collected within one hour, 2 hours, 24 hours, 48 hours and 72 hours. The primary outcome was treatment failure within 72 hours. The failure of CPAP for infants with a low PEEP level was defined as the need for a high PEEP level as determined by FiO_2 or the need for endotracheal intubation and mechanical ventilation or escalation to NIPPV (for those started on CPAP) and the failure of CPAP for infants with a high PEEP level was defined as the need for endotracheal intubation and mechanical ventilation or NIPPV (for those started on CPAP) as determined by FiO_2 . The secondary outcome was survival, mortality or complications such pneumothorax, and IVH within 72 hours. Within 72 hours, the following parameters were collected: PEEP level; FiO_2 ; SpO_2 ; respiratory rate; blood pressure, including the mean arterial pressure (MAP); temperature; heart rate; and the occurrence of complications, such as pneumothorax and IVH. Blood pressure was determined via noninvasive oscillatory BP monitoring. Within 72 hours, each participant was visited at 1 hour, 2 hours, 24 hours, 48 hours and 72 hours.

Preterms infants were managed based on the latest (2022) national and local guidelines. Surfactant is administered at different fraction of inspired oxygen (FiO_2) requirements based on the size of the baby: $\text{FiO}_2 > 30\%$ for smaller neonates and a $\text{FiO}_2 > 40\%$ for larger neonates. where smaller neonate was defined as neonate born before 30 weeks of gestation and

larger neonate defined as a neonates born after 30 weeks of gestation.

Surfactant is administered through Minimally Invasive Surfactant Therapy (MIST) and Intubate, Surfactant administered and Extubate (INSURE) back to CPAP method.

Neonates on CPAP who failed to maintain saturation $> 90\%$, an $FiO_2 > 0.60$ with a CPAP level of 7 cm H₂O, pH < 7.25 with increasing Partial pressure of carbon dioxide (PaCO₂) > 60 mm Hg, increased recession and tachypnea, recurrent apnoea are escalated to mechanical ventilation if a ventilator is available. Those who could not be ventilated remained on CPAP until the mechanical ventilator was available. CPAP is weaned if the infant maintain saturation $> 94\%$ while on $< 30\%$ fraction, increased work of breathing has resolved. PEEP was lowered by 1 cm every 2 to 4 hours until a level of 4 to 5 cmH₂O is obtained. Neonates weaned off CPAP are managed with nasal prong oxygen 0.5 to 2 l/min to maintain saturation $> 90\%$.

All preterm infants are empirically started on antibiotics and intravenous fluids. Caffeine is given to all preterm infants < 34 weeks of gestation.

Data management and analysis

Data was entered into Stata and transferred to SPSS version 20 for analysis. Baseline characteristics were summarized in tables, mean was computed for continuous variables and frequencies for categorical variables. A p value less than 0.05 was considered statistically significant at the 95% confidence interval. To determine the optimal PEEP level for the initiation of treatment

for RDS among preterm infants, all different initial PEEP levels determined by clinicians were collected and analysed via receiver operating characteristic (ROC) curve analysis. Those who experienced PEEP failure and those who did not were represented by the area under the ROC curve (AUC). The AUC was in the range of 0.5 to 1.0, where an AUC of 0.5 indicated that the classification model was of no value, and a value of 1.0 was designated perfect diagnostic accuracy. In turn, the cut-off point of the ROC curve was the particular PEEP level that provided the truest and the least false indications of treatment failure and therefore best predicted the treatment effect. The best PEEP level obtained after analysis was considered the optimal initial PEEP level for the treatment of RDS in preterm infants. DeLong's test was done to obtain a p-value for whether low PEEP has a significantly different AUC than high PEEP.

Results

A total of 204 preterm newborns were enrolled and followed up for 72 h. The recruitment process can be seen in supplementary Figure 1. Maternal characteristics can be seen in Supplementary Table 1 and Neonatal characteristics can be seen in Table 2. Distribution of patients with different PEEP levels can be seen in Table 3, Failure and success rates of different PEEP levels can be seen in Figure 2. ROC curve to discriminate between two PEEP levels can be seen in Figure 3.

Complications at different PEEP level can be seen in Figure 4 and supplementary table.

Maternal characteristics. Table 1 represents maternal characteristics. Of the mothers, 104(51%) were aged between 20 and 30 years, 117(57.3%) were primiparous, 126 (61.8%) mothers had vaginal deliveries, 48 (23.5%) mothers had preeclampsia and 4 (2%) of them was diabetic. A summary of the baseline characteristics is shown in Table 1.

Neonatal characteristics. The results reported in Table 2 show that males preterm infants represented 57% of the study population, 53.9% of preterm infants were less than 30 weeks gestation and 83 preterm infants (40.7%) weighed between 1000 to 1500g. Half of the preterm infants 109(53.4%) had an Apgar score > 7 at 5 minutes, 164 (80.4%) had a Downes score of 4-7 at admission. The majority of the mothers of study infants had not received any antenatal corticosteroids (68.1%). All study infants were on ampicillin and gentamycin, and none of them was on inotropic support during the study period.

Distribution of patients with different PEEP levels. The results in table 3 show that a total of 45 (22.1%) and 159 (77.9%) preterm infants were started on low and high PEEP levels, respectively.

Among one hundred and twenty eight who failed in either PEEP level, 12 (9.4%) were initiated on low PEEP level, while 116(90.6%) were initiated on

high PEEP level. The rates of failure at high PEEP levels were statistically significant (p value <0.001).

Complications of different PEEP level. The result in figure 4 show that two (1.3%) participants with high PEEP levels developed pneumothorax, whereas nine (5.7%) developed intraventricular haemorrhage. Findings in supplementary table show that a total of 24 (15.1%) participants with high PEEP levels died, whereas 4 (8.9%) participants with low PEEP levels died.

ROC curve to discriminate between two PEEP levels. The area under the curve (AUC) for the two PEEP levels closed to 0.5 indicated that high and low PEEP levels do not have differential abilities to determine PEEP success and failure. The AUCs of both low and high PEEP levels were close and not significantly different; hence, one is not better than the other (p=0.4083).

Discussion

The optimal PEEP level in management of preterm infants with RDS remains unknown. Studies recommend an initial PEEP level of 5–6 cmH₂O but state that there is no stronger evidence to recommend any particular level of pressure (23).

In this study, Evidence was not sufficient to determine the optimal PEEP level. The two PEEP levels (low and high) were not significantly different; hence, neither was better than the other. The difference between the AUCs of the two PEEP levels was not statistically significant ($p=0.4083$). Bamat N et al., during a systematic review to determine the optimal initial PEEP level using a level ≤ 5 cmH₂O as the low PEEP level and a level > 5 cmH₂O as the high PEEP level, reported similar findings of insufficient data to determine the optimal PEEP level. Their study had some methodological differences from our study in that they included neonates born at less than 37 weeks of gestation, and the use of bubble CPAP, CPAP delivered by ventilator, CPAP delivered by variable flow(8).

Other similar findings were recorded in two studies performed in India by Murki S et al. and Dhir SK et al., both of which compared initial PEEP levels in a low- to middle-income country (India); however, in these studies, 7 cmH₂O was used as the high PEEP level, but the low PEEP level was similar to that in our study (5 cmH₂O). Furthermore in their study, they included neonates born at 27-34 weeks of gestation, they used different types of CPAP machine (Fischer &Paykel healthcare,Anckland, Newzeland)(9, 10). In addition, the optimum PEEP level that most effectively treats respiratory distress syndrome in preterm infants remains unknown in the current literature. Most large clinical trials and guidelines recommend a wide range of PEEP levels (4–8 cmH₂O) (11; 12).

Conclusions and recommendations

In this study, low positive end expiratory pressure was associated with low failure rate and complications. However low and high positive end expiratory pressure levels were not significantly different to determine the optimal initial PEEP. Further randomized studies are needed to determine the optimal PEEP.

Limitations

This was a single-centre study with small number of enrolled cases; hence, the results are unlikely to be generalizable. In addition, this was not a randomized clinical trial due to the short period of the training program and lack of fund. Further multi-centres and randomized study with a large sample size are needed to interrogate current findings. Furthermore, in this study clinicians determined whether patients received high or low PEEP at their discretion due to the lack of a scientific allocation method, the absence of clear guidelines and a consensus on who should receive low or high PEEP levels.

List of abbreviations

AUC: Area Under the Curve

BP: Blood Pressure

CPAP: Continuous positive Airway Pressure

FRC: Functional Residual Capacity

- 377 FiO₂: Fraction Inspired Oxygen
- 378 GA: Gestational Age
- 379 IVH: Intraventricular Haemorrhage
- 380 LMICs: Low and Middle Income Countries
- 381 MTRH: Moi Teaching and Referral Hospital
- 382 MV: Mechanical Ventilation
- 383 NICU: Neonatal Intensive Care Unit
- 384 NBU: Newborn Unit
- 385 NIPPV: Nasal Intermittent positive Pressure Ventilation
- 386 PaCO₂: Partial pressure of carbon dioxide
- 387 PEEP: Positive End Expiratory Pressure
- 388 RA: Research Assistant
- 389 RDS: Respiratory Distress Syndrome
- 390 ROC: Receiver Operating Characteristic
- 391 WHO: World Health Organization

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Data availability

All data generated or analyzed during this study are included in this published article.

Clinical Trial number

Clinical trial number: not applicable

Declarations Ethics approval

Ethical clearance was obtained from the Institutional Research and Ethics Committee (IREC) MTRH/MU on 15 June 2023 under **FAN: 0004443**, administrative approval from the Chief Executive Officer (CEO) of MTRH, and a research permit from the National Commission for Science, Technology and Innovation (NACOSTI). Informed consent was obtained from the mothers of eligible study infants after giving detailed information about the study. All study procedures were performed according to approved protocol and the units' daily procedures.

Consent to publish

Not applicable.

Competing interests

There are no competing interests.

Authors' contributions

All authors made significant contributions to the manuscript.

D.M. drafted the proposal; A.M. contributed to the research design; S.A., A.C, P.A, and A.M. critically polished the proposal; D.M. trained supervised the data collection and approved the completeness of data collection; and A.M., S.A., A.C., P.A and D.M. validated the analysis. D.M. drafted the manuscript; P.A. critically polished the manuscript; and A.M., S.A., P.A., A.C., and D.M. validated the manuscript. All authors have read and approved the final version of the manuscript. Therefore, all authors agree to be accountable for the content of the work.

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Fig. 1 Flow diagram showing the recruitment process

Fig 2: Failure and success rates of different PEEP levels

Fig 3: ROC curve to discriminate between two PEEP levels(in cmH2O)

complications of different PEEP levels

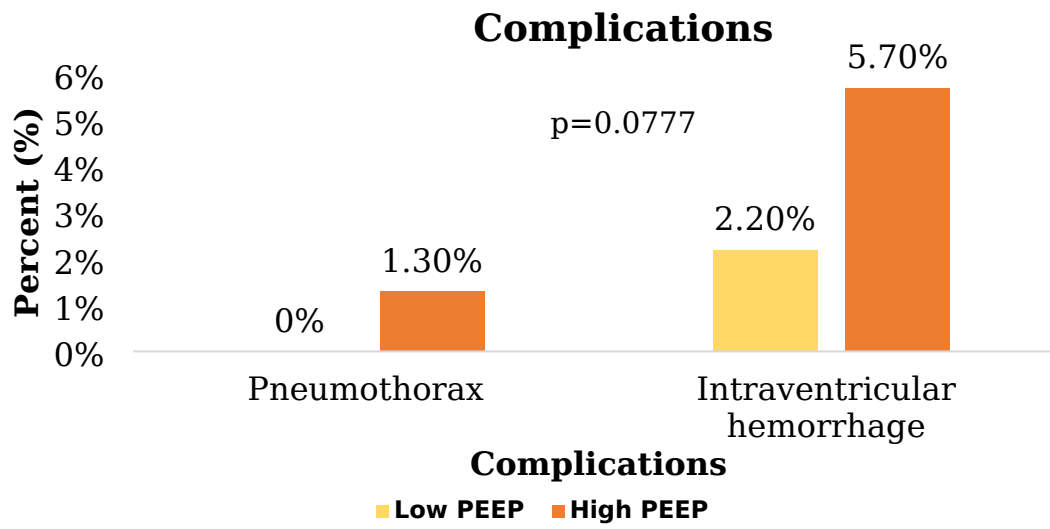


Figure 4: Complications of different PEEP level

Table 1: Maternal characteristics

Variable	Frequency	Percentage
Age (years)		
<20	23	11.3
20-30	104	51
31 - 40	71	34.8
>40	6	2.9
Min. - Max.	15.0 - 46.0	
Mean $\pm$ SD.	27.50 $\pm$ 6.87	
Median (IQR)	26.0 (22.0-33.0)	
Parity		
Primiparous	117	57.3
Multiparous	79	38.7
Grand multiparous	8	3.9
Mode of delivery		
Caesarean section	70	34.3
Assisted vaginal delivery	8	3.9
Vertex delivery	126	61.8
Maternal comorbidity		
PET/Eclampsia	48	23.5
Bacterial infection	5	2.5
Diabetes	4	2.0
Chronic HTN	6	2.9
Cancer	2	1.0
Antenatal corticosteroid use		
Yes	65	31.9
No	139	68.1

PET: preeclampsia; HTN: hypertension; IQR: interquartile range; SD: standard deviation

Table 2: Neonatal characteristics

Variable	Frequency	Percentage (%)
Sex		
Male	116	56.9
Female	88	43.1
Birth weight (grams)		
<1000	58	28.4
1000-1500	83	40.7
1600-2000	48	23.5
2100 - < 2500	15	7.4
GA (weeks)		
≤ 30 (28-30)	110	53.9
>30 (30-34)	94	46.1
Twins:		
Yes	65	31.9
No	139	68.1
Apgar score at 5 minutes	90	44.1
6-7	109	53.4
>7	5	2.5
NA (not indicated)		
Downes score		
<4	19	9.3
4-7	164	80.4
≥ 7	21	10.3
Place of birth		
Home	3	1.5
Hospital/Health centre	199	97.5
Ambulance	2	1

GA: gestational age; Apgar: appearance, pulse, grimace, activity, and respiration

Tableau 3: Distribution of patients with different PEEP levels (n=204)

	No.	%
nCPAP(PEEP in cmH2O)		
Low PEEP ≤ 5 cmH2O	45	22.1
4 cmH2O	5	2.5
5 cmH2O	40	19.6
High PEEP ≥ 6 cmH2O	159	77.9
6 cmH2O	135	66.2
7 cmH2O	22	10.8
8 cmH2O	2	1.0