Comparison of continuous positive airway pressure and non-invasive positive pressure ventilation as modes of non-invasive respiratory support for neonates in a Level III neonatal intensive care unit

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Abstract

Objectives: To compare the effectiveness of continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NIPPV) in neonates with mild to moderate respiratory distress.

Method: A single centre randomized controlled trial was conducted at the Sri Jayawardenepura General Hospital, Sri Lanka from January to December 2015. The trial was registered with The Clinical Trials Registry 'Clinical Trials.gov' retrospectively. Eighty neonates admitted to the neonatal intensive care unit (NICU) were randomly allocated to NIPPV and CPAP. Outcomes of respiratory support were observed and information on risk factors were obtained by going through the bed head tickets of the study cohort. Data analysis was done using SPSS 20 software.

Results: Infants treated with NIPPV and CPAP had comparable demographic data and clinical status at the time of enrolment into the study. Infants treated initially with NIPPV needed less endotracheal ventilation than infants treated with CPAP (35% vs 40%, p = 0.644) but this difference is not statistically significant.

Conclusions: The risks for respiratory failure and the need for ventilation were not statistically significantly different whether using NIPPV or CPAP.

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Introduction

Respiratory distress accounts for 30-40% of admissions to neonatal intensive care units (NICUs) and special care baby units (SCBUs)[1]. Whilst non-invasive respiratory support causes minimal damage to the developing neonatal lung parenchyma and minimal systemic damage, invasive ventilation can lead to permanent lung damage with poor respiratory capacity, frequent wheezing and broncho-pulmonary dysplasia. Invasive ventilation also predisposes the neonate to ventilator associated pneumonia, bacterial and fungal sepsis, prolonged NICU stay, over-crowding and is an economic burden to the parents and state[2,3].

National Emergency Obstetric and Neonatal Care Needs Assessment Country Report published in 2012 by the Ministry of Health and the Family Health Bureau of Sri Lanka shows total ventilation as a percentage of total admissions to neonatal care units to be 5.4% and nasal CPAP support as 3.9%. There is no data regarding NIPPV use. Most centres in Sri Lanka use CPAP as a non-invasive method and conventional ventilation as an invasive method.

NIPPV is the augmentation of CPAP with superimposed inflations to a set peak pressure. Mechanism of action of NIPPV remains uncertain. Hypotheses include increasing pharyngeal dilation, improving respiratory drive, increasing mean airway pressure, allowing recruitment of alveoli, increasing functional residual capacity and increasing tidal and minute volume[4,5,6]. Previous studies on comparison between CPAP and NIPPV on weaning from invasive ventilation showed, weaning to NIPPV leads to better outcome[4,7-10]. A recent synchronised NIPPV study demonstrated a relative risk reduction for intubation in the first 72 hours in the NIPPV

group compared to CPAP (RR 0.60, 95% CI 0.43, 0.83)[11]. There is some evidence to suggest that NIPPV may be useful as a mode of primary respiratory support, but the evidence is not conclusive[12]. However, in Sri Lanka, such studies have not been done.

Objectives

- To compare the effectiveness of CPAP and NIPPV in neonates with mild to moderate respiratory distress.
- To describe neonatal factors associated with CPAP and NIPPV support.
- To compare the length of hospital stay in neonates who received CPAP and NIPPV
- To compare the time taken to achieve full enteral nutrition in neonates who received CPAP and NIPPV.

Method

Study design: Randomized controlled trial. The trial was registered with The Clinical Trials Registry 'Clinical Trials.gov' retrospectively and the reference number is NCT03347136.

Study setting: Study was carried out in the NICU of the Sri Jayawardenepura General Hospital (SJGH) from January to December 2015. There are 06 infant ventilators in NICU of SJGH (3 SLE 2000 and 3 Bear CUB 750 PSV). Respiratory support (conventional ventilation, CPAP and NIPPV) was given through these ventilators. The neonatal soft tip curved nasal cannula with tubing was used for non-invasive respiratory support. The nasal cannula is connected to the ventilator via an endotracheal tube connector. Systems were regularly monitored. Cannula size was chosen to comfortably fit the infant's nostrils. CPAP was started with PEEP 05 and increased up to PEEP 09 according to severity of baby's condition[13]. NIPPV was started with IMV rate 30, PIP 20 and PEEP 5. Settings were increased according to the severity of baby's condition[13].

Inclusion criteria: All neonates with mild to moderate respiratory distress, requiring non-invasive respiratory support on admission as defined by one or more of the following[8,13,14]:

- Respiratory distress needing 3 litres of oxygen to maintain saturation more than 90%
- Silverman Anderson score of 4 – 6
- Apnoea
  a. More than 2 apnoeic attacks needing tactile stimulation for recovery
  b. One apnoeic attack needing resuscitation

Exclusion criteria:

- Major congenital anomalies
- Presence of cardiovascular instability [sepsis, anaemia or severe intraventricular haemorrhage (IVH)].
- Intubation needed on admission to the NICU
- Major cardiac disease excluding patent ductus arteriosus (PDA)

Sample size: Sample size calculation was done based on the percentage needing ventilation in the comparison study of Kugelman A *et al.*[15]. Significance level was taken as 5%. Power of study was taken as 80%. Ratio of subjects of the two arms needing intubation was 1: 2. Percentage needing ventilation in CPAP arm was 31% and in NIPPV arm was 62%. Applying these numbers to the sample size calculation formula gives need for 40 neonates in each arm with a total sample size of 80.

Sampling method: All neonates fulfilling inclusion and exclusion criteria were registered in the study and a serial number issued. They were allocated to the two arms of the study randomly based on a previously generated random allocation schedule.

Data collection: All the medical officers as well as the nursing staff were educated with practical demonstrations on how to assess babies with respiratory distress and how to carry out a Silverman Anderson Score.

The neonates who were included in the study were monitored and managed according to the SJGH NICU management protocol.

After initiation of non-invasive ventilation the outcome was measured in the following ways:

- Failure of non-invasive respiratory support by requirement for endotracheal ventilation within 72 hours of starting treatment.
- Time to stop oxygen support (on room air without respiratory distress or apnoea)
- Incidence of grade III/IV IVH
- Time taken to achieve full enteral feeds.
- Length of hospital stay.

Neonates with failure of non-invasive ventilation were given invasive respiratory support. The criterion for failure of

non-invasive support was considered as one of the following[2,3,13]:

- Clinical deterioration (Worsening tachypnoea, persistent grunting, gasping, respiratory exhaustion)
- Silverman score ≥7
- Blood gases: pH≤ 7.25, pCO2≥50 mmHg, PaO2≤ 50 mm Hg
- Arterial oxygen saturation by pulse-oximetry (SpO2) <90% while on FiO2 55%
- Apnoea (>2 apnoeic attacks needing tactile stimulation for recovery or one apnoeic attack needing resuscitation)

Ethical aspects: Ethical approval was obtained from the Ethical Review Committee of SJGH, Kotte. Written informed consent was obtained from parents or guardians of eligible infants before randomization. The data sheets did not contain names and were anonymous. Data was stored under lock and key with restricted access only to the principal investigators. The computerized data were password protected and were only available to the investigators.

Statistical analysis: All data were collected into an Excel database and analysed using SPSS 20 software. Relative risk was calculated for main outcome and Chi square significance was assessed for association with risk factors. P value less than 0.05 was considered statistically significant.

Results

Total sample of 80 newborns was randomly equally allocated into two treatment categories; NIPPV (n=40) and CPAP (n=40). As shown in Table 1, the distribution of the demographic and birth variables in the 2 groups did not demonstrate statistically significant differences.

Table 1*: Demographic data of the neonates included in the study*

Variable	NIPPV*(n=40)* No. (%)	CPAP *(n=40)* No. (%)	Total *(n=80)* No. (%)	Level of significance
Gender				
Male	25 (62.5)	24 (60.0)	49 (61.3)	X^2= 0.05,
Female	15 (37.5)	16 (40.0)	31 (38.7)	*p*=0.818
POA (weeks)				
28-30	05 (12.5)	02 (05.0)	07 (08.8)	
31-33	13 (32.5)	08 (20.0)	21 (26.3)	X^2=3.78,
34-36	08 (20.0)	12 (30.0)	20 (25.0)	*p*=0.287
37 or >	14 (35.0)	18 (45.0)	32 (40.0)	
Birth weight (g)				
<1500	10 (25.0)	09 (22.5)	19 (23.8)	X^2=2.037,
1500-2500	16 (40.0)	11 (27.5)	27 (33.8)	*p*=0.361
>2500	14 (35.0)	20 (50.0)	34 (42.5)	
Mode of delivery				
Normal vaginal	03 (07.5)	08 (20.0)	11 (13.8)	
Elective LSCS	05 (12.5)	10 (25.0)	15 (18.75)	X^2=5.86,
Emergency LSCS	31 (77.5)	21 (52.5)	52 (65.0)	*p*=0.118
Instrumental	01 (02.5)	01 (02.5)	02 (02.5)	
Diagnosis				
Congenital pneumonia	06 (15.0)	06 (15.0)	12 (15.0)	
RDS	29 (72.5)	23 (57.5)	52 (65.0)	X^2=2.94,
Other	05 (12.5)	11 (27.5)	16 (20.0)	*p*=0.230
Maternal risk factors				
No Risk	16 (40.0)	23 (57.5)	39 (48.8)	
GDM	04(10.0)	03 (07.5)	07 (08.8)	X^2= 10.79,
PIH	14 (35.0)	03 (07.5)	17 (21.3)	*p*=0.013
Other	03 (07.5)	08 (20.0)	11 (13.8)	

POA: Period of amenorrhoea, LSCS: lower segment caesarean section, RDS: respiratory distress syndrome, GDM: gestational diabetes mellitus, PIH: pregnancy induced hypertension

Babies born through emergency caesarean section needed more respiratory support than other modes of deliveries. Type of respiratory support did not show any association with period of amenorrhoea (POA), birth weight (BW), mode of delivery (MOD) or cause of

respiratory distress. Around half the sample (48.7%) of neonates who needed respiratory support were babies born to mothers with no risk factors. Among the risk factors, pregnancy induced hypertension (PIH) was the commonest (21% of total sample). Association with maternal risk factors was statistically significant (p=0.013). Effectiveness of CPAP and NIPPV in neonates with mild to moderate respiratory distress is shown in Table 2.

Table 2: ***Effectiveness of CPAP and NIPPV in neonates with mild to moderate respiratory distress***

	Respiratory support	
	NIPPV	**CPAP**
Non-invasive respiratory support failure	14 (35%)	16 (40%)
Absence of non-invasive respiratory support failure	26 (65%)	24 (60%)
Total	**40 (100%)**	**40 (100%)**

Risk of developing respiratory failure was 1.14 (95%CI 0.65-2.01) times higher among CPAP than NIPPV but this was not statistically significant (p=0.644).

Association between type of respiratory support and grades 3 and 4 intraventricular haemorrhage (IVH) is shown in Table 3.

Table 3: ***Association between type of respiratory support and Grades 3 and 4 IVH***

		NIPPV	**CPAP**	**Level of significance**
IVH	Presence	02 (05%)	01 (2.5%)	RR= 2 (CI 0.18-21.18), p=0.56
	Absence	38 (95%)	39 (97.5%)	

IVH: intraventricular haemorrhage

There were two neonates with grade 3/4 IVH in the NIPPV group and only one neonate in CPAP group. As the number was small, an association could not be calculated using the Chi square test. Data showed twice the risk of developing IVH among NIPPV compared to CPAP but this was not statistically significant (p=0.56). There was no significant difference in the presence of IVH between the two groups of respiratory support.

Comparison of duration of support and length of hospital stay is shown in Table 4.

Table 4: ***Comparison of duration of support and length of hospital stay***

	Mean	**Standard deviation**	**Mean difference**	**Level of significance**
Duration of respiratory support				
NIPPV	6.23	3.919	0.825	p=0.381
CPAP	5.40	4.448		
Duration of hospital stay				
NIPPV	7.23	4.312	0.550	p=0.584
CPAP	6.68	4.621		

Neither duration of respiratory support nor length of hospital stay showed a statistically significant difference among neonates who received NIPPV and CPAP.

Comparison of time taken to achieve full enteral nutrition among neonates receiving NIPPV and CPAP is shown in Table 5.

Table 5: ***Comparison of time taken to achieve full enteral nutrition***

	Mean duration of hospital stay	**Standard deviation**	**Mean difference**	**Level of significance**
Time taken to achieve full enteral nutrition				
NIPPV	6.50	3.138	0.000	p=1.00
CPAP	6.50	4.391		

Mean duration of hospital stay was similar in both groups. There was no statistically significant difference noted in time taken to achieve full enteral feed.

Discussion

In this randomised trial, we found reduced need for endotracheal intubation and invasive ventilation overall within the first 72 hours in

the NIPPV group (35%) when compared with CPAP (40%) but this was not statistically significant. This finding could mean that there was actually no difference with the two methods or the effect could have been masked because of sample size and heterogeneity of the sample.

The Cochrane meta-analysis done in 2016 concluded that "Early NIPPV does appear to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation and endotracheal tube ventilation among preterm infants with respiratory distress syndrome"[16]. Our results not showing a significant difference may also be due to it consisting of all the newborn with respiratory distress due to various pathologies. In future research, we need to specifically target groups such as preterm. The devices used are different in other research when compared to our study.

The incidence of severe IVH is high in the NIPPV group compared to CPAP arm, but due to the very small number Chi square test cannot be applied to our study. But it showed a relative risk of 2 (95% CI 0.18-21.18) which is not statistically significant. Other trials which compared the incidence of severe IVH among non-invasive respiratory support showed no difference in CPAP or NIPPV arm[15-19].

In our study neither duration of respiratory support nor length of hospital stay showed a statistically significant difference between neonates who received NIPPV and CPAP. Armanian et al[20] demonstrated a reduction in duration of hospital stay (22 days in the NIPPV group vs 29 days in the CPAP group) while Ramanathan et al[18] demonstrated a reduction in the number of days on oxygen among infants who received NIPPV (29 days vs 38 days). The difference may be due to slow weaning protocol of NIPPV group in our hospital management protocol. Other studies including a meta-analysis did not show a difference in duration of hospital stay[11].

In this research no statistically significant difference was noted in the time taken to achieve full enteral feed. In both arms the mean duration to achieve full feed was 6.5 days. Previous studies did not show a reduction in necrotizing enterocolitis stage 2[15-18,20-23] or time to achieve full feed[4,7,24,25] greater in one treatment group compared with the other.

Limitations of the study include the small sample size, the impossibility to blind caregivers and the heterogeneity of the pathogenesis in the study cohort. Future researche should focus on the effectiveness, safety and long term outcomes such as long-term survival, chronic lung disease and neurodevelopmental impairment of early NIPPV in comparison to CPAP and should focus not only on surfactant deficiency lung disease but also various other disease conditions.

Conclusions

In our study, the risks for respiratory failure and the need for ventilation were not statistically significantly different whether using NIPPV or CPAP.

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