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EFFECT OF POSITIONING ON DURATION OF RESPIRATORY SUPPORT IN PRETERM NEONATES (<34 WEEKS)- A RANDOMIZED CONTROLLED TRIAL FROM A LOW-MIDDLE-INCOME COUNTRY

Neonatology

Dr Gunjana Kumar	Assistant Professor, Department of Neonatology, National Institute of Medical Sciences, Jaipur, Rajasthan
Dr Amit Kumar	Assistant Professor, Department of Neonatology, National Institute of Medical Sciences, Jaipur, Rajasthan
Dr Susheel Kumar Saini	Assistant Professor, Department of Pediatrics, National Institute of Medical Sciences, Jaipur, Rajasthan
Dr Jai Krishan Mittal*	Professor and Head, Department of Neonatology, National Institute of Medical Sciences, Jaipur, Rajasthan *Corresponding Author

ABSTRACT

Introduction: Positioning neonates in a prone position is considered an effective strategy for improving tissue oxygenation but is yet to be objectively evaluated in clinical trials. **Objective:** To evaluate the effect of prone positioning on the duration of non-invasive respiratory support in preterm neonates (<34 weeks). **Methodology:** Open-labelled, randomized controlled trial conducted at a tertiary care institute enrolled 122 neonates of $26^{0/7}$-$33^{6/7}$ weeks of gestation requiring non-invasive respiratory support to the intervention group (n=60) and standard group (n=62). **Results:** Baseline characteristics were comparable between the two groups. There was no difference in the duration of non-invasive respiratory support in the two groups (h; 96 [30 to 220] vs. 90.5 [40 to 256]), median difference (h) -5.5, 95% CI: -10 to 36, P=0.47). Neonates enrolled in the prone position group had significantly lower peak FiO2 requirements (30 [30-30] vs. 35 [30-60], P=0.01). **Conclusion:** Prone positioning could not reduce the duration of respiratory support in preterm neonates but could improve oxygenation as it lowers the peak oxygen requirement.

KEYWORDS

Preterm Neonate, Prone Position, Respiratory support

INTRODUCTION

Prone positioning has been considered a standard of care for acute severe respiratory distress syndrome (ARDS) in adults, as it improves oxygenation through several mechanisms including more homogenous inflation distribution and decreasing chest wall compliance compared to supine position.[1] The recent pandemic has emphasised improvement in gas exchange associated with prone positioning. Although a non-invasive, simple and inexpensive therapy, the effect of prone positioning on neonatal respiration and hemodynamics is not well studied.

Appropriate positioning of neonates is an essential component of developmentally supportive care, prompting sensory, motor, and neural development.[2] Inappropriate positioning of the neonatal head and neck has been linked to changes in jugular-venous drainage, leading to venous congestion, altered cerebral perfusion, and increased intracranial pressure, culminating in an increased risk of germinal matrix and intraventricular haemorrhage.[2] This demands training of the nursing personnel for apt handling and positioning.

Preterm infants suffering from respiratory distress syndrome (RDS) have a reduced end-expiratory lung volume (EELV) and lung compliance, leading to impaired ventilation and oxygenation[3]. Moreover, prematurity being a stressful state, experiences cardio-respiratory instability, manifesting as recurrent apnea, bradycardia, and/or transient hypoxemic episodes.[4,5] Placing preemies in a prone position has been predicted to reduce cardio-respiratory instability along with minimizing ventilatory requirements.[6-8] The American Academy of Pediatrics stated that prone position may be considered for sick preterm neonates under supervision as being associated with improvement in oxygenation.[9] In addition, neonates placed prone are less active when awake and are in more optimal sleep states.[10]

Dean et al reported an increase in oxygenation by the change of gravitational force on the lung in prone positioning thus increasing the ventilation and perfusion ratio.[11] Asynchronous movement of the intercostal muscles with diaphragmatic contraction resulting in rib-cage distortion in the supine position lowers the efficacy of breathing. Whereas, prone positioning reduces the paradoxical chest movements and improves the chest wall synchrony by splinting the diaphragm.[12] A recently published quasi-randomised controlled study by Loi et al, demonstrated improved gas exchange and lung aeration with 6h prone positioning in neonates with recovering RDS, evolving BPD or neonatal ARDS without relevant hemodynamic effect[13]. If proven beneficial, this strategy would decrease the need for respiratory support and the total duration of hospital stay reducing the financial burden and appropriate utilization of the resources especially in low-middle income countries (LMIC) where overcrowding of the neonatal units is a concerning issue. Hence, the study was conducted to evaluate the effect of prone positioning in comparison to supine position on the need for total duration of respiratory support in preterm neonates (<34 weeks).

MATERIAL AND METHODS

This study was conducted at a tertiary care hospital with a level III NICU in an LMIC. The study was carried out over 18 months from 29th June 2022 to 29th December 2023. Ethical approval was obtained from the Institutional Ethics Committee for human research. The study was performed in preterm neonates with a gestational age of $26^{0/7}$ to $33^{6/7}$ weeks, on any modality of non-invasive respiratory support [Continuous positive airway pressure (CPAP), Heated humidified high flow nasal cannula (HHHFNC) or Non-invasive positive pressure ventilation (NIPPV) or low flow oxygen] either as a primary or post-extubation modality enrolled within 7 days of birth. Those neonates requiring mechanical ventilation for more than 7 days, having persistent pulmonary hypertension, gross congenital abnormality, air leak, and umbilical venous/arterial catheter in situ were excluded. Due to the risk of displacement of the endotracheal tube, neonates on invasive ventilation were not included. After evaluating the neonates for eligibility, written informed consent was obtained from the parents/guardian. Both inborn and outborn neonates were recruited in the study. After enrolment, randomisation was done for eligible neonates by opening the sealed envelope. In the case of multiple births, each neonate was randomised independently. Randomisation was done either before or within 6 hours of initiation of non-invasive respiratory support. Neonates were randomised into two groups: Group 1: Intervention Group (Prone positioning), Group 2: Control (Supine positioning).

Neonates in the intervention group were nursed in the prone position for 120 minutes, followed by 120 minutes in non-supine state. The time duration of 2 hours was considered as the neonates were being given feeds every 2 hourly as a standard unit protocol, this avoids frequent handling of neonates with a bundle-care approach. Whereas neonates in the control group were nursed in supine and lateral positions with the change in position every 2 to 3 hours.

During the study period, neonates were managed as per the unit

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protocol for weaning or escalation of therapy. Being an open-labelled randomised trial, blinding of the investigators was not feasible.

Outcome measures:

The primary outcome of the study was to determine the total duration of respiratory support required by neonates on non-invasive respiratory support undergoing either prone or supine positioning. Secondary outcome parameters assessed were peak Fio2 required, number of apneic episodes, and duration of hospital stay. The endpoint of the study is defined as the time when the neonate is weaned off from respiratory support for atleast 72 hours with no evidence of respiratory distress.

In case the baby in the prone positioning group needs assessment and the position has to be changed to supine/lateral positioning, the same is documented in the proforma and is based on the clinician's decision.

Sample size –

The mean (SD) duration of respiratory support required in $26^{0/7}$-$33^{6/7}$ neonates was 16 ± 4.5 days. During the study, we expected that the prone positioning would reduce the duration of non-invasive respiratory support by at least 3 days. A sample of 36 in each group, (total of 72) would detect this difference with 80% power and an α error of 5%.

Statistical analysis -

Data analysis was performed using SPSS version 21. Descriptive statistics were used wherever possible in the form of proportions and means with SD. Quantitative and continuous variables were analyzed using the Mann-Whitney Test (for non-normally distributed data) and independent t-test (for normally distributed data). Quantitative and categorical variables were analyzed using the Chi-Square test/Fisher's Exact test. For statistical significance, p value of less than 0.05 was considered significant.

RESULTS-

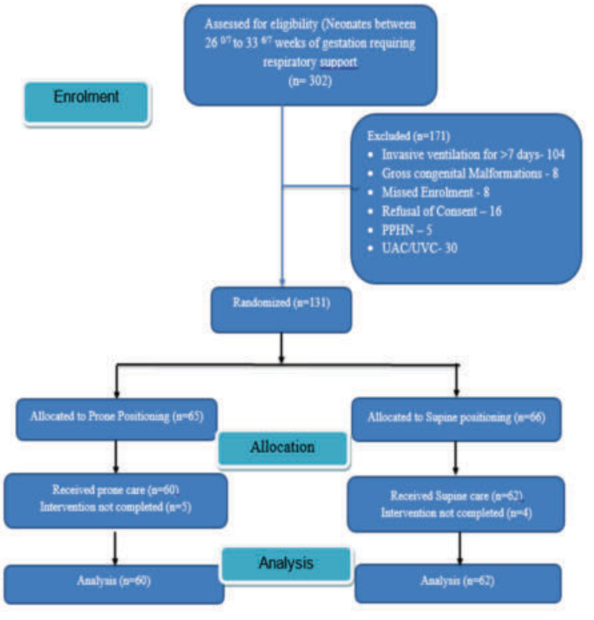

Fig 1: Consort Flow Diagram: Study Enrolment, Intended Randomization, Actual Randomization

During the study period, 29th June 2022 to 29th November 2023, a total of 499 neonates were admitted to neonatal intensive care unit (NICU) with a gestational age of $26^{0/7}$ to $33^{6/7}$ weeks. Of these, 302 infants required some form of respiratory support, irrespective of aetiology. Considering the inclusion criteria, 131 neonates were enrolled, 65 to group 1 (prone positioning group) and 66 to group 2 (supine positioning group) as depicted in the Consort flow diagram (Fig 1).

The baseline characteristics of the neonates in the two groups were similar as depicted in Table 1. Age at the start of the intervention (Median) was also comparable (1.5 hours vs. 1 hour, p = 0.5).

Table 1: Demographic Characteristics of Study Subjects

	Group 1 Prone positioning group N = 60	Group 2 Supine positioning group N=62	P value
Mean Birth Weight (SD; grams)	1286(468)	1200(456)	0.31
Mean GA (SD; weeks)	30.0(1.2)	30.3(1.6)	0.25
Male, (%)	34(56.7%)	36(58.1%)	0.88
SGA, (%)	14(23.3%)	16(25.8%)	0.75
Resuscitation required at birth	17(28.3%)	16(25.8%)	0.76
Cesarean section	18(30%)	19(30.6%)	0.94
Complete Antenatal steroids coverage	22(36.7%)	24(38.7%)	0.82
Outborn	18(30%)	20(32.2%)	0.79
Cause of respiratory distress: a. RDS	38(63.3%)	36(58%)	0.55
b. TTNB	12(20%)	10(16.1%)	0.58
c. Others	10(16.7%)	16(25.8%)	0.22
Maternal Characteristics			
Primigravida	26(43.3%)	29(46.8%)	0.70
Infant of Diabetic Mother	3(5.0%)	01(1.6%)	0.29
Anemia	26(43.3%)	25(40.3%)	0.74
Pre-eclampsia	16(26.6%)	20(32.2%)	0.50
Multiple gestation	06(10%)	09(14.5%)	0.45
AREDF	06(10%)	05(8.1%)	0.71
APH	06(10%)	07(11.3%)	0.81
PPROM	26 (43.3%)	28 (45.2%)	0.84
Mean Admission-delivery interval (SD; h)	27.5 (34.4)	27.9 (48.8)	0.96
* AREDF- Absent/Reversal end diastolic flow, APH- Antepartum hemorrhage, GA- Gestational age, PPROM- Preterm premature rupture of membrane, RDS- Respiratory distress Syndrome, SD- Standard deviation, SGA- Small for gestational age, TTNB- Transient tachypnea of newborn			

Primary outcome

The median duration of non-invasive respiratory support in the intervention group was 96(30-220)h and 90.5(40-256)h in the control group (p= 0.4). **(Table 2)**

Secondary outcomes

Both groups were compared for the pre-specified secondary outcomes. The mean duration of prone position is 10 ± 3.2 hours in group 1. Considering the overall duration of respiratory support which is similar in both groups, the peak FiO2 requirement was significantly less in the intervention group [30% (30-30) vs. 35% (30-60), p-0.01]. The frequency of apnea per day was also lower in the prone group [0.5(0.5-1) vs 1(0.5-1.8), p-0.04].

Table 2: Effect of prone positioning in comparison to supine positioning on ventilatory parameters

Outcome Parameters	Intervention group (N=60)	Control group (N=62)	p value
Non-invasive respiratory Support duration (h); Median (IQR)	96(30-220)	90.5(40-256)	0.47
Duration of respiratory support (h)			
Total duration of respiratory support (h); Median (IQR)	304(56-454)	316(59.5-482)	0.5
Heated humidified high-flow nasal cannula (h); Mean (SD)	67.4(44.6)	77.6(63.5)	0.30
CPAP (h); Mean (SD)	167(135)	178(131)	0.65
NIMV (h) Mean (SD)	67 (65)	77 (67)	0.40

Ventilator parameters			
FiO2 at start of intervention (%); Mean (SD)	32 (9)	35 (11)	0.1
Maximum FiO2 requirement (%); Mean (SD)	30(30-30)	35 (30-60)	0.01
Maximum MAP cm H2O; Median (IQR)	6(6-7.5)	6(6.1-7.9)	0.2
Maximum PEEP cm H2O; Median (IQR)	6(5-6)	6(5-6)	0.1
Maximum PIP cm H2O; Median (IQR)	16(16.5-17.5)	17(16-17.5)	0.3
Frequency of apnea/day Median (IQR)	0.5(0.5-1)	1(0.5-1.8)	0.04
CPAP failure (%)	16(26.6)	17(27.4)	0.9
BPD (%)	12(20%)	10(16.1%)	0.58
Death during hospital stay (%)	2(3.3%)	1(1.6%)	0.54
Duration of hospital stay Mean (SD)	25(20)	23(22)	0.6
*BPD- Bronchopulmonary dysplasia, CPAP- Continuous positive airway pressure, h- hour, IQR- Interquartile range SD: Standard deviation			

DISCUSSION

Unveiling the effect of prone positioning in preterm neonates, the current study demonstrated improvement in terms of need for peak oxygen requirement during the weaning phase with improvement in the frequency of apnea, but no significant effect is demonstrated on the duration of total or non-invasive respiratory support.

A recently published study by Loi et al demonstrated improved gas exchange and lung aeration in the prone position in neonates with recovering RDS as well as in evolving bronchopulmonary dysplasia (BPD) and this effect was overturned in the alternate position, except for lung aeration in neonatal ARDS with no adverse effect on hemodynamic stability[13]. The effects were more in patients recovering from RDS than in those with evolving BPD and ARDS. This could be attributed to better carbon dioxide elimination and recruitment of well-perfused but previously collapsed alveoli and the reduced overdistended pulmonary units that can collapse alveolar capillaries and increase the dead space[1,14]. This study has evaluated the effect of 6 h pronation and has also included neonates on invasive ventilation, which differs from our study and might be the reason for differing results.

Several earlier studies suggested better respiratory parameters with reduced work of breathing and less apnoea in pronated neonates. Heimler et al reported reduced frequency of central apnea and periodic breathing in prone placement in stable preterm infants with recent episodes of apnea and bradycardia.[15] In contrast an inconsistent result with no significant difference in the incidence of apnea, bradycardia, or desaturation was noted in a randomized cross-over trial by Keene et al in preterm neonates (<34 weeks) receiving CPAP.[16] Metanalysis of the currently available literature favoured prone positioning in invasively ventilated neonates with slightly improved oxygenation (low to moderate certainty of the evidence). However, the studies included were limited by a small sample size and did not include neonates on non-invasive ventilation which is currently the modality of choice[17]. Moreover, these studies were performed in neonates with variable gestational age and differed in their inclusion criteria, diagnosis as well as clinical severity.

In the present study, the effect of positioning in neonates while on non-invasive respiratory support is evaluated which is currently accepted modality by all neonatologists. The study demonstrated no adverse event associated with prone positioning and has a short learning curve for nursing staff. It is safe, and feasible and matches the NICU standards, as the bundle care was followed and the neonates were handled 2 hourly with feeding.

In a prospective observational study, Bhat et al studied the effect of prone and supine positions on sleep, apnea, and arousal in 24 preterm neonates, out of which 14 neonates had BPD at a median postconceptional age of 37 weeks. Neonates in prone positions slept longer and had greater sleep efficiency in quiet sleep but had more central apnea. Arousal being an important survival response to a life-threatening event, increases behavioural-evoked ventilation and hence reemphasises the need for supine sleeping after discharge. However, the population differed from the above-mentioned studies as Bhat et al enrolled asymptomatic neonates whereas others included neonates with apnea and/or bradycardia[18].

Gouna et al, in a similar RCT in preterm neonates receiving CPAP, reported both left lateral and prone position to be associated with improvement in lung function with reduced peak FiO2 requirement in the prone position, which is similar to the current study[19]. A similar effect of prone positioning was documented during invasive ventilation favouring more rapid reduction of ventilator settings, such as PIP and ventilator rate.[20] As the beneficial effect of pronation depends on more uniform gas/tissue ratio, a patient with greater inhomogeneity can be benefitted more from this intervention[1,14].

Acknowledging the limitations, due to the nature of the intervention blinding could not be established, also the data of desaturation and apneic episodes were collected based on the alarm monitors, which could have missed self-recovering transient episodes. Also, the study results are limited to neonates receiving non-invasive respiratory support. Although, the study demonstrated lesser peak FiO2 requirement and apnea frequency in the prone group, but the neonates enrolled were stable and hence the results could not be generalised. This calls for a need to conduct a study on hemodynamically compromised critically ill neonates as these neonates might maximally be benefitted from the intervention.

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