RESEARCH PAPER

Cardiorespiratory Adverse Events after First Vaccination in Preterm Neonates With Gestational Age ≤30 Weeks

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Objectives: To document the adverse cardiorespiratory events following first routine immunization in preterm neonates. **Methods**: We retrieved records of neonates with gestational age ≤30 weeks, and included those who developed cardiorespiratory events after first vaccines before discharge. Our Unit's protocol is to administer Bacillus Calmette-Guerin (BCG), hepatitis B vaccine to those discharged at <8 weeks postnatal age. Hexavalent, BCG, pneumococcal vaccine and rotavirus vaccines are given at 8 weeks of age, if hospital stay is predicted to be longer. Unit compliance to vaccination administration at appropriate ages were also measured. **Results**: Data of 161 neonates ≤30 weeks (17.4% <27 week) who completed care in the unit was studied. Cardio-respiratory adverse events were reported in 21(13.7%). None of these required initiation of invasive ventilation. High flow nasal cannula therapy and caffeine restart were required for these events in 14 (9.3%) and 6 (3.9%) neonates, respectively. Lower gestational age, bronchopulmonary dysplasia and sepsis were significant risk factors on univariate analysis. On multivariate analysis, continued need for respiratory support at 4 weeks of age (*P*=aOR 14.5 (95% CI 5-59.1) was the only independent risk factor for post-vaccination cardiorespiratory adverse events. Of 38 who were not vaccinated at recommended ages by unit policy, 25 were missed opportunities, the rest were deemed unstable for vaccinations at that age by the clinical team. **Conclusion**: Adverse cardiorespiratory events were uncommon after first vaccinations in very preterm neonates. Administering vaccines in this group before discharge would allow monitoring for these events, especially for those who require long-term respiratory support.

Keywords: *AEFI, BCG vaccine, Missed opportunity for vaccination, Ventilation*.

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Vaccination is an effective intervention to reduce the morbidity and mortality due to vaccine preventable diseases (VPD). Available data supports the fact that vaccines are immunogenic and tolerated by preterm infants [1,2]. Preterm infants are susceptible to postnatal acquisition of VPD, they should ideally undergo immunization without correction of gestational age. The World Health Organization [3] and Advisory Committee on Vaccines and Immunization Practices of the Indian Academy of Pediatrics [4] recommend that all infants receive immunization regardless of any restriction based on gestational age or birth weight, with the qualified exception of hepatitis B vaccine, as the birth dose is not counted toward the full schedule due to reduced immune response. There is lack of literature about vaccination policies and actual practices from centers which care for very preterm neonates [5]. Measuring clinically significant adverse events would be the first step to design recommendations on optimal timing of the vaccines.

Our unit has a written policy towards planning vaccinations in very preterm infants in the NICU itself according to their chronological age. These infants can then be monitored for adverse events, if any. This study was planned to analyze the factors associated with cardiorespiratory adverse events following first vaccination in very preterm neonates.

METHODS

This review of hospital records was conducted in a 33-bedded Level IIIB (national Neonatology Forum India) neonatology department in Kerala. The unit has in place written policies for respiratory support of preterm neonates, caffeine therapy for apnea of prematurity, and discharge criteria [6]. Those ≤30 weeks of gestation who completed care in the unit between June, 2018 and June, 2022 were included. Relevant details were retrieved from electronic medical records (EMR).

We studied as primary outcome, proportion of very preterm neonates, who developed predefined cardiorespiratory events (CRE) after first vaccination before discharge. Our unit protocol is to administer BCG, Hepatitis B to those discharged before eight weeks

postnatal age. Since, discharge is generally not expected till beyond two weeks of life in these preterm babies, we do not administer birth dose OPV to ≤30 weeks infants [7]. Hexavalent vaccine (DTaP+IPV+Hib+Hepatitis B), BCG vaccine, pneumococcal, and rotavirus vaccine are given (staggered over 2 days) at 8 weeks postnatal age, if hospital stay is expected/predicted longer than that. Post-vaccination, these infants are monitored in the neonatal intensive care unit (NICU) with pulse oximetry for at least 48 hours. If there are ongoing supports or if CRE are noted, then multi-parameter monitoring with (ECG) and (NIBP) are also done. If the infant had been roomed-in before the eligible postnatal age for vaccinations, they were shifted back to NICU for that period of observation post-vaccination. Unit compliance to vaccine administration at appropriate ages, reasons for non-compliance, and risk factors for CRE were also measured. CRE was defined as apnea with drop in saturation below 80% and any one of: *i*) heart rate <100/min, *ii*) poor respiratory effort requiring positive pressure ventilation, *iii*) need to start/increase respiratory support for more than one hour by high flow nasal cannula/continuous positive pressure ventilation/mechanical ventilation, and *iv*) restart or increase dose of caffeine therapy due to recurrent apnea.

Presuming the incidence of adverse events following vaccination in preterm as 13% based on a previous study [8], we planned a sample size of 174, to achieve a precision of 5% and confidence level of 95%.

Statistical analysis: We used STATA ver 16.0 for analysis. Outcomes were expressed as proportions. Univariate analysis of risk factor association with CRE was done using Fisher-exact test, and logistic regression was used for multivariate analysis. Institute ethics committee clearance was obtained for retrieving de-identified data from the electronic medical records.

Table I Baseline Characteristics of Study Participants (*N*=161)

Characteristic	*Value*
Gestational age	
29-30 wk	76 (47.2)
27-29 wk	57 (35.4)
24-26 wk	28 (17.4)
Birthweight (g)[a]	1045 (875,1250)
Respiratory support	157 (97.5)
Duration of respiratory support (d)[a]	8 (4,29)
Need for support at 4 wk age	41(25.5)
Bronchopulmonary dysplasia	14 (8.7)
Culture positive sepsis	27 (16.7)
Periventricular leukomalacia (≥grade 2)	4 (2.5)
Anemia requiring transfusion	46 (28.6)

Values in no. (%) or median (IQR).

RESULTS

Data of 161 neonates with gestational age ≤30 weeks (17.4% <27 weeks) who completed care in the unit were included. The median (IQR) gestational age at birth was 28 (27-29) weeks. Most infants (97.5%) required some form of respiratory support during their NICU care; the median (IQR) duration of invasive ventilation was only 1(0,3) days (**Table I**). Important observations relevant to vaccine administration are represented in **Table II**. First vaccines were given at median postnatal age of 51(42,61) days; at postmenstrual age of 35 (35,36) weeks.

Predefined and clinically relevant cardiorespiratory adverse outcomes (CRE) were noted in 21(13.7%) of all those included. Of these, 20 infants had bradycardia, which qualified as pre-defined CRE. However, none of the CRE required re-institution of mechanical ventilation or CPAP (**Table II**). Similarly, there were no episodes of hypotension, or need for commencement of parenteral fluids after vaccination. In 11 (52.3% of those who had CRE) infants, the events were noted within 12 hours of vaccination; 10 (47.6%) occurred between 12-24 hours post-procedure; only 1 (4.7%) infant had the CRE after 24 hours. None happened during the process of injections per se. Although lower gestational age, BPD and sepsis were also significant risk factors on univariate analysis; on multivariate analysis, continued need for respiratory support at 4 weeks of age was an independent and significant risk factor for CRE post-vaccination, aOR 14.5(95% CI 5-59.1) (**Table III**). It would be prudent to monitor these high risk infants for at least 48 hours in an equipped environment for CRE after vaccines.

Table II Details of Vaccines Received by Preterm (≤30 Weeks) Neonates (*N*=61)

Detail	*Value*
Received hexavalent vaccine, PCV, Rotavirus vaccines along with BCG as first doses before discharge	99 (64.3)
Postnatal age of vaccination (d)[a]	51 (42,61)
Postmenstrual age of vaccination (wk)[a]	35 (35,36)
Cardiorespiratory adverse events (CRE) related requirements	
Mechanical ventilation or CPAP required	0
High flow nasal cannula	14 (9.3)
Caffeine restart	6 (3.9)
Combinations of more than one therapy	5 (3.5)

Values in no. (%) or [a]median (IQR). BCG: Bacille Calmette-Guerin; CPAP: continuous positive airway pressure; PCV: pneumococcal vaccine.

Table III Factors Associated With Cardiorespiratory Events Post-vaccination in Preterm (≤30 Week) Neonates (*N*=161)

Risk factor	*CRE, n=21*	*OR (95% CI)*
Gestational age <27 wk[a]	10 (35.7)	6.2 (2-18.4)
Respiratory support at 4 wk[a]	18 (44)	30.5 (7.8-169.3)
Culture positive sepsis[a]	9 (33)	5.1 (1.6-15.2)
BPD (36 wk PMA)[a]	7 (50)	9.5 (2.4-36.3)
Invasive ventilation	17 (5.5)	2.1 (0.64-9.2)

Values in no (%). CRE:cardiorespiratory events; BPD: bronchopulmonary dysplasia; PMA: postmenstrual age. [a]P<0.001.

The unit was compliant to appropriate age for vaccinations according to the policy in 123 (76.4%) infants. Of 38 infants where the vaccinations were delayed, 25 were clearly missed opportunities. We realized that there is scope for quality improvement in this regard. A conscious decision by the clinical team to delay the vaccines based on ongoing respiratory instability was made in the remaining 13 infants.

DISCUSSION

The proportion of very preterm infants who developed CRE within 48 hours of first vaccinations before discharge was 13.7% in our study. Vaccination was done at the appropriate age as per unit policy in only 76.4% infants.

Many reports suggest adequate seroprotection after vaccines in preterm neonates [1,2,4]. Many Indian authors have expressed concern about delay in vaccination of preterm infants, mainly due to safety concerns either by healthcare professionals or parents [5,9]. Fear of adverse events in those with ongoing respiratory instability at appropriate age of vaccination seems to be evident.

In an observational study of 78 preterm infants [10], transient cardiorespiratory events (apnea, bradycardia, desaturations) were noted in 47% of infants. Schulze, et al. [8] studied preterm neonates with mean gestational age of 28 weeks. Apnea and bradycardia following immunization with hexavalent/pentavalent vaccine was found to be 13%. Older studies with small number of patients have reported adverse events in nearly one-third of preterm infants, especially when vaccinated before 70 postnatal days [11]. In our cohort, all those who had CRE had received hexavalent vaccine. Faldella, et al. [12] reported the safety of hexavalent vaccines in very preterm, concluding that these infants can be given the vaccines at 8 weeks of age with monitoring. They also reported no adverse effects on cardiac electrical activity or cerebral blood flow variations associated with first vaccination [12].

Risk of adverse events following immunization in preterm infants are better predicted by underlying cardiorespiratory instability at the time of vaccination than by gestational age or birth weight [5]. Faldella, et al. [12] noted apnea/bradycardia/desaturations in those who had chronic underlying illnesses. We too noted that continued need for respiratory support up to and beyond 4 weeks of age as a significant and independent risk factor for cardiorespiratory events. Pre-existing cardiorespiratory symptoms, those who had similar clinical manifestations in the 24 hours prior to vaccination, or those with the most severe illnesses at birth are at higher risk of adverse events post procedure [10]. Authors of a recent multicentric retrospective study reported that sepsis evaluations, need for intubations and respiratory support were higher in the 3-day post vaccination period in extreme preterm infants who received either single dose or combination vaccines [13].

Our study is limited by the retrospective study design. We had data on only 28 (17.4%) infants below 27 weeks. More research is required to make recommendations in this group, who often require longer duration of respiratory supports and have potentially higher risk of post-vaccination adverse events. Since our unit protocol includes only combination (hexavalent) vaccines at 8 weeks, there was no comparison possible between different types of vaccines. Hence, no definite conclusions on safety of hexavalent vaccines can be drawn from our findings.

Clinically relevant cardiorespiratory adverse events within 48 hours of first vaccinations given before discharge were noted in 13.7% of preterm neonates of less than 30 weeks gestation. Need for respiratory support till 4 weeks of postnatal age was a significant and independent risk factor for CRE. This data supports the recommendations that vaccinations need not be delayed for very preterm infants. Administering first vaccines based on chronological age before discharge would allow appropriate monitoring, especially in those who required long-term respiratory support.

Ethics approval: EIC, KIMS; No. KIMS/IHEC/TP030/2022 dated September, 2022.
Contributors: NJ conceived the study; HS, FP, NJ designed the study; HS collected data; FP and NJ conducted data analysis. FP drafted the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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WHAT THIS STUDY ADDS?

- Cardiorespiratory events are not common after first vaccinations in very preterm neonates, if done at recommended chronological ages.
- Neonates requiring long-term respiratory care need to be monitored post-vaccination.

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