

Short Term Neurobehavioral Outcomes in Late Preterm Neonates Born to Pre-Eclamptic Mothers

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Objective: To study the effect of maternal pre-eclampsia on the short-term neurobehavioral outcomes in late preterm neonates using Neurobehavioral Assessment of Preterm Infants (NAPI) score. **Methods:** 30 late preterm neonates born to mothers with preeclampsia, and thirty controls born to mothers without pre-eclampsia were enrolled, and followed up to 40 weeks of post-menstrual age. They were evaluated by NAPI score of MDV (Motor development-vigor) and AO (Alertness orientation) at 40 wk. **Results:** The mean NAPI score of MDV in cases was 60.1 (9.56) as compared to 70.0 (11.48) in controls ($P < 0.001$). The mean NAPI score of AO in cases was 37.45 (11.04) as compared to 45.6 (13.33) in controls ($P = 0.006$). **Conclusions:** Late preterm neonates born to mothers with pre-eclampsia have poor short term neurobehavioral outcomes.

Keywords: NAPI score, Eclampsia, Pregnancy induced hypertension.

The neurodevelopmental outcomes in infants born to mother with preeclampsia are highly variable [1,2], with some studies showing reduced incidence of cerebral palsy [3] whereas others showing poor neurodevelopmental outcomes [4]. Neurobehavioral assessment of preterm infants (NAPI) is a neurobehavioral assessment tool which is designed to measure the relative maturity of functioning in preterm infants aged 32 weeks conceptional age to term. NAPI has a positive co-relation with the neurobehavioral status at 18 months as assessed by Bayley scales of infant development (BSID) [4]. The main objective was to study the effect of maternal pre-eclampsia on neurobehavioral outcome in late preterm neonates by NAPI score.

METHODS

This observational study was conducted from January 2014 to January 2015 in a tertiary-care neonatal unit at Kalawati Saran Children's Hospital, Lady Hardinge Medical College, New Delhi, India. The study was approved by the Institutional ethics committee, and informed consent was taken from each parent before inclusion in the study.

All late preterm infants (34-36⁶ wk) born to mothers with pre-eclampsia were included as Cases, defined as per ACOG criteria [20]. Gestational age assessment was done by last menstrual period (LMP) or by first trimester

scan, if LMP was not available. Patients with major congenital malformation, eclampsia (seizures in mother), mothers on antipsychotic drugs, clinical chorioamnionitis, and birth asphyxia were excluded from the study. An equal number of late preterm neonates born to mothers without pre-eclampsia were enrolled as Controls.

Demographic data, maternal history, labor details and neonatal details were recorded in a tested proforma. Admitted neonates were managed as per standard treatment protocol of the department. The parents of all the enrolled neonates were instructed to report for follow up at 40 weeks PMA of the baby. The parents were reminded telephonically two days before and on the day of follow-up.

NAPI is a standardized kit of neonatal neurobehavioral status [7] which measures the progression of the neurobehavioral performance and can be used effectively to screen preterm infants, monitor their individual progress and assess the effects of NICU interventions. NAPI is appropriate for infants between 32 weeks post conceptional age (PCA) and term.

At 40 weeks PMA, each baby underwent an assessment for the neurobehavioral status according to the NAPI score. Scoring was done on the record forms provided with the standard NAPI kit. The examination was carried out in the nursery/neonatal ward, 45 minutes prior to next feeding time. The infant to be examined was

placed under a radiant warmer with temperature probes attached. At the beginning of the examination, the behavioral state was observed and recorded according to the categories stated in the record form provided. The NAPI items were administered in an invariant sequence and assessment was done for two clusters, Motor Development-Vigor and Alertness-Orientation. Subsequently raw scores were transposed into percentage scores to ensure comparability between items, combined and averaged into clusters. For all participants, NAPI was administered by one investigator who was blinded about the group allotment.

Primary outcome variable was Neurobehavioral score by NAPI at 40 weeks of PMA for MDV (Motor development- vigor) and AO (Alertness-orientation). Neonates identified as neurobehaviorally deviant were referred for early stimulation and developmental rehabilitation.

For a power of 80% with an alpha error of 0.05 and an assumed difference of 20% between the groups, the total sample size estimated was 48 (24 in each limb). Assuming a lost to follow-up/dropout rate of 10-15% and rounding off, a total of 60 preterm neonates were enrolled.

Statistical analysis: The quantitative variables were compared using Mann-Whitney test. The qualitative variables were compared using Chi-square/Fisher's exact test. A *P* value of <0.05 was considered statistically

significant. SPSS version 15.0 software was used for statistical analysis.

RESULTS

The flow of participants into the study is presented in **Fig.1**. There was no significant difference between the two groups with respect to general demographic profile, antenatal findings and resuscitation details, except more males among controls (**Table I**).

The median NAPI score of MDV (Motor development- vigor) and AO (Alertness-orientation) in babies of pre-eclamptic mothers in cases were significantly lower as compared to the controls [60.8 (53.64-64.4) vs 66.4 (61.58-78.61); $P < 0.001$ for MDV] and [36.4 (27.76 - 45.25) vs 44.6 (35.25 - 56.89); $P = 0.006$ for AO]. This indicates that neonates born to mothers with pre-eclampsia had less mature neurobehavior as compared to babies born to mothers without pre-eclampsia.

DISCUSSION

In the present study NAPI assessment was done at 40 weeks of post conceptional age. The mean NAPI score of MDV and AO was less in pre-eclampsia group as

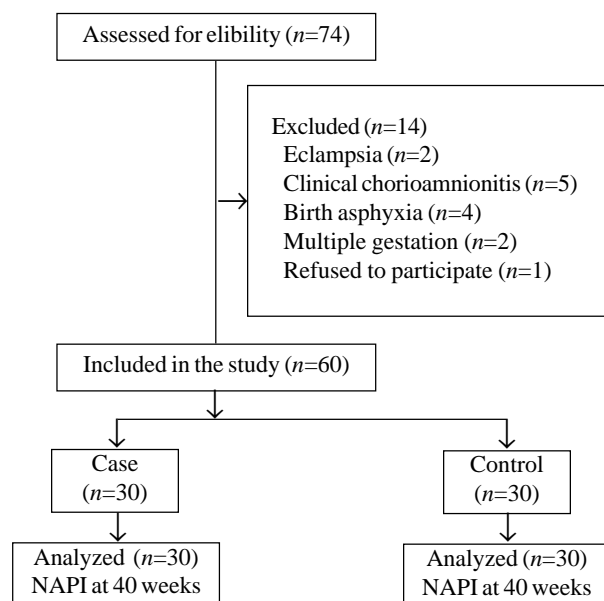


FIG. 1 Study flow diagram.

TABLE I COMPARISON OF BASELINE CHARACTERISTICS OF NEONATES BORN TO MOTHERS WITH PRE-ECLAMPSIA AND CONTROLS

Parameters	Cases (n=30)	Controls (n=30)
*Males	16 (53.3)	18 (60)
Birth weight (g)	2128 (1800-2500)	2225 (1812-2390)
Gestational age (wk)	35 (34-36)	36 (35-36)
[§] Maternal age (y)	27 (24.25-29)	24 (22-27)
*Oligohydramnios	1 (3.3)	1 (3.3)
*Fetal distress	1 (3.3)	1 (3.3)
*Antenatal steroids	10 (33.3)	6 (20)
*Normal delivery	18 (60)	13 (43.3)
*Ventouse	1 (3.3)	0
APGAR score		
1 min	8 (8-8)	8 (7.25-8)
5 min	9 (9-9)	9 (9-9)
Length (cm)	45 (42-47)	46 (42-47)
Head circumference (cm)	31.25 (30-32.4)	30.25 (29-32)
Abdominal circumference (cm)	28 (27-29)	27 (26-29)
Ponderal index	2.43 (2.18-2.63)	2.30 (2.04-2.58)

All values in median (IQR) except *no. (%); [#] $P = 0.03$; [§] $P = 0.004$.

WHAT THIS STUDY ADDS?

- Late preterm neonates (34-36 week gestational age) born to mothers with pre-eclampsia have poor neurobehavioural outcomes at 40 week post-menstrual age.

compared to controls which indicates that neonates born to mothers with pre-eclampsia had less mature neurobehavior.

NAPI has been evaluated as a tool to assess neurobehavior in preterm neonates including late preterm neonates has not shown any difference in SGA and AGA neonates [21]. There are no published studies in the literature, to the best of our knowledge, which have evaluated the neurobehavioral outcomes in late preterms born to pre-eclamptic mothers. It is thus postulated that pre-eclampsia independently affects the neurobehavioral maturity of preterm neonates.

A recent study by Salzbank, *et al.* [11] evaluated the effect of pre-eclampsia on neurobehavior of infants at 6 months postpartum. The neurobehavioral assessment in this study was done using Infant Behaviour Questionnaire-Revised at six months post-partum [11]. There are many other studies which have evaluated neurodevelopmental outcomes in neonates born to pre-eclamptic mothers at later age. Previous authors [12,13] have shown that neonates born to pre-eclamptic mothers had lower MDI (Mental Development Index) scores at 24 months of age and lower mean PPVT-R (Peabody picture vocabulary test) scores.

There is also a positive correlation between NAPI and scales of neurodevelopment done at later age. Studies have shown positive correlation between NAPI and BSID at 18 months [14,15]. Other studies [16] suggest that early or short term neurobehavioral assessment is a useful tool for early identification and rehabilitation of infants at risk for a poor outcome [16].

There are many probable reasons for poor neurobehavioral outcomes in neonates of mothers with pre-eclampsia. Most of these patients have reduced placental blood flow resulting in decreased fetal growth with IUGR and low birth weight. Chronic placental insufficiency present in pre-eclampsia has the potential to influence fetal brain perfusion and lead to long-term effects on brain development and intelligence ischemic model of pre-eclampsia [17]. The episodes of placental hypoxia or re-perfusion result in oxidative stress, and excessive systemic inflammatory response of pre-eclampsia could directly affect the growing brain of the fetus [18]. The antiangiogenic state of the mother is also

shared by the fetus, as cord blood VEGF and placental growth factor levels are decreased, whereas sFlt-1 levels are increased. This may contribute to poor outcome in these neonates [18].

The major limitation of the study is that the role of pre-eclampsia on neurodevelopment was not assessed in very and extreme preterm neonates, who are more likely to be susceptible to disabilities. The importance of the study lies in the fact that babies with poor neurobehavior can be detected early and appropriate intervention measures can be undertaken. The follow-up of study subjects was only conducted till 40 weeks and a longer follow up for deviant neurodevelopmental outcomes would have been prudent at 12 and 18 months of chronological age using structured neurodevelopment assessment tools.

This study raises the possibility of poor neurobehavioral outcomes in late preterm neonates born to mothers with pre-eclampsia, and the possibility of early identification, thereby assisting in interventions and close follow-up.

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