Original Article

Effect of Repeated Painful Stimuli on Pain Response in Term and Late Preterm Neonates: An Obstetric - Neonatal Continuum - Based Prospective Cohort Study

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Abstract

Background: It is documented that neonatal pain perception is well structured, but the and capacity of repeated painful procedures carried out at early neonatal life stages in changing consecutive pain responses is disputed. Obstetric factors that affect fetal stress, maturity, and admission of newborns to the neonatal intensive care unit (NICU) can be critical in the modulation of neonatal pain processing; yet, they are frequently not adequately represented in studies of neonatal pain. The objective is to assess how repeated painful stimuli affect behavioural pain response in neonates 34 weeks old or older, after conception, and combine/ ingest any prenatal and birth-related obstetric factors that could moderate neonatal pain adjustment. **Material and Methods:** It was a prospective cohort study conducted at a tertiary-care teaching hospital from October 2021 to September 2022. A total of 100 neonates (34 weeks post-conceptional age) were recruited and divided into cases (undergoing more than 10 painful procedures in the NICU) and controls (undergoing fewer than three painful procedures). The matching of the groups was based on post-conceptional age, postnatal age (within a range of 7 days), and sex. A uniform, painful stimulus was used: intramuscular injections of Hepatitis B vaccine at the time of discharge. Duration of cry (Primary outcome), latency to cry, and Modified Facial Coding Score (MFCS) were used to evaluate the behavioural pain reactions. Obstetric variables, including details of antenatal, intrapartum, and delivery-room care, were prospectively documented and studied as possible factors in modifying the response to pain. **Results:** The median length of cry was not significantly different between cases [26 seconds (IQR 20 48 seconds)] and controls [30.5 seconds (IQR 20 78 seconds)] ($p > 0.05$). There was equal latency to cry. Immediately after the injection, the MFCS scores in NICU-exposed neonates were much higher, but the disparities resolved by 1 and 3 minutes. Antenatal complications, mode of delivery, and delivery-room interventions remained unaffected in the independent effects of obstetric risk factors on pain response when gestational maturity was factored in. **Conclusion:** Repeated exposure to painful procedures in infants with a neonatal age of at least 34 weeks after conception gained no significant changes in general behavioural pain response. Neonatal pain processing seems to be moderated by gestational maturity factor and obstetric antecedents rather than being influenced by cumulative procedural exposure per se. These results highlight the role of combined obstetric-neonatal interventions, focused on reducing stress in the first days and improving neurodevelopmental outcomes.

Keywords: Neonatal pain; Repeated painful procedures; Gestational maturity; Late Preterm neonates; Neonatal intensive care unit; Behavioural pain response.

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Introduction

The perception of pain in the human newborn has now become a dynamic and complex neurobiological process rather than a mere reflex. The anatomical pathways of nociception, such as peripheral receptors, spinal synapses, and supraspinal pathways, are present from early fetal life. However, at the time of delivery, the organization of the pathways is immature.[1] Specifically, descending pathways that inhibit the input of nociceptive peripheral neurons by the brainstem and cortex mature in late gestation and early postnatal life.[2]

Animal experiments have shown that when repetitive noxious stimuli are experienced during critical developmental stages of neuronal development, permanent changes in nociceptive systems, the pain window, and stress sensitivity can be induced.[3] It has not been easy to translate these

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findings into human neonates, and the evidence available is also inconsistent. Some clinical studies indicate increased sensitivity to painful procedures, or hyperalgesia, in later life when repeated painful procedures occur during early life.[4,5] Still, other studies show attenuation or no significant change in pain response.[6–8]

The biggest weakness of the previous study of neonatal pain is the relative emphasis on obstetric antecedents. It is known that antenatal and intrapartum factors such as maternal stress, infection, hypertensive disorders, mode of delivery, and intrapartum analgesia are known to impact neuroendocrine functioning of the fetus and the neonatal stress physiology.[2,10] These aspects as well predispose to NICU admission and subject exposure to various painful procedures, thus being upstream determinants of neonatal pain experience.

Moreover, gestational maturity is important in influencing the development of pain modulation. Infants who are born with extremely low gestational ages experience immature inhibitory control and hyper-responsive behavioural reactions to pain, and Late Preterm and term infants portray more organised neurobehavioral functions.[5,11] Nonetheless, there are limited data on the interaction between repeated exposure to pain and gestational maturity beyond 34 weeks of gestational age, past the conceptional age.

The current research study was planned within the context of the obstetric-neonatal continuum, and the hypothesis was that neonates of at least 34 weeks post-conceptional age with repeated exposure to painful procedures in the early neonatal period would exhibit an exaggerated behavioural response to a subsequent standardised unpleasant stimulus. By integrating detailed antenatal and intrapartum variables, this study aims to clarify the relative contributions of neonatal procedural pain and obstetric determinants to pain processing in Late Preterm and term infants.

Materials and Methods

Study Design and Setting: This prospective cohort study was conducted in the NICU and immunization clinic of the Department of Paediatrics at a tertiary-care teaching hospital in North India between October 2021 and September 2022. Institutional Ethics Committee approval was obtained, and written informed consent was secured from parents or guardians.

Study Population: Neonates with post-conceptional age ≥34 weeks at the time of assessment were eligible.

Case Group: Neonates admitted to NICU who had undergone more than 10 documented painful procedures during their hospital stay.

Control Group: Neonates of comparable post-conceptional age, postnatal age (±7 days), and sex who had been exposed to fewer than three painful procedures and had not required prolonged NICU care.

Exclusion Criteria

- NICU stay >15 days
- 25 painful procedures
- Apgar score <5 at 5 minutes
- Major congenital anomalies
- Major surgical intervention
- Fever (>100°F) at time of vaccination
- Exposure to analgesics, sedatives, or neuromuscular blockers in the preceding 24 hours

Obstetric Data Collection

To strengthen the obstetric contribution, the following variables were prospectively recorded from maternal and delivery records for all enrolled neonates:

Antenatal Factors

- Gestational age at delivery
- Antenatal corticosteroid exposure (complete / incomplete / none)
- Maternal infections (chorioamnionitis, PROM >18 hours, UTI)
- Hypertensive disorders of pregnancy
- Intrauterine growth restriction
- Maternal hospitalization or significant antenatal stress

Intrapartum Factors

- Mode of delivery (vaginal, instrumental, caesarean)
- Indication for operative delivery
- Duration of labour (normal vs prolonged)
- Intrapartum analgesia or anaesthesia
- Evidence of fetal distress

Delivery-Room Factors

- Need for resuscitation (stimulation, bag-mask ventilation, suctioning)
- Time to first cry
- Early mother–infant contact

Neonates were categorized into low-, moderate-, or high-obstetric-risk strata based on cumulative antenatal and intrapartum risk factors.

Definition of Painful Procedures

Painful procedures included heel lance, venipuncture, IV cannulation, arterial puncture, nasogastric tube insertion, repeated oral/nasal suctioning, and urinary catheterization. Each episode was prospectively documented.

Standardized Pain Stimulus

All neonates received 0.5 ml intramuscular Hepatitis B vaccine at discharge using:

- 2-ml syringe
- 23-gauge, 1-inch needle
- Anterolateral thigh

Vaccination was chosen as an ethically acceptable, clinically necessary, and standardized pain stimulus.

Pain Assessment Protocol

To minimize confounding:

- All infants were fed within 3 hours, but not within 30 minutes of injection
- Procedure conducted in a warm, quiet environment
- Infants held by mother without rocking or verbal soothing
- No non-nutritive sucking or swaddling
- All procedures performed in Prechtl's state 3 or 4

Blinding and Recording

The vaccinator and video recorder were blinded to neonatal exposure status. Events were digitally recorded from needle insertion to 3 minutes post-injection.

Outcome Measures

Primary Outcome

- Duration of cry (seconds)

Secondary Outcomes

- Latency to cry (seconds)
- Modified Facial Coding Score (MFCS) immediately, at 1 minute, and at 3 minutes

MFCS included brow bulge, eye squeeze, nasolabial furrow, open mouth, chin quiver, and trunk movement (score 0–6).

Sample Size and Statistical Analysis

Fifty neonates per group provided 80% power at α=0.05. Data were analysed using STATA 9.1. Continuous variables were analysed using Student's t-test or Mann–Whitney U test; categorical variables using chi-square or Fisher's exact test. Obstetric variables were explored as covariates.

Results

Study Population and Baseline Characteristics

A total of 100 neonates with post-conceptional age ≥34 weeks were enrolled, comprising 50 neonates exposed to repeated painful procedures during NICU stay (cases) and 50 controls with minimal pain exposure. The two groups were comparable with respect to post-conceptional age, postnatal age at assessment, sex distribution, and time elapsed since last feed [Table 1].

Table 1: Baseline Characteristics of the Study Population

Characteristic	NICU-Exposed Neonates (n = 50)	Controls (n = 50)	p-value
Post-conceptional age (weeks), mean ± SD	35.6 ± 1.2	37.2 ± 2.1	>0.05
Postnatal age at assessment (days), median (range)	8(3-20)	7.5(3-18)	>0.05
Birth weight (kg), mean ± SD	2.27 ± 0.41	2.67 ± 0.47	0.003
Male sex, n (%)	27 (54%)	25 (50%)	>0.05
Time since last feed (minutes), mean ± SD	62.5 ± 30.4	62.0 ± 30.1	>0.05

NICU-exposed neonates had significantly lower mean birth weight compared to controls (2.27 ± 0.41 kg vs 2.67 ± 0.47 kg; p = 0.003), reflecting higher antenatal and perinatal morbidity in this group. There was no significant difference in gestational age between groups (35.6 ± 1.2 weeks vs 37.2 ± 2.1 weeks; p = 0.08).

Obstetric risk profiling revealed a higher proportion of moderate-to-high obstetric risk among NICU-exposed neonates, including increased rates of antenatal complications and operative deliveries; however, gestational age distributions overlapped substantially between groups [Table 2].

Table 2: Obstetric Risk Profile of Study Neonates

Obstetric Risk Category	NICU-Exposed Neonates (n = 50)	Controls (n = 50)	p-value
Low risk	14 (28%)	31 (62%)	<0.01
Moderate risk	22 (44%)	15 (30%)	>0.05
High risk	14 (28%)	4 (8%)	<0.01

Obstetric risk categories were based on cumulative antenatal and intrapartum factors.

Primary Outcome: Duration of Cry

The median duration of cry following intramuscular Hepatitis B vaccination was 26 seconds (IQR 20–48) in NICU-exposed neonates compared with 30.5 seconds (IQR 20–78) in controls. This difference was not statistically significant (p = 0.41, Mann–Whitney U test).

The median difference in cry duration between groups was −4.5 seconds (95% CI −14.2 to 6.1), indicating no clinically meaningful prolongation of crying associated with prior exposure to repeated painful procedures (Table 3).

Table 3: Primary Outcome – Cry Response Following Hepatitis B Vaccination

Outcome	NICU-Exposed Neonates (n = 50)	Controls (n = 50)	p-value
Duration of cry (seconds), median (IQR)	26 (20–48)	30.5 (20–78)	0.41
Latency to cry (seconds), mean ± SD	1.95 ± 1.05	2.00 ± 1.10	0.78

Gestational Age Subgroup Analysis

When neonates were stratified by gestational maturity, late preterm infants (34–35⁶⁄₇ weeks) demonstrated a significantly longer duration of cry compared to infants ≥36 weeks post-conceptional age, irrespective of pain exposure status (median 38 seconds vs 24 seconds; p = 0.04).

Within each gestational age stratum, prior exposure to repeated painful procedures was not associated with a significant difference in cry duration (interaction term p = 0.62), suggesting that gestational maturity, rather than cumulative pain exposure, was the dominant determinant of cry duration.

Secondary Outcomes

Latency to Cry

- Mean latency to cry was similar between NICU-exposed neonates and controls (1.95 ± 1.05 seconds vs 2.0 ± 1.1 seconds; p = 0.78†), indicating preserved immediate nociceptive perception in both groups.
- Latency to cry did not differ significantly by mode of delivery (p = 0.64), obstetric risk category (p = 0.59), or antenatal steroid exposure (p = 0.71).

Modified Facial Coding Score (MFCS)

- MFCS scores assessed immediately after needle insertion were significantly higher in NICU-exposed neonates compared to controls (median 5.76 vs 5.26; p = 0.01), indicating greater immediate behavioural expression of pain.
- At 1 minute post-injection, MFCS scores declined

markedly in both groups, with no statistically significant difference observed (1.40 vs 1.06; p = 0.47). Similarly, MFCS scores at 3 minutes were comparable between NICU-exposed neonates and controls (0.88 vs 0.66; p = 0.55).

There was a weak positive correlation between the number of prior painful procedures and immediate MFCS score (Spearman's ρ = 0.21), which did not reach statistical significance (p = 0.07), suggesting a trend toward increased immediate pain expression with greater cumulative exposure [Table 4].

Table 4: Modified Facial Coding Score (MFCS)

Time Point	NICU Babies	Control	p-value
Immediately after injection	5.76 ± 0.55	5.26 ± 1.19	0.01
1 minute after injection	1.40 ± 2.19	1.06 ± 1.99	0.47
3 minutes after injection	0.88 ± 1.80	0.66 ± 1.50	0.55

Adjusted Analysis

In a multivariable linear regression analysis adjusting for gestational age, birth weight, sex, obstetric risk category, and mode of delivery, prior exposure to repeated painful procedures was not an independent predictor of cry duration (β = −1.8 seconds; 95% CI: −8.9 to 5.3; p = 0.62).

As mentioned in Table 5, Gestational age emerged as a significant independent predictor of cry duration, with each additional week of gestation associated with a reduction in crying time (β = −2.1 seconds per week; 95% CI −4.0 to −0.2; p = 0.03).

Birth weight and obstetric risk category were not independently associated with cry duration after adjustment.

Table 5: Multivariable Linear Regression Analysis for Duration of Cry

Predictor Variable	β Coefficient (seconds)	95% CI	p-value
Repeated painful procedures (NICU exposure)	−1.8	−8.9 to 5.3	0.62
Gestational age (per week increase)	−2.1	−4.0 to −0.2	0.03
Birth weight (kg)	−1.2	−4.6 to 2.1	0.48
Male sex	0.9	−3.8 to 5.7	0.70
High obstetric risk	1.4	−4.9 to 7.6	0.66

Summary of Key Findings

Immediate behavioural pain expression (MFCS) was significantly higher in neonates with prior NICU pain exposure

Prior painful procedures did not significantly alter the duration and latency of cry

Gestational maturity, rather than cumulative pain exposure, was the strongest predictor of pain response

Obstetric risk factors influenced NICU admission but did not independently modify pain recovery in neonates ≥34 weeks

Discussion

This prospective cohort study demonstrates that repeated exposure to painful procedures during early neonatal life does not result in sustained alteration of behavioural pain response to a subsequent standardized painful stimulus in neonates with post-conceptional age ≥34 weeks. Although the immediate facial expression of pain was much stronger among neonates with prior NICU experience, this effect did not persist. It did not result in more chronic crying, delayed recovery, or increased or decreased latency to cry. Notably, gestational maturity is a statistically significant, standalone predictor of pain response, highlighting the primacy of neurodevelopmental maturation over cumulative exposure to the procedure in this population.

Acute Pain Expression as compared to Prolonged Pain Response.

The substantial improvement in MFCS scores immediately after needle insertion in NICU-exposed neonates indicates increased initial behavioural reactivity to pain. This result is in line with previous research showing that repeated early noxious stimulation can temporarily sensitise behavioural expression pathways, especially in facial motor responses.[4,6] Nevertheless, the brisk agreement of MFCS scores in groups at times 1 and 3 implies maintained pain modulation and recovery. The fact that the average duration of cry and latency to cry have no significant differences between the unadjusted and adjusted analysis indicates that the duration during which the infants were exposed to repeated painful interventions in the case does not lead to the development of persistent hyperalgesia or dysfunctional pain control in infants who were exposed at the age of 34 weeks post-conception. These results provide evidence that behavioural expressions of pain and pain recovery are distinct constructs, with the latter more closely related to inhibitory and maturational neural processes.

Role of Gestational Maturity in Determining Pain Response.

One major and statistically significant result of this study is that there is an independent relationship between gestational age and the length of the cry. An extra week of gestation was associated with a substantial decrease in the duration of crying; this persisted despite efforts to control for birth weight, obstetric risk, and prior exposure to crying. This finding is consistent with neurodevelopmental findings showing faster maturation of descending inhibitory pathways and cortical modulation in late gestation.[1,10]

This was further supported by the analysis of the gestational age subgroup, where late preterm babies (3435 -7 weeks) had a very high gestation period and longer cry duration than infants who had at least 36 weeks, regardless of whether they had been exposed to pain before. This underscores the idea of late preterm infants as a physiologically vulnerable group, although they are clinically comparable to the term newborn infants.

Comparison extended to previous studies.

The current results agree with those of Oberlander et al., who also showed similar bio-behavioural pain expression in infants with former extremely low birth weight and term controls at more mature corrected ages, indicating the elimination of initial differences with maturation.[7] In a similar vein, Peters et al. found no evidence of exaggerated pain responses to immunization in infants who had undergone significant surgery in the past, thereby avoiding the suggestion of plasticity and recovery in the developing nervous system.[8]

Conversely, experimental results published by Taddio et al. showed greater pain responses after repeated heel lancing in full-term neonates.[4] In contrast, Grunau et al. showed exaggerated pain reactivity in very low birth weight infants.[5] These inconsistencies probably indicate differences in gestational age at exposure, pain stimulus intensity, and time of evaluation. Babies delivered at more premature gestations are also susceptible to the effects of long-lasting sensitization because they might not have adequate inhibitory modulation.

Prioritizing children over 34 weeks of post-conceptual age, the current research provides valuable depth to the existing literature, indicating a gestational cutoff point beyond which the ability to cope with cumulative exposure to pain becomes apparent.

Barriers to OB: Obstetric Determinants and Continuum of Care.

A merit of this study is that antenatal and intrapartum variables are incorporated into the examination of neonatal pain response. Hypertensive disorders, intrauterine growth restriction, maternal infection, and operative delivery are obstetric complications that have been known to affect the physiology of fetal stress and the neurobehavior of the newborn.[2,10] The factors had been more prevalent between NICU-exposed neonates, but the obstetric risk category failed to show its independent predictability on prolonged pain response following adjustment.

The finding implies that the obstetric-neonatal continuum model holds: obstetric factors predispose to an NICU admission and early exposure to procedural pain, but have no direct or long-lasting impact on pain modulation among Late Preterm and term neonates. Rather, gestational maturity seems to counteract the joint influences of stress during pregnancy and its postnatal anguish.

From an obstetric perspective, such findings underline the second but important role of antenatal care in influencing the experiences of birth pain in newborns. Early preterm birth prevention, maximization of intrapartum care, and encouragement of early contact with the mother can potentially decrease the number of NICU hospitalizations as well as cumulative pain, in turn, promoting neuroprotective care.

Relevance in the Clinic, Contemporary.

When applied to contemporary neonatology, in which pain has become a critical indicator of a crucial ethical concern, these results offer tentative comfort to the stability of Late Preterm and term newborns. Nevertheless, the high rate of sudden pain expression in NICU infants indicates the necessity of routine pain-reduction measures for all newborns, irrespective of gestational maturity.[9,12]

In addition, the fact that gestational age is one of the most important factors influencing pain reaction supports the existing recommendation on increased monitoring and supportive care of late preterm babies, who, despite their Late Preterm appearance, are physiologically vulnerable.

Strengths and Limitations of the Study

This research has several strengths. It answers a clinically relevant question that still faces daily clinical questions in neonatal practice, especially the responses to pain in late preterm and term infants who have had exposure to the NICU before. The study limits itself to neonates 34 weeks old and above, after conceptional age, to obtain a relatively more mature sample, which neonatal pain research has been comparatively underserved. Internal validity is improved through the prospective design, standardized pain stimulus, and the controlled assessment environment. Notably, incorporating comprehensive antenatal, intrapartum, and delivery-room factors into an obstetric-neonatal continuum model provides a more complete explanation of the determinants of neonatal pain response. Cases and controls (matching) on post-conceptional age, postnatal age, and sex are further. It is through the use of numerous behavioural pain markers that it becomes possible to distinguish between short-term pain manifestations and recovery, which gives the interpretation of pain modulation in the neonate a certain depth.[10] These advantages favor the clinical applicability and relevance of the research in modern practice.

But some limitations are required. Pain evaluation was based solely on behavioural measures, and the lack of physiological or biochemical measures limits understanding of the autonomic or neuroendocrine response to stress. The single standardized painful stimulus, though methodologically safe, may not be entirely representative of reactions to other NICU procedures to which one might be exposed. Whereas obstetric variables were well documented, the cumulative obstetric risk classification might fail to capture the timing, severity, and chronicity of antenatal stress exposure. The sample size is sufficient to detect primary outcomes, but it limits power for subgroup analyses, especially in smaller gestational age groups. Since the research was conducted at a single tertiary care centre, the study may not be fully applicable to other healthcare environments. Lastly, the study does not have a longitudinal follow-up, which makes it difficult to conclude neurodevelopmental or pain-related effects on individuals who were exposed to procedures at an early age.

Conclusion

Future research on this topic needs to include multimodal measures of pain, examine epigenetic and neuroendocrine measures, and assess neurodevelopmental outcomes of early neurodevelopmental changes, especially among infants who have late preterm birth.

Repeated exposure to painful procedures in the early neonatal life of the neonates who are older than the post-conceptional age of 34 weeks does not have a long-lasting difference in behavioural pain response. Gestational maturity, rather than cumulative procedure pain or obstetric risk, is the main predictor of pain modulation. These observations indicate the relevance of

obstetric-neonatal approaches to optimizing maturity at birth, reducing unnecessary exposure to pain, and facilitating early neurodevelopment.

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Conflicts of interest
There are no conflicts of interest.

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