

Original Research Article

Variations in physiological responses to painful stimuli in preterm and term neonates: an observational study

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ABSTRACT

Background: Appropriate neonatal pain assessment and management is a key component of quality medical care. Assessment of pain, however, is a challenge due to their inability to verbalize this subjective sensation. Preterms are hyper-sensitive to pain and experience it for prolonged periods but it is postulated that they may not express it as robustly and reliably as term neonates. This paper aims to assess and compare the behavioral and physiological pain responses in these groups.

Methods: This prospective observational study was conducted in the outpatient and post-natal wards of a tertiary care teaching hospital. 90 clinically stable term and late preterm neonates requiring IV cannulation, IV blood sampling or heel prick were included. NIPS Pain Scale Scores and physiological parameters (heart rate, respiratory rate, SpO₂, mean arterial pressure, total crying time) were recorded before and after the procedure.

Results: 90 neonates were analysed. Significant pain response was noted in both groups post-procedure. In response to the same procedures, preterm neonates demonstrated lower NIPS Scores (4.00 vs. 4.93, $P=0.003$) and shorter cry times (64.30s vs. 87.35s, $P<0.05$). Also noted were higher heart rates and respiratory rates with a prolonged fall in SpO₂ and Mean Arterial Pressures in this group.

Conclusions: Preterms, compared to term neonates demonstrate a blunted behavioral response to pain but a heightened and prolonged physiological response. This potential underestimation of pain in preterms indicate the need for incorporation of behavioral cues, physiological parameters and gestational age in the assessment of pain in newborns.

Keywords: Crying (physiology), Infant, Newborn, Pain (physiopathology, prevention & control), Pain management, Pain measurement

INTRODUCTION

Pain is often defined as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”.¹ The subjective nature of pain coupled with the inability of a neonate to express it, verbally or otherwise makes assessing and managing pain a difficult endeavour. Previously a topic of debate, it is now well accepted that neonates, both term and preterm, do in fact feel pain with extensive research demonstrating the presence and functioning of all aspects of the pain pathways (from

active nociceptors, intact pain pathways and complex neural responses to pain) in both term and preterm newborns.² With the recent advances in medical science, not only have the rates of preterm births been rapidly rising, but also rising is the proportion of surviving preterms.³

Research shows that newborns in the hospital setting are subjected to a significant number of painful procedures, with the average NICU admitted baby experiencing between 8.09 and 97.11 painful procedures per day, with about 13% of these procedures carried out on the first day

of admission.⁴ The most common procedures include heel prick, adhesive removal and oral, tracheal and nasal suctioning.

Assessment of pain remains a challenge in the neonatal age group, with the two most common bedside methods being crude visual estimation and the use of conjugate pain scales. Visual estimation relies on behavioral cues such as changes in facial features and cry, done usually by parents and healthcare professionals. Pain Scales are commonly implemented in the clinical setting for the assessment/quantification of pain and/or level of sedation in neonates.

Over 40 validated scales are used commonly, however only two are validated for use in preterms. The NIPS pain scale, implemented in this study, is one such validated, simple tool for neonatal pain assessment, suitable for use in any gestation.⁵ Although pain responses in newborns have been extensively studied, it is theorized that, in response to painful stimuli, significant variances exist between neonates of different gestational ages, corresponding to their stage of neuro-development. This study aims to explore and compare the physiological responses to single painful procedures in term and preterm neonates.

METHODS

Study type

Prospective observational study.

Study place

This study was carried out in the outpatient unit and post-natal wards of BGS Global Institute of Medical Sciences, a tertiary care teaching hospital in Bangalore, India.

Study duration

The study was conducted for a period of 12 months between September 2022 to August 2023.

Sample size

Previous studies and pilot data indicated a significant difference in mean NIPS score between the two groups (MD=1.1). To achieve a power of 80% ($\beta=0.20$) and a significance level of 0.05 ($\alpha=0.05$), the sample size was calculated to be 89. After rounding, a sample size of 90 was taken for the present study.

Sampling method

Purposive sampling was used.

Ethical approval

Written informed consent was obtained from the parent/legally acceptable representative. Institutional Ethics committee approval was obtained.

Inclusion criteria

All clinically stable term and late preterm neonates having an indication for IV cannulation/IV blood sampling/heel prick were included in the study.

Exclusion criteria

Excluded from the study were perinatal asphyxia, Birth trauma, Cardiorespiratory instability, any apparent CNS anomalies, any previous surgery, maternal use of opioids, sedatives, analgesics, use of paracetamol (For analgesic or non-analgesic purposes) or any other analgesic in the baby.

Methodology

The neonates underwent venipuncture or heel lance as part of a medically indicated workup for routine indications such as bilirubin estimation, blood sugar estimation or blood sampling.

NIPS pain scale scores and physiological parameters (Heart rate, Respiratory rate, SpO₂, mean arterial pressure, total crying time) were measured and recorded by a trained nurse/resident pediatrician at 3 timepoints - T1 : 2 minutes pre - procedure, T2 : 30 seconds post - procedure and T3 : 5 minutes post - procedure. The neonate was observed for 15 further minutes and later returned to parent/LAR.

Statistical analysis

Mean and standard deviation (SD) was calculated for continuous variables, frequencies and percentages for categorical variables were determined. Associations were analyzed by using Chi-Square test for categorical variables. Unpaired t Test was used to compare mean of quantitative variables between study groups. Pearson's correlation coefficient was calculated between gestational age and change in parameters. Level of significance was set at 0.05.

RESULTS

A total of 90 Late preterm and term neonates were included in the study of which 26 (28.9%) were late preterm and 64 (71.1%) were term gestation.

No statistically significant difference was found in all groups related to age, gender, mode of delivery, 5 minutes APGAR score and procedure done. A significant pain response (measured as an increase in NIPS pain scale scores) were noted post procedure in both term and preterm groups. A Statistically significantly lower mean ($\pm$ SD) NIPS score was noted at 30 seconds post

procedure in the preterm cohort 4.00 (1.56) when compared to terms 4.93 (1.3) ($p=0.003$). The difference however was not statistically significant at 5 minutes' post procedure (Table 1). We found a statistically significantly lower mean (SD) crying time in the preterm group (64.30 (42.58)) when compared to terms (87.35 (52.56)) ($p\leq 0.05$) (Table 2). A statistically significantly higher heart rate was noted in the preterm group 157.64 (11.93) versus the term group 151.09 (9.77) ($p=0.006$) at 30 seconds post procedure when compared to baseline values (138.45 (8.34); 130.63 (9.71)). The percent change in the preterm group (17.98 (12.16)) and the term group (14.66 (12.16)) however was not significant ($p=0.216$) (Table 3). A fall in SpO₂ was noted post procedure in both groups at both time points post procedure. A statistically significant fall was noted at 5 minutes post procedure in the preterm group when compared to terms (92.55 (3.40); 93.91 (2.82)). The percent change of SpO₂ was found to be significant only at 30 seconds post procedure time point (4.92 (3.54); 2.99 (4.05)) ($p=0.025$) (Table 4). A statistically significant rise in respiratory

rate was noted at 30 seconds post procedure in the preterm group when compared to terms (54.48 (6.15); 52.09 (3.46); ($p=0.020$)). Percentage of change in RR was not significant at both timepoints (24.54 (16.97), 21.18 (12.94) ($p=0.294$); 11.01 (7.71), 12.52 (12.75) ($p=0.567$)) (Table 5). The rise in MAP noted post procedure was found to be statistically insignificant in both groups, however was significant at 5 minutes' post procedure (49.21 (5.92); 53.37 (5.95); $p=0.002$). The percent rise was found to be significant both at 30 seconds post procedure (13.66 (7.71); 6.25 (5.47); $p\leq 0.001$) and at 5 minutes post procedure (5.04 (9.19); 1.98 (3.45); $p=0.027$) (Table 6). Table 7 demonstrates percent change in all the parameters tested in both groups. Only the changes in Spo₂ between pre-procedure (T1) values and 30 seconds post procedure (T2) (4.92 (3.54); 2.99 (4.05), $p=0.025$) and change in MAP between pre procedure (T1) and both 30 seconds post procedure (13.66 (7.71); 6.25 (5.47); $p\leq 0.001$) and 5 minutes post procedure (5.04 (9.19), 1.98(3.45), $p=0.027$) were found to be significant.

Table 1: Comparison of NIPS between study groups.

NIPS	Group		P value
	Preterm (n=33), Mean (SD)	Term (n=57), Mean (SD)	
Pre-procedure	1.03 (0.81)	1.18 (0.92)	0.456
30 sec post-procedure	4.00 (1.56)	4.93 (1.30)	0.003*
5 min post-procedure	1.61 (1.19)	1.84 (1.39)	0.419

Unpaired t Test, P value * Significant

Table 2: Comparison of crying time between study groups.

Crying time (sec)	Group	
	Preterm (n=33), Mean (SD)	Term (n=57), Mean (SD)
	64.30 (42.58)	87.35 (52.56)

Unpaired t Test, P value= <0.05 , Significant

Table 3: Comparison of heart rate between study groups.

Heart rate	Group		P value
	Preterm (n=33), Mean (SD)	Term (n=57), Mean (SD)	
Pre-procedure	138.45 (8.34)	130.63 (9.71)	<0.001 *
30 sec post-procedure	157.64 (11.93)	151.09 (9.77)	0.006*
5 min post-procedure	144.55 (9.08)	140.63 (9.85)	0.065

Unpaired t Test, P value * Significant

Table 4: Comparison of SPO₂ between study groups.

SPO ₂	Group		P value
	Preterm (n=33), Mean (SD)	Term (n=57), Mean (SD)	
Pre-procedure	94.30 (2.36)	94.23 (2.56)	0.891
30 sec post-procedure	90.36 (3.38)	91.68 (3.16)	0.066
5 min post-procedure	92.55 (3.40)	93.91 (2.82)	0.043*

Unpaired t Test, P value * Significant

Table 5: Comparison of respiratory rate between study groups.

Respiratory rate	Group		P value
	Preterm (n=33), Mean (SD)	Term (n=57), Mean (SD)	
Pre-procedure	44.03 (3.82)	43.28 (3.69)	0.362
30 sec post-procedure	54.48 (6.15)	52.09 (3.46)	0.020*
5 min post-procedure	48.61 (3.42)	48.37 (3.68)	0.763

Unpaired t Test, P value * Significant

Table 6: Comparison of MAP between study groups.

MAP	Group		P value
	Preterm (n=33), Mean (SD)	Term (n=57), Mean (SD)	
Pre-procedure	47.06 (6.19)	52.40 (6.27)	<0.001*
30 sec post-procedure	53.27 (6.03)	55.49 (5.47)	0.078
5 min post-procedure	49.21 (5.92)	53.37 (5.95)	0.002*

Unpaired t Test, P value * Significant

Table 7: Gestational age with percent change in various parameters in the study.

Percent change	Gestational age		P value
	Preterm, Mean (SD)	Term, Mean (SD)	
NIPS (T1 vs T2)	71.03 (27.33)	73.25 (25.74)	0.701
NIPS (T1 vs T3)	25.50 (64.74)	27.16 (61.27)	0.904
Heart rate (T1 vs T2)	17.98 (12.16)	14.66 (12.16)	0.216
Heart rate (T1 vs T3)	6.46 (8.89)	8.17 (10.39)	0.431
SPO2 (T1 vs T2)	4.92 (3.54)	2.99 (4.05)	0.025*
SPO2 (T1 vs T3)	2.20 (4.63)	0.754 (3.71)	0.108
Respiratory rate (T1 vs T2)	24.54 (16.97)	21.18 (12.94)	0.294
Respiratory rate (T1 vs T3)	11.01 (10.63)	12.52 (12.75)	0.567
MAP (T1 vs T2)	13.66 (7.71)	6.25 (5.47)	<0.001*
MAP (T1 vs T3)	5.04 (9.19)	1.98 (3.45)	0.027*

DISCUSSION

Neonatal pain has been known to be associated with acute effects such as hemodynamic and behavioral changes, alteration of sleep and feeding patterns, increased energy consumption, altered hormone secretion and even long term effects such as altered pain sensitivity, emotional and cognitive impairments, endocrine disruptions and disruptions in overall health noticed as soon as in adolescence.⁶ The long term effects of early pain exposure on somato-sensory sensations and on altered pain sensitivity is probably owing to the multi-dimensional nature of pain and nociception.⁷

This study shows that both term and preterm neonates exhibit significant responses to pain stimuli. We also found that in response to similar painful stimuli, preterm neonates expressed a more subdued behavioral pain response as demonstrated by both a lower mean NIPS scores (measuring changes in facial expressions and body movements) and also reduced mean crying time when compared to term neonates. We noted an exaggerated physiological response to pain in preterms when compared to their term counterparts (Demonstrated as a statistically significantly greater rise in heart rates,

respiratory rates and MAP with a significantly greater fall in SpO₂). A more prolonged fall in SpO₂ and MAP was also noted in preterms, which could suggest a more sustained pain perception phenomenon. Research suggests that preterms, due to the lack of maturity of pain inhibiting descending pathways, demonstrate not only increased pain intensity, but also increased duration of pain when exposed to noxious stimuli, when compared to term neonates.⁸ We hypothesize that they, however, might not be able to fully express this sensation externally in the form of changes in facial expressions or even verbally (in the form of crying) to the extent of term neonates.

Shapiro et al demonstrated in a study that when trained NICU nurses were asked to judge the intensity of pain in a term versus preterm neonate exposed to similar painful stimuli, they consistently assigned higher pain scores to term newborns when compared to preterms. The difference being attributed to term newborns being more vigorous and vocal, with louder cry and higher activity levels.⁹ Most of the commonly used pain scales implement behavioral changes as the primary metric for assessment and quantification of pain, with only some incorporating physiological parameters.¹⁰ Our findings

suggest that the isolated use of these pain scales for both terms and preterms may result in underestimation of pain intensity in preterms. A systematic review by Menin et al, mirrored our findings, noting an inverse relation with Gestational age (GA) and postmenstrual age (PMA) in relation to facial pain response, with more premature infants having a dampened response.¹¹

Our study strengths include robust methodologies and the use of both the highly validated NIPS pain scale and physiological parameter assessments, providing a comprehensive understanding of neonatal pain.

We acknowledge some limitations. Being a single centre study, there is a need for more such papers to validate and generalize our findings. Although we recorded a total cry time, we did not record consolidated recovery time. The exclusion of sick infants, NICU graduates and neurologically impaired babies means our results may not generalize to these populations, as their illness and neurological state could affect pain perception and expression were the limitations of the study.

CONCLUSION

Based on this study we can conclude that in response to similar noxious stimuli, preterm neonates exhibit not only a blunted behavioural response but also a contrastingly heightened and more prolonged physiological pain response when compared to term neonates. Hyperalgesia in preterms, due to under-developed descending inhibitory pain pathways and incomplete cortical organization is a well understood hypothesis. This study, by assessing and quantifying the altered pain response in preterms, highlights the potential for under-estimation of pain in this group when relied solely on behavioural cues. The consideration and inclusion of physiological parameters and, importantly, gestational age as a crucial determinant of a neonate's capacity to produce reliable and robust signs of pain may guide us in effective pain assessment and management in the future.

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