Original Article

Comparison of Neonatal Pain, Agitation, and Sedation Scale with Premature Infant Pain Profile for the Assessment of Acute Prolonged Pain in Neonates on Assisted Ventilation: A Prospective Observational Study

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Abstract

Aim: This study aimed to compare Neonatal Pain, Agitation, and Sedation Scale (N-PASS) with Premature Infant Pain Profile (PIPP) for the assessment of acute prolonged pain in ventilated neonates. **Methods:** This study was conducted in two phases. In phase 1 of the study, we assessed whether neonates on assisted ventilation experienced acute prolonged pain. In phase 2, the aim was to compare N-PASS with PIPP for the assessment of acute prolonged pain in neonates on assisted ventilation.. **Design:** This is a prospective observational study. **Study Setting and Duration:** This study was conducted at a tertiary care neonatal intensive care unit for 6 months. **Inclusion Criteria:** Neonates on assisted ventilation for >48 h were selected for this study. **Exclusion Criteria:** Neonates with lethal congenital anomalies and severe encephalopathy were excluded from the study. N-PASS and PIPP tools were used to assess acute prolonged pain in ventilated neonates. Taking PIPP as gold standard and N-PASS as a new test, the correlation coefficient was calculated. The sensitivity, specificity, positive predictive value, and negative predictive value were also computed. The time taken to administer the tools was also computed. **Results:** The average PIPP score for ventilated neonates was 8.33. The correlation coefficient of N-PASS when compared to PIPP was 0.62. The average time taken to apply the N-PASS scale was 4.42 min as compared to 8.20 min for PIPP scale. In term neonates, the sensitivity, specificity, positive predictive value, and negative predictive value of N-PASS were 75%, 100%, 100%, and 60%, respectively. The corresponding values in preterm neonates were lesser. **Conclusions:** The study proves that neonates on assisted ventilation experience acute prolonged pain. N-PASS is clinically reliable and valid to assess acute prolonged pain in ventilated term neonates. The N-PASS is quicker than PIPP in assessing acute prolonged pain in ventilated neonates. **Future Directions:** The modified N-PASS tool (including the gestational age) should be developed.

Keywords: Neonates, pain, ventilation

INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1] Pain in neonates can be categorized into three types. First is acute procedural pain, where pain results from a specific self-limiting event, the second being acute prolonged pain, with a clear beginning and an expected end point, and the third being chronic pain, a pathological pain state persisting beyond the normal tissue healing time, usually 3 months.[2] Hospitalized neonates experience an average of 14 painful procedures per day during the first 2 weeks of life.[3]

The inability to communicate pain verbally does not rule out the distress and agony which these newborns suffer. They provide behavioral and physiological cues to indicate the presence of pain which needs to be recognized by the health-care provider. Contrary to the past belief, it is now clear that all neonates have the neuro-anatomic pathways from

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periphery to cortex required for pain perception. Further, the premature neonates have increased stress response to pain because of immature descending pathways which inhibit the pain sensation.[3-5] Chronic pain may lead to permanent changes in brain processing, impaired brain development, altered pain sensitivity, and maladapted behavior in the future.[5,6]

Several infant pain assessment tools have been developed for acute procedural pain. The American Academy of Pediatrics and Canadian Pediatric Society policy statement on the prevention and management of pain in the neonate recommends routine pain assessment in neonates and lists nine commonly used pain assessment scales for acute procedural pain.[7] However, there is a scarcity of literature for the assessment of acute prolonged and chronic pain in neonates.

Neonates on assisted ventilation experience acute prolonged pain.[[3,4] Although primarily an acute procedural assessment tool, the Premature Infant Pain Profile (PIPP) is widely used clinically for the assessment of prolonged pain.[4] Hummel *et al.* have found Neonatal Pain, Agitation, and Sedation Scale (N-PASS) as an useful tool for the assessment of acute prolonged pain in ventilated neonates.[4] However, they have emphasized the need for further studies to routinely recommend the use of this scale for the assessment of prolonged pain in neonates on assisted ventilation.[4] Hence, the rationale of the study is to compare a newer tool, i.e., N-PASS with PIPP for the assessment of acute prolonged pain in ventilated neonates.

To our knowledge, this is the first study from India for the assessment of clinical reliability and validity of N-PASS for the assessment of acute prolonged pain in neonates and its comparison with PIPP.

METHODS

Ethics
This study was conducted after obtaining approval by the Institutional Ethics Committee. Informed consent in local language from parents prior to enrollment was procured.

Study design
This is a prospective observational study.

Study site
This study was conducted at Level IIIB neonatal intensive care unit (NICU) in a tertiary care hospital.

Study participants
- Inclusion criteria: Neonates on assisted ventilation for >48 h
- Exclusion criteria: Neonates with lethal congenital anomalies and severe encephalopathy.

Study duration
This study was carried out for 6 months.

Outcome
The primary outcome was to compare N-PASS with PIPP for the assessment of acute prolonged pain in neonates on assisted ventilation.

The secondary outcome was to compare the N-PASS tool with the PIPP tool according to the time taken to apply the scales.

Sample size
Sample size calculation for phase 1 of the study was computed using formula for hypothesis of one sample mean. Hypothesizing a baseline score of 5 and postprocedural pain score of 7 with allowable difference of 0.1 and expected variance of 0.01 (α error of 0.05 and β error of 0.10 and power of 90%), the estimated sample size was 15 neonates.

It was assumed that, between the two tools of pain assessment of N-PASS and PIPP, a simple correlation of the tune of $r = 0.5$ was possible. Using a two-sided test, 5% significance level test ($\alpha = 0.05$) with 90% power ($\beta = 0.1$), the required sample size is approximately 38 ($n = 38$).

Methodology
This study was conducted in two phases. In phase 1 of the study, we assessed whether neonates on assisted ventilation experienced acute prolonged pain. In phase 2, the aim was to compare N-PASS with PIPP for the assessment of acute prolonged pain in neonates on assisted ventilation.

Prior to commencement of the study, all senior residents were trained to assess pain in neonates using the N-PASS and PIPP tools. All senior residents were certified for competency in assessment of pain by the senior faculty. Neonates on assisted ventilation for >48 h were enrolled for the study. The birth weight was recorded in the labor room on an electronic infant weighing scale with an accuracy of ± 1 g. The gestational age was assessed using date of the last menstrual period and the first trimester ultrasonography. In case of discrepancy, the New Ballard Score was considered definitive for gestational age assessment.

The neonate on assisted ventilation was observed for pain assessment after 48 h of initiation of ventilation when no additional procedure/intervention was being done: for example, heel prick, intravenous cannula insertion, blood collection, orogastric and nasogastric tube insertion, lumbar puncture, endotracheal tube placement, suction, central line insertion, and changing of nappies.

One senior resident assessed pain using PIPP [Annexure 1] and simultaneously the other senior resident assessed pain using N-PASS [Annexure 2]. Each neonate was assessed for pain only once. The senior resident assessing the score was blinded from other's observation.

The PIPP is a behavioral measure of pain for neonates [Annexure 1]. PIPP includes seven components, i.e., gestational age, behavioral state, change in heart rate during the painful stimulus, change in oxygen saturation during the painful stimulus, brow bulge during the painful stimulus, eye squeeze during the painful stimulus, and nasolabial furrow during the painful stimulus. The minimum score in PIPP tool is 0 and maximum score is 21. In PIPP tool, moderate pain is

indicated when the score is ≥6 and severe pain is indicated when the score is >12.

In N-PASS tool, five indicators are included as follows: crying/irritability, behavior/state, facial expression, extremities/tone, and vital signs (heart rate, respiratory rate, blood pressure, and/or oxygen saturation) [Annexure 2]. Each of the five criteria are graded from −2 to +2. A score >+3 indicates pain, and a score of >−3 indicates sedation. A high pain/agitation score indicates more frequent or intense behaviors, and a low sedation score indicates a decreased response to stimulation, or a deeper level of sedation [Annexure 1].

The heart rate and oxygen saturation were recorded using the Masimo pulse oximeter (model radical 7) which uses the signal extraction technology. Video recording of the neonate was done while assessing the pain. A stop watch was used to estimate the time needed for both the tools.

Statistical analysis

Statistical analyses were performed with the use of SPSS software for Windows (SPSS, Inc., Chicago, IL, USA) for the primary outcome. Nonparametric Spearman's rho correlation coefficient, sensitivity, specificity, positive and negative predictive values were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Phase 1 of the study comprised 15 neonates on assisted ventilation with the average gestational age being 34.3 ± 4.56 weeks and the average birth weight being 1566 ± 468.36 g. The average pain score assessed by the PIPP tool in neonates on assisted ventilation without any intervention was 8.33.

In phase 2 of the study, 42 neonates with average gestational age of 33.5 ± 4.23 weeks and average birth weight of 1686 ± 380.46 were enrolled. The demographic characteristics of the enrolled neonates are shown in Table 1.

In phase 2 of the study, the average pain score by PIPP scale in neonates on assisted ventilation was 7.88. During subgroup analysis, the average pain score by PIPP scale in neonates on invasive ventilation was 8.19 whereas on noninvasive ventilation was 7.47. The average pain score by N-PASS scale in neonates on assisted ventilation was 4.70. The average pain score by N-PASS scale in neonates on invasive ventilation was 5.25 whereas on noninvasive ventilation was 4.31. The nonparametric Spearman's rho correlation coefficient for N-PASS tool when compared to PIPP was 0.62 [Figure 1].

The time taken to apply the N-PASS tool was 4.42 min as compared to an average of 8.20 min required for applying the PIPP tool [Table 2].

The sensitivity, specificity, positive predictive value and negative predictive value for N-PASS tool as compared to PIPP in term neonates were 75%, 100%, 100%, and 60%,

respectively, whereas for preterm neonates, the corresponding values were 65%, 87%, 94%, and 47%, respectively [Table 3].

The sensitivity, specificity, positive predictive value, and negative predictive value of N-PASS tool for noninvasive ventilation were 67%, 100%, 100%, and 50%, respectively, whereas for invasive ventilation, the corresponding values were 75%, 100%, 100%, and 50%, respectively [Table 3].

DISCUSSION

In phase 1 of the study, the average pain score assessed by PIPP scale in ventilated neonates without any intervention was 8.33. This reiterates the fact that neonates on assisted ventilation experience acute prolonged pain as PIPP score ≥6 indicates moderate pain. However, the assessment of this acute prolonged pain has not been adequately emphasized in the medical literature.

The average pain scores by PIPP and N-PASS scales in neonates on assisted ventilation were 7.88 and 4.70, respectively. The average pain score by N-PASS scale in neonates on invasive

Table 1: Demographic characteristics of the neonates enrolled

Demographic characteristics	*n* (%)
Total number of neonates (*n*)	42
Females (*n*)	16 (38.09)
Average birth weight (g)	1686.52±848.23
Average gestational age (weeks)	33.15±4.7
Neonates on noninvasive ventilation (*n*)	21 (50.00)
Preterm neonates (*n*)	31 (73.80)

Table 2: Comparison of time taken to apply Neonatal Pain, Agitation, and Sedation Scale as compared to Premature Infant Pain Profile

	PIPP	N-PASS	*P*
Mean±SD	8.20±5.58	4.42±3.75	0.0005

PIPP: Premature Infant Pain Profile, N-PASS: Neonatal Pain, Agitation, and Sedation Scale, SD: Standard deviation
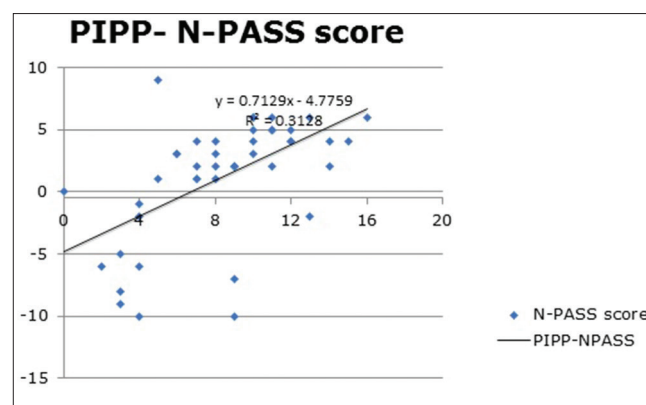

Figure 1: Correlation analysis of Neonatal Pain, Agitation, and Sedation Scale as compared to Premature Infant Pain Profile

Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of Neonatal Pain, Agitation, and Sedation Scale as compared to Premature Infant Pain Profile according to gestational age and mode of ventilation

	Term neonates (%)	Preterm neonates (%)	Invasive mode (%)	Noninvasive mode (%)
Sensitivity	75	65	75	67
Specificity	100	87	100	100
Positive predictive value	100	94	100	100
Negative predictive value	60	47	50	50

ventilation was 5.25 whereas on noninvasive ventilation was 4.31. In our study, the correlation between the PIPP and the N-PASS scales was modest with nonparametric Spearman's rho correlation coefficient being 0.62 [Figure 1].

Hummel *et al.* studied pain assessment using N-PASS tool in ventilated and postoperated neonates ranging from 0 to 100 days.[4] They also studied inter-rater reliability and found high intraclass coefficient value. The convergent validity testing revealed a strong correlation of 0.83 at high pain scores, but modest correlation coefficient of 0.61 at low pain scores in their study. Thus, N-PASS tool was found to be valid and reliable in that study.

The time taken to apply the N-PASS tool was 4.42 (±3.75) min as compared to 8.20 (±5.58) min required to apply the PIPP tool with a statistically significant value of 0.0005, thus implying that N-PASS is a quicker tool for pain assessment. There are no studies till date to compare the time taken for pain assessment.

The sensitivity, specificity, positive and negative predictive values of N-PASS when compared to PIPP for ventilated term neonates were comparable proving that N-PASS is reliable and valid for acute prolonged pain assessment in ventilated term neonates. However, the same results did not hold true for preterm neonates. The possible explanation is that the gestational age is not considered for N-PASS tool. Consideration of gestational age is important as preterm neonates are less able to exhibit signs of pain when compared to term neonates.[8-10] Hence, the PIPP scale considers additional points for prematurity scores higher as compared to N-PASS scale for pain assessment.[4,10] More research is needed on the appropriateness of adding points for prematurity in the N-PASS tool. There is inadequacy of medical literature regarding the validity and reliability of pain assessment tools according to the gestational age.

The sensitivity, specificity, positive predictive value, and negative predictive value of N-PASS tool for neonates on noninvasive ventilation and invasive ventilation were comparable to those of PIPP scale, thus implying that N-PASS is valid for use in ventilated neonates irrespective of the mode of ventilation [Table 3].

Lack of objective parameters for pain assessment has left the clinician with only behavioral assessment and clinical judgment to assess and guide pain management.[8] This study was conducted to test the clinical reliability and validity of a new scale, i.e., N-PASS (based on the behavioral assessment

parameters) to assess acute prolonged pain in ventilated neonates.

Limitations

The intra- and inter-rater reliability testing was not done in this study. The generalizability is limited to one NICU.

Implications for future research

Pain assessment of neurologically compromised neonates is clinically challenging, requiring further research. The modified N-PASS tool taking into consideration the gestational age for assessment of acute prolonged pain in preterm neonates should be considered for further studies.

Conclusions

Our study proves that neonates on assisted ventilation experience acute prolonged pain. This research provides evidence that the N-PASS is a clinically reliable and valid tool to assess acute prolonged pain in ventilated term neonates. N-PASS is a quicker tool for pain assessment in ventilated neonates.

What is already known?

- Neonates experience acute prolonged pain on assisted ventilation.

What this study adds?

- There is moderate pain associated with assisted ventilation in neonates
- N-PASS is a clinically reliable and valid tool for the assessment of acute prolonged pain associated with ventilation in term neonates
- N-PASS is not a clinically reliable and valid tool for the assessment of acute prolonged pain associated with ventilation in preterm neonates
- N-PASS tool is quicker in assessing acute prolonged pain as compared to PIPP.

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ANNEXURES

Annexure 1: Premature Infant Pain Profile

Overview: The Premature Infant Pain Profile (PIPP) is a behavioral measure of pain for premature infants. It was developed at the Universities of Toronto and McGill in Canada.

Indicators:
1. Gestational age
2. Behavioral state before painful stimulus
3. Change in heart rate during painful stimulus
4. Change in oxygen saturation during painful stimulus
5. Brow bulge during painful stimulus
6. Eye squeeze during painful stimulus
7. Nasolabial furrow during painful stimulus.

Interpretation: Minimum score: 0; moderate pain >5; maximum score: 21

Indicator	Finding	Points
Gestational age	≥36 weeks	0
	32-35 weeks, 6 days	1
	28-31 weeks, 6 days	2
	<28 weeks	3
Behavioral state	Active/awake eyes with open facial movements	0
	Quiet/awake eyes open with no facial movements	1
	Active/sleep eyes with closed facial movements	2
	Quiet/sleep eyes closed with no facial movements	3
Heart rate change	0-4 beats/min increase	0
	5-14 beats/min increase	1
	15-24 beats/min increase	2
	≥25beats/min increase	3
Oxygen saturation minimum	0%-2.4% decrease	0
	2.5%-4.9% decrease	1
	5.0%-7.4% decrease	2
	7.5% decrease or more	3
Brow bulge	<9% of time	0
	10%-39% of time	1
	40%-69% of time	2
	>70% of time	3
Eye squeeze	<9% of time	0
	10%-39% of time	1
	40%-69% of time	2
	>70% of time	3
Nasolabial furrow	<9% of time	0
	10%-39% of time	1
	40%-69% of time	2
	>70% of time	3

Annexure 2: Neonatal Pain, Agitation, and Sedation Scale

Five indicators are included in the Neonatal, Pain, Agitation, and Sedation Scale, chosen for their established validity, clinical applicability, and ease of assessment: crying/irritability, behavior/state, facial expression, extremities/tone, and vital signs (heart rate, respiratory rate, blood pressure, and/or oxygen saturation).

Five criteria are graded 0, 1 or 2 for pain/agitation, and 0, −1, or −2 for sedation. A high pain/agitation score indicates more frequent or intense behaviors, and a low sedation score indicates a decreased response to stimulation, or a deeper level of sedation.

Annexure 2: Neonatal Pain, Agitation, and Sedation Scale

Assessment criteria	Sedation		Sedation/pain	Pain/agitation	
	−2	−1	0/0	+1	+2
Crying irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	No sedation/no pain signs	Irritable or crying at intervals Consolable	High-pitched or silent, continuous cry Inconsolable
Behavioral state	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	No sedation/no pain signs	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or arouses minimally/no movement (not sedated)
Facial expression	Mouth is lax No expression	Minimal expression with stimuli	No sedation/no pain signs	Any pain expression intermittent	Any pain expression continual
Extremity tone	No grasp reflex Flaccid tone	Weak grasp reflex Muscle tone	No sedation/no pain signs	Intermittent clenched toes, fists, or finger splay Body is not tense	Continual clenched toes, fists, or finger splay Body is tense
Vital signs HR, RR, BP, SaO$_2$	No variability with stimuli Hypoventilation or apnea	<10% variability from baseline with stimuli	No sedation/no pain signs	10%-20% from baseline SaO$_2$ 76%-85%	↑20% from baseline SaO$_2$ ≤75% with stimulation – slow recovery Out of synchronization with ventilation

HR: Heart rate, BP: Blood pressure, RR: Respiratory rate