Mother's Own Milk as a Nutritional Analgesic Intervention for Procedural Pain in Preterm Neonates: A Prospective Cohort Study

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Abstract: *Background*: Effective pain management in preterm neonates is essential to prevent physiological instability and adverse neurodevelopmental outcomes. As neonates cannot verbally express pain, validated assessment tools and safe, evidence-based interventions are critical. Human milk administration has emerged as a promising non-pharmacological analgesic strategy.

Objective: To evaluate the effectiveness of mother's own milk in reducing procedural pain among preterm infants in a tertiary care NICU.

Methods: In this prospective pre-post cohort study, 55 preterm neonates (28-37 weeks' gestation) admitted between February 2024 and March 2025 were assessed for procedural pain using the Premature Infant Pain Profile (PIPP) and Neonatal Pain, Agitation, and Sedation Scale (N-PASS). Pain scores were recorded before (<12 hours) and after (>48 hours) administration of 2-5 ml of mother's own milk given orally 2-3 minutes prior to painful procedures. Statistical analysis included paired t-tests, correlation analyses, and 95% confidence interval calculations.

Results: Human milk administration resulted in significant pain reduction. Mean PIPP scores decreased from 12.75 ± 2.54 to 7.93 ± 2.36 (mean difference 4.82, 95% CI: 4.21-5.43; $p<0.001$), while N-PASS scores improved from 6.25 ± 2.37 to 3.80 ± 1.74 (mean difference 2.45, 95% CI: 1.96-2.94; $p<0.001$). Severe pain decreased from 49.1% to 3.6%, while minimal/no pain increased from 1.8% to 29.1%. The intervention was effective across gestational ages, birth weights, and respiratory support categories.

Conclusion: Mother's own milk provides statistically and clinically significant analgesia in preterm neonates and represents a safe, low-cost, and effective first-line non-pharmacological strategy for procedural pain management in the NICU.

Keywords: Neonatal pain assessment, preterm, human milk, PIPP scale, N-PASS scale, non-pharmacological pain management, procedural pain.

INTRODUCTION

Pain in neonates represents one of the most challenging aspects of modern pediatric healthcare, with profound implications for immediate patient care and long-term developmental outcomes. The assessment and management of pain in newborn infants, particularly in term and preterm populations, has emerged as a fundamental priority in neonatal intensive care units worldwide, driven by evidence that untreated pain can result in significant physiological instability and potentially devastating neurodevelopmental consequences [1]. The recognition that neonates possess the neuroanatomical and neurophysiological capacity to experience pain has fundamentally transformed neonatal care practices, moving from historical assumptions of pain incapacity to a contemporary understanding that neonatal pain perception may be heightened due to immature descending inhibitory pathways and increased sensitivity to noxious stimuli [2].

The complexity of neonatal pain assessment stems from the inability of newborns to verbally communicate their pain experience, necessitating specialized assessment tools that rely on behavioral, physiological, and biochemical indicators [3]. The development of standardized pain assessment instruments specifically designed for neonatal populations has been a significant advancement, with multiple validated tools now available for different clinical contexts [4]. Physiological responses to pain in neonates involve activation of the hypothalamic-pituitary-adrenal axis, stimulation of the sympathetic nervous system, and release of stress hormones, which can profoundly affect cardiovascular stability, respiratory function, and overall homeostasis [5]. These perturbations are particularly concerning in preterm infants, whose immature organ systems make them especially vulnerable to pain-induced stress responses [6]. The neurological implications extend beyond immediate responses, with evidence suggesting that repeated painful stimuli during critical developmental periods can result in permanent alterations in pain processing pathways and neurodevelopmental outcomes [7, 8].

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Pharmacological pain management presents unique challenges related to immature hepatic and renal function, altered drug metabolism, and potential adverse effects in neonates [9]. Non-pharmacological interventions have gained recognition as valuable alternatives, encompassing techniques including sucrose administration, non-nutritive sucking, skin-to-skin contact, and human milk administration [10]. These interventions offer favorable safety profiles and the potential to enhance parent-infant bonding. Human milk is increasingly recognized not only as optimal nutrition for preterm neonates but also as an effective non-pharmacological intervention for procedural pain management. Beyond its nutritional value, a mother's own milk contains bioactive compounds, including tryptophan, endogenous opioids, and hormones that may modulate nociceptive pathways and reduce stress responses in neonates. Oral administration of human milk prior to painful procedures has been associated with reduced behavioral and physiological pain indicators, improved autonomic stability, and potential neuroprotective benefits by attenuating repeated stress exposure during critical periods of brain development. These properties make mothers' own milk a particularly attractive intervention in neonatal intensive care settings, where repeated painful procedures are unavoidable and safe, low-cost analgesic strategies are essential [11].

Hospital-based prospective studies provide optimal frameworks for investigating neonatal pain assessment and intervention strategies, allowing real-time observation while maintaining clinical relevance. The distinction between term and preterm infants in pain assessment is crucial, as these populations exhibit significant differences in neurological maturity, physiological stability, and vulnerability to pain-related complications. Despite growing recognition of the importance of neonatal pain management, significant gaps remain in optimal assessment techniques and intervention strategies, underscoring the need for continued research to establish evidence-based guidelines that can be consistently applied across clinical settings.

Aim and Objectives

Aim

To evaluate the procedural pain experienced by neonates in a neonatal intensive care unit (NICU) setting and to assess the effectiveness of interventional methods in mitigating pain in preterm neonates.

Objectives

1. To evaluate the procedural pain experienced by neonates in assisted ventilation and to determine the corresponding pain grades.

2. To compare the Neonatal Pain, Agitation and Sedation Scale (N-PASS) with the Premature Infant Pain Profile (PIPP) for assessment of acute prolonged pain in neonates.

3. To compare the effectiveness of cost-effective interventional methods of pain control - administration of mother's milk prior to painful procedures.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Pediatrics, Level IIIA NICU, BLDE (DU) Shri B.M. Patil Medical College, Hospital and Research Center, Vijayapur, Karnataka, over an 18-month period from February 2024 to September 2025. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from the parents or legal guardians of all participating neonates prior to enrollment. The consent process included a detailed explanation of study objectives, procedures, potential risks and benefits, and the voluntary nature of participation.

A randomized control design was not employed because administration of mother's own milk is considered a safe and beneficial component of routine neonatal care, and withholding it during painful procedures in preterm neonates was considered ethically challenging. Therefore, a prospective pre-post cohort approach was adopted in which each neonate served as their own control, allowing assessment of intervention-related changes while minimizing inter-individual variability in pain responses.

Inclusion criteria encompassed all preterm neonates (<37 weeks of gestation) born via normal vaginal delivery or lower segment cesarean section who were on assisted ventilation at 5 hours, 48 hours, and beyond 48 hours, with an average gestational age of 34 ± 4 weeks. Exclusion criteria included neonates with severe birth trauma, severe asphyxia, shock, metabolic encephalopathy, moderate-severe hypoxic-ischemic encephalopathy, severe cardiopulmonary disease, major congenital malformations, facial dysmorphisms, facial nerve injuries, facial surgery, and other conditions affecting facial pain evaluation. Neonates

who had received analgesic medications (opioids such as morphine and fentanyl, or non-opioid medications such as acetaminophen and ibuprofen) or sedative medications (benzodiazepines such as midazolam, or other sedative agents such as propofol and dexmedetomidine) were excluded to ensure focus on natural pain responses. Additionally, procedures requiring premedication, such as endotracheal intubation, retinopathy of prematurity fundus examination, thoracentesis, and wound treatment, were not included as painful procedures.

Eligible preterm neonates meeting the inclusion criteria were enrolled consecutively during the study period to minimize selection bias and enhance representativeness of the NICU population. Standardized inclusion and exclusion criteria were applied uniformly to all admissions. Pain assessments were performed using validated tools (PIPP and N-PASS) by trained healthcare personnel following standardized assessment protocols to reduce observer variability and measurement bias.

Comprehensive baseline data were collected for each enrolled neonate, including gestational age, birth weight, mode of delivery, APGAR scores, maternal obstetric history, type of assisted ventilation, blood group compatibility, and relevant clinical parameters. Two validated pain assessment scales were employed: the Neonatal Pain, Agitation and Sedation Scale (N-PASS) and the Premature Infant Pain Profile (PIPP). The N-PASS assessment evaluated crying/irritability, behavioral state, facial expression, extremity tone, and vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation), with scores ranging from -10 to +10. The PIPP assessment included gestational age, behavioral state, heart rate change, minimum oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow, with total scores ranging from 0 to 21. Both scales were applied by trained nursing staff and physicians who received specific training in neonatal pain assessment techniques.

In the intervention protocol, mothers' own milk was administered 2-3 minutes prior to painful procedures to evaluate its immediate procedural analgesic effect under routine NICU care conditions. Baseline pain assessment was performed within the first 12 hours of admission to capture early procedural pain responses before substantial clinical adaptation occurred. A follow-up assessment at 48 hours was selected to allow repeated exposure to the intervention during routine procedures while reducing the influence of transient physiological instability commonly observed immediately after NICU admission. Although some improvement in clinical status over time may have contributed to reduced pain scores, the standardized timing of assessments and use of each neonate as their own control were intended to minimize variability and partially address this potential confounding effect.

All physicians and nursing staff involved in neonatal pain assessment underwent structured training sessions prior to study initiation, including orientation to PIPP and N-PASS scoring criteria, interpretation of behavioral and physiological indicators, and supervised practical demonstrations. Standardized assessment protocols and operational definitions were used throughout the study to minimize observer variability. During the initial phase of the study, inter-rater reliability was assessed by having trained assessors simultaneously score selected neonates under faculty supervision, and discrepancies were discussed to achieve uniformity and consistency in pain scoring.

Statistical Analysis

Results were presented as mean ± standard deviation for continuous variables and as counts and percentages for categorical variables. Continuous variables between two groups were compared using an independent t-test for normally distributed data or the Mann-Whitney U test for non-parametric data. Categorical variables between groups were compared using the chi-square test. Correlation coefficient analysis was performed to determine relationships between N-PASS and PIPP scores. Continuous variables were summarized as mean ± standard deviation, along with 95% confidence intervals for key outcome measures. Prior to the application of parametric tests, data distribution and normality of score differences were assessed using graphical inspection and normality testing. Because the pain score distributions were approximately normal, paired t-tests and independent t-tests were used to compare continuous variables. Nonparametric tests were used when assumptions for parametric analysis were not met. Statistical significance was defined as $p<0.05$ using two-tailed analysis.

Sample Size Calculation: The sample size was calculated based on an anticipated correlation of 0.62 between N-PASS and PIPP scores, using 95% confidence level and greater than 90% power, yielding a requirement of 52 neonates. A total of 55 term and preterm neonates admitted to the NICU were enrolled.

Pain assessment was conducted using two validated scales, the Premature Infant Pain Profile (PIPP) and the Neonatal Pain, Agitation and Sedation Scale (N-PASS), at two time points: baseline (within 12 hours of admission) and post-intervention (after 48 hours of human milk administration). Demographic and clinical characteristics were documented, and statistical analyses included descriptive statistics, paired t-tests for pre-post comparisons, correlation analysis between scales, and chi-square tests for categorical associations. All analyses were performed using SPSS version 20 with a significance level set at $p<0.05$.

RESULTS

The study population consisted of 55 preterm infants, predominantly assessed on the first day of life (Table **1**). The gender distribution showed a slight male predominance (54.5%). Gestational age distribution revealed that very preterm infants (28-32 weeks) comprised the largest group (50.9%), followed by moderate-late preterm infants (32-37 weeks, 45.5%), with only 3.6% being extremely preterm. Birth weight categories indicated a high-risk population with 18.2% extremely low birth weight, 34.5% very low birth weight, and 41.8% low birth weight infants. Respiratory support requirements included CPAP in 45.5% of infants, HFNC in 40.0%, and less intensive support modalities in the remaining infants, reflecting the critical nature of this population.

Human milk intervention resulted in a highly significant pain reduction across both validated assessment scales (Table **2**). PIPP scores decreased from 12.75 ± 2.54 (indicating moderate-severe pain) to 7.93 ± 2.36 (mild-moderate pain), representing a mean difference of 4.82 ± 2.25 points ($p<0.001$) with a large effect size of 2.14. Similarly, N-PASS scores improved from 6.25 ± 2.37 to 3.80 ± 1.74, with a mean difference of 2.45 ± 1.81 points ($p<0.001$) and a large effect size of 1.35. These reductions represent clinically meaningful improvements of 37.8% for PIPP and 39.2% for N-PASS scores, moving infants from concerning pain levels to more acceptable comfort levels. The mean reduction in PIPP score was 4.82 points (95% CI: 4.21-5.43; $p<0.001$), while the mean reduction in N-PASS score was 2.45 points (95% CI: 1.96-2.94; $p<0.001$).

The categorical pain distribution demonstrated dramatic improvements following human milk intervention (Table **3**). The proportion of infants experiencing severe pain decreased markedly from 49.1% (n=27) to 3.6% (n=2), representing a 92.6% reduction. Conversely, infants with minimal or no pain

Table 1: Demographic and Clinical Characteristics of Study Population (n=55)

Characteristic	Category	n (%)
Day of Assessment	Day 1	53 (96.4%)
	Day 2	2 (3.6%)
Gender	Male	30 (54.5%)
	Female	25 (45.5%)
Gestational Age	Extremely Preterm (≤28 weeks)	2 (3.6%)
	Very Preterm (28-32 weeks)	28 (50.9%)
	Moderate-Late Preterm (32-37 weeks)	25 (45.5%)
Birth Weight	Extremely Low (≤1.0 kg)	10 (18.2%)
	Very Low (1-1.5 kg)	19 (34.5%)
	Low (1.5-2.5 kg)	23 (41.8%)
	Normal (≥2.5 kg)	3 (5.5%)
Respiratory Support	CPAP	25 (45.5%)
	HFNC	22 (40.0%)
	Hood O_2	5 (9.1%)
	NPO_2	2 (3.6%)
	Combined Support	1 (1.8%)

Table 2: Pain Assessment Scores Before and After Human Milk Intervention (n=55)

Pain Scale	Pre-Intervention Mean ± SD	Post-Intervention Mean ± SD	Mean Difference	P-value	Effect Size
PIPP Score	12.75 ± 2.54	7.93 ± 2.36	4.82 ± 2.25	<0.001*	2.14 (Large)
N-PASS Score	6.25 ± 2.37	3.80 ± 1.74	2.45 ± 1.81	<0.001*	1.35 (Large)
% Reduction	-	-	37.8% (PIPP)	-	-
% Reduction	-	-	39.2% (N-PASS)	-	-

Table 3: Categorical Pain Distribution and Clinical Significance (n=55)

Pain Category	Pre-Intervention n (%)	Post-Intervention n (%)	Change	Percentage Change
Minimal/No Pain (PIPP ≤6)	1 (1.8%)	16 (29.1%)	+15	+1,500%
Moderate Pain (PIPP 7-12)	27 (49.1%)	37 (67.3%)	+10	+37.0%
Severe Pain (PIPP ≥13)	27 (49.1%)	2 (3.6%)	-25	-92.6%
Overall Pain Reduction	-	-	70% reduction in severe pain	8-fold increase in minimal pain

increased from 1.8% (n=1) to 29.1% (n=16), a fifteen-fold increase. Moderate pain cases increased from 49.1% to 67.3% as infants transitioned from severe pain categories. These categorical shifts represent substantial clinical improvements, with 70% reduction in severe pain burden and an eight-fold increase in infants achieving minimal pain status, indicating meaningful enhancement in patient comfort and care quality.

Subgroup analysis demonstrated consistent trends toward reduction in pain scores across gestational age, birth weight, and respiratory support categories, although the magnitude of improvement varied among individual neonates and clinical subgroups (Table **4**). Infants requiring CPAP support demonstrated the largest PIPP score reductions (5.12 ± 1.72 points), while those on less intensive support showed smaller but significant improvements. Notably, the most vulnerable extremely low birth weight infants (<1 kg) exhibited excellent responses, with a 5.20 ± 2.10 PIPP reduction, indicating a particular benefit for high-risk populations. Correlation analysis between pain scales showed moderate agreement before intervention (r=0.352, p=0.008), which disappeared after intervention (r=0.087, p=0.529), suggesting that the scales may measure different aspects of pain relief. Both scales demonstrated strong test-retest reliability (PIPP: r=0.580, p<0.001; N-PASS: r=0.650, p<0.001),

Table 4: Subgroup Analysis and Correlation between Pain Assessment Scales

Parameter	Category/Comparison	N	PIPP Reduction (Mean ± SD)	N-PASS Reduction (Mean ± SD)
Respiratory Support	CPAP	25	5.12 ± 1.72	2.64 ± 2.29
	HFNC	22	4.73 ± 3.07	2.14 ± 1.50
	Nasal Prongs	8	3.39 ± 1.86	1.75 ± 1.58
Birth Weight	ELBW (<1 kg)	10	5.20 ± 2.10	2.80 ± 1.90
	VLBW (1.1-1.5 kg)	19	4.89 ± 2.35	2.42 ± 1.88
	LBW (1.6-2.49 kg)	23	4.57 ± 2.18	2.35 ± 1.75
	Normal Weight (≥2.5 kg)	3	4.00 ± 2.65	2.00 ± 1.73
Scale Correlation	Pre-Intervention (PIPP vs N-PASS)	55	r = 0.352 (p=0.008)*	Moderate correlation
	Post-Intervention (PIPP vs N-PASS)	55	r = 0.087 (p=0.529)	No correlation
Test-Retest Reliability	PIPP Pre-Post correlation	55	r = 0.580 (p<0.001)*	Strong reliability

*Statistically significant (p<0.05); CPAP: Continuous Positive Airway Pressure; HFNC: High Flow Nasal Cannula; ELBW: Extremely Low Birth Weight; VLBW: Very Low Birth Weight; LBW: Low Birth Weight.

confirming their consistency as measurement tools. The consistency of positive outcomes across all weight categories, gestational ages, and respiratory support types confirms the intervention's broad applicability and effectiveness in diverse clinical scenarios.

DISCUSSION

This study demonstrated the remarkable effectiveness of human milk administration as a pain intervention in preterm infants undergoing routine painful procedures, with PIPP scores decreasing from 12.75 to 7.93 (37.8% reduction) and N-PASS scores improving from 6.25 to 3.80 (39.2% reduction), both with large effect sizes (2.14 and 1.35, respectively) and highly significant p-values (<0.001). These findings align with previous research: Shah *et al.* [11] demonstrated that breastfeeding provided significant advantages for one-time painful procedures, with improved standardized pain scores (PIPP, DAN, NIPS, and NFCS) compared to other interventions. Our baseline pain scores were higher than those reported by Desai *et al.* [12], who found average PIPP scores of 8.33 in ventilated neonates, possibly because they included various painful procedures rather than focusing solely on mechanically ventilated patients. The universal effectiveness observed across all study participants is particularly noteworthy and consistent with that reported by Napiórkowska-Orkisz *et al.* [13], who found that non-pharmacological interventions, including breastfeeding, resulted in effective pain management with 62.2% experiencing no pain or mild discomfort during heel puncture. Our study used both the PIPP and N-PASS scales, demonstrating a strong correlation before the intervention (r=0.352, p=0.008), which aligns with findings from Xie *et al.* [14] who evaluated multiple pain assessment scales and found that PIPP had good clinical utility for evaluating procedural pain in premature infants with high internal consistency (p<0.001). However, the correlation between the scales disappeared after the intervention (r=0.087, p=0.529) in our study, suggesting that these scales may respond differently to pain relief interventions and measure different aspects of pain, which differs from Huang *et al.* [15] who found strong correlations between different pain scales throughout their assessment period.

The clinical significance of our findings is evident in categorical pain changes: severe pain cases decreased dramatically from 49.1% to 3.6% (92.6% reduction), while minimal/no pain cases increased from 1.8% to 29.1% (1,500% increase), demonstrating not just statistical but meaningful clinical improvement (Table **3**). This substantial shift in pain categories surpasses the improvements reported by Zargham-Boroujeni *et al.* [16], who compared massage and breastfeeding effects, reporting significant pain reduction with breastfeeding, though massage was slightly more effective. Our subgroup analysis revealed effectiveness across all respiratory support categories and birth weight groups (Table **4**), with extremely low birth weight infants showing excellent responses (5.20 ± 2.10 PIPP reductions), indicating particular benefit for high-risk populations. Infants on CPAP showed the largest PIPP reductions (5.12 ± 1.72 points), suggesting more critically ill infants may derive greater benefit, possibly due to higher baseline pain or greater physiological stress. While our study focused on human milk, comparison with other interventions is relevant: Mahmud *et al.* [17] investigated oral dextrose effectiveness, reporting mean pain scores of 4.31 with 10% dextrose compared to 6.26 with sterile water, though the magnitude appears smaller than our observed improvements, suggesting human milk may offer superior analgesic properties.

The analgesic effects observed in the present study may be related to previously proposed mechanisms described in the literature, including activation of endogenous opioid pathways, modulation of stress responses, activation of the parasympathetic nervous system, and comforting oral sensory stimulation. However, these mechanisms were not directly assessed in our study and should therefore be interpreted as hypothetical explanations requiring further mechanistic investigation.

Although subgroup analyses demonstrated consistent analgesic benefits across gestational age, birth weight, and respiratory support categories, these findings should be interpreted cautiously, as some subgroups had relatively small sample sizes. Therefore, subgroup-specific observations are primarily exploratory and hypothesis-generating rather than definitive.

Recent evidence further supports the effectiveness of non-pharmacological interventions for procedural pain management in preterm neonates. Lopes *et al*., in a systematic review and network meta-analysis, demonstrated that several non-pharmacological strategies significantly reduce procedural pain in NICU infants, while also emphasizing variability in effectiveness among different interventions [18]. Their findings support the growing role of safe, low-cost

supportive measures in neonatal pain management and reinforce the importance of integrating evidence-based non-pharmacological approaches into routine NICU care.

Similarly, Das *et al*. (2025) reported that expressed breast milk (EBM) facilitated tucking and that the combination significantly reduced PIPP pain scores in preterm neonates undergoing heel-stick procedures. The study demonstrated meaningful reductions in pain scores at both 1-minute and 4-minute post-procedure assessments, supporting the analgesic potential of EBM-based interventions [19].

Our findings are consistent with these observations, as administration of mother's own milk in the present study was associated with clinically significant reductions in both PIPP and N-PASS scores. Together, these studies suggest that human milk-based interventions may represent an effective and feasible component of multimodal non-pharmacological pain management strategies in preterm neonates. However, differences in study design, intervention combinations, and pain assessment methodologies across studies warrant cautious interpretation and highlight the need for larger multicenter randomized trials.

Future research warrants randomized controlled trials comparing human milk to other established pain management interventions, exploring optimal timing, volume, and administration methods, investigating dose-response relationships and duration of analgesic effect, and conducting long-term follow-up studies to assess whether improved neonatal pain management translates to better neurodevelopmental outcomes. The integration of human milk administration into standardized pain management protocols represents an important quality improvement opportunity, with policy development focused on creating standardized protocols that ensure consistent implementation across different clinical settings and support broader recognition of pain as a significant clinical issue in neonatal care, deserving dedicated attention and resources.

STRENGTHS AND LIMITATIONS

This prospective study strengthens internal validity through real-time data collection and the use of two validated neonatal pain scales (PIPP and N-PASS), enabling a robust, comparative assessment of procedural pain in preterm infants. Inclusion of very preterm and extremely low birth weight neonates enhances clinical relevance, and the pre-post design, with each infant serving as their own control, reduces inter-individual variability. The intervention-administration of mother's own milk-is safe, inexpensive, and readily implementable in routine NICU practice.

However, the single-center design may limit generalizability. The absence of a randomized control group limits the ability to definitively attribute observed reductions in pain scores solely to the intervention, as temporal clinical improvement and adaptation may have contributed to the findings. The modest sample size restricts the strength of subgroup inferences, and outcomes were limited to short-term pain response without long-term neurodevelopmental follow-up. Lack of assessor blinding and absence of direct comparison with other non-pharmacological interventions are additional limitations.

CONCLUSION

This prospective pre-post cohort study suggests that administration of mother's own milk prior to routine painful procedures may be associated with clinically meaningful reductions in procedural pain scores among preterm neonates admitted to the NICU. The observed benefits were noted across different gestational age, birth weight, and respiratory support categories, supporting the potential utility of a mother's own milk as a safe, feasible, and low-cost non-pharmacological supportive strategy for neonatal procedural comfort. However, given the observational design, absence of a randomized control group, and potential confounding factors, the findings should be interpreted cautiously. Further large-scale randomized controlled studies are warranted to confirm these observations and evaluate long-term clinical and neurodevelopmental outcomes.

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