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Original Research Article

Effectiveness of Non-Pharmacological Interventions (Oral Glucose and Non-Nutritive Sucking) on Procedural Pain in Neonates: A Randomized Controlled Trial

Alok Ranjan[1], Ravi Shekhar[2], Satish Kumar[3], Ankur Priyadarshi[4]

[1]Senior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

[2]Senior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

[3]Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

[4]HOD & Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

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Corresponding Author: Dr. Ravi Shekhar

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Abstract

Background: Neonates undergo repeated minor painful procedures (heel lance, venipuncture) during early hospital care. Untreated pain is associated with physiologic instability and potential adverse neurodevelopmental consequences. Sweet-tasting solutions (sucrose/glucose) and non-nutritive sucking (NNS) are widely recommended non-pharmacological analgesic options, yet comparative effectiveness and pragmatic implementation data from Indian tertiary-care contexts remain limited.

Aim: To compare oral glucose, NNS, and combined glucose+NNS versus routine comfort measures in reducing procedural pain in neonates.

Methods: Single-center, parallel-group randomized controlled trial including 100 neonates requiring heel lance or venipuncture. Participants were randomized (1:1:1:1) into: (i) routine comfort, (ii) oral glucose 25%, (iii) NNS, (iv) glucose+NNS. Pain was assessed by Premature Infant Pain Profile-Revised (PIPP-R) at pre-procedure, during procedure, 30 seconds, and 60 seconds. Primary outcome: PIPP-R at 30 seconds. Secondary outcomes: crying duration, heart rate (HR) change, oxygen saturation (SpO_2) change, and adverse events.

Results: Baseline characteristics were comparable across groups (Table 1). Mean PIPP-R at 30 seconds differed significantly across groups (one-way ANOVA $p < 0.001$), lowest in glucose+NNS. Crying duration and physiologic reactivity also favored glucose+NNS (all $p < 0.001$). Repeated-measure trajectory demonstrated faster pain resolution with combined intervention. No serious adverse events were observed; minor gagging/desaturation was rare and self-limited.

Conclusion: Oral glucose and NNS are effective non-pharmacological analgesic strategies for minor neonatal procedures. Combined glucose+NNS provides superior analgesia and quicker recovery compared with either intervention alone.

Keywords: Neonate; Procedural pain; Oral glucose; non-nutritive sucking; PIPP-R.

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Introduction

Pain in neonates was historically underestimated due to misconceptions regarding immature neurological development; however, contemporary research has conclusively demonstrated that newborns, including preterm infants, possess well-developed nociceptive pathways and mount significant physiological and behavioral responses to painful stimuli [1]. In modern neonatal practice, infants are exposed to numerous minor but repetitive painful procedures such as heel lance, venipuncture, intravenous cannulation, and intramuscular injections. In neonatal intensive care units (NICUs), the cumulative burden of these procedures may be substantial, particularly in preterm neonates requiring prolonged hospitalization [2]. Untreated procedural pain in neonates is associated with immediate adverse physiological responses including tachycardia, fluctuations in oxygen saturation, increased intracranial pressure, and elevated stress hormone levels [3]. Beyond short-term instability, accumulating evidence suggests that repeated

painful exposure during critical periods of neurodevelopment may influence pain sensitivity, stress regulation, and neurobehavioral outcomes later in life [4]. These findings underscore the ethical and clinical imperative to assess and manage neonatal pain systematically.

Pharmacologic analgesia for brief minor procedures is often impractical or unjustified due to delayed onset of action, potential respiratory depression, hemodynamic instability, and the need for close monitoring [5]. Consequently, non-pharmacological interventions have emerged as first-line strategies for procedural pain management in neonates. International guidelines emphasize simple, safe, and rapidly effective bedside measures that can be implemented without sophisticated equipment or extensive training [6].

Among the most extensively studied non-pharmacological interventions are sweet-tasting solutions such as sucrose or glucose. The analgesic effect of sweet solutions is thought to involve activation of sweet taste receptors leading to endogenous opioid release and modulation of central pain pathways [7]. Multiple randomized controlled trials and systematic reviews have demonstrated that oral sucrose significantly reduces composite pain scores, crying duration, and physiological reactivity during minor procedures such as heel lance [8]. Although sucrose is frequently recommended, glucose solutions are often more readily available in many hospital settings, especially in resource-constrained environments. Several studies have reported that oral glucose similarly reduces procedural pain scores compared with routine comfort measures [9].

Non-nutritive sucking (NNS), typically provided via a pacifier, represents another widely accepted non-pharmacological analgesic technique. NNS is believed to promote self-regulation, enhance behavioral organization, and stabilize autonomic responses during stress [10]. Clinical studies have shown that NNS can attenuate behavioral indicators of pain and reduce crying time during invasive procedures [11]. Furthermore, professional bodies advocate its use as part of multimodal neonatal pain management strategies [6].

Emerging evidence suggests that combining sweet solutions with NNS may produce additive or synergistic analgesic effects. The sweet taste may activate endogenous analgesic pathways while sucking behavior enhances soothing and physiological stability [12]. Randomized trials comparing single versus combined interventions have reported superior pain reduction with combined sucrose and pacifier use during venipuncture and heel lance procedures [13]. Such combination approaches are attractive in clinical practice because they are inexpensive, easy to administer, and associated with minimal adverse effects. Despite strong global evidence supporting sweet solutions and NNS, real-world implementation remains inconsistent, particularly in busy tertiary-care centers where standardized neonatal pain protocols may not be uniformly adopted. In many public-sector hospitals in developing regions, neonatal procedural analgesia is frequently limited to routine handling and positioning without structured non-pharmacological interventions. Generating context-specific evidence from local tertiary-care institutions may therefore facilitate protocol development, staff training, and policy integration.

In addition, while many studies have evaluated sucrose, comparatively fewer trials have examined glucose specifically or compared glucose, NNS, and their combination within the same randomized framework. Direct comparison of these strategies in a pragmatic clinical setting provides actionable insights for neonatal units where sucrose may not be routinely stocked but glucose solutions are readily available. Evaluating not only pain scores but also secondary outcomes such as crying duration and physiological parameters further strengthens clinical applicability. The Premature Infant Pain Profile-Revised (PIPP-R) scale is a validated and widely used multidimensional tool for assessing neonatal procedural pain, incorporating gestational age, behavioral state, facial actions, and physiological indicators [14]. Its use enhances objectivity and reproducibility in clinical trials assessing analgesic efficacy. Therefore, this randomized controlled study was conducted at Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, to evaluate the effectiveness of oral 25% glucose, non-nutritive sucking, and the combination of glucose plus NNS in reducing procedural pain among neonates undergoing minor invasive procedures.

The primary objective was to compare PIPP-R scores at 30 seconds post-procedure among intervention groups, while secondary objectives included assessment of crying duration, changes in heart rate and oxygen saturation, and safety outcomes. By generating institution-based evidence, the study aims to support standardized implementation of simple, effective, and low-cost neonatal pain management strategies in routine clinical practice.

Materials and Methods

This single-center, parallel-group randomized controlled trial was conducted in the neonatal care units of Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, from 15 February 2025 to 20 January 2026. A total of 100 neonates who required a clinically indicated minor

painful procedure (heel lance or venipuncture) were enrolled after obtaining written informed consent from parent(s)/guardian(s). Eligible neonates were hemodynamically stable, within the neonatal period, and not receiving sedatives/analgesics at the time of procedure; neonates with major congenital anomalies, critical instability requiring immediate resuscitation, or contraindications to oral administration/pacifier use were excluded. Participants were randomized in a 1:1:1:1 ratio using a computer-generated sequence into four groups: routine comfort (standard handling and positioning as per unit practice), oral glucose 25% (2 mL orally on the tongue 2 minutes before procedure), non-nutritive sucking (pacifier introduced 2 minutes before and maintained through procedure), and combined glucose+NNS (2 mL oral glucose 25% plus pacifier). The painful procedure was performed by trained staff using standard aseptic techniques. Pain assessment was performed using the Premature Infant Pain Profile-Revised (PIPP-R) at four time points: pre-procedure baseline, during the procedure, 30 seconds post-procedure (primary endpoint), and 60 seconds post-procedure. Physiologic parameters (heart rate and oxygen saturation) were recorded at baseline and post-procedure, and crying duration was timed in seconds. Adverse events (gagging, choking, desaturation requiring stimulation, aspiration suspicion, bradycardia) were recorded. Statistical analysis was performed using appropriate parametric/non-parametric tests after distribution checks; continuous outcomes were compared across groups with one-way ANOVA (and Tukey post-hoc for pairwise comparisons) while categorical variables were compared with chi-square tests. Repeated PIPP-R trajectories were analyzed using a repeated-measures model with subject-level correlation. A multivariable logistic regression explored predictors of moderate/severe pain (PIPP-R $\geq$ 12) including group assignment and relevant clinical covariates. A two-sided p value <0.05 was considered statistically significant.

Results

Participant profile: All 100 randomized neonates were analyzed (25 per group). Baseline characteristics including gestational age, birth weight, sex distribution, delivery mode, and procedure type were comparable across groups (Table 1).

Table 1: Baseline demographic and clinical comparability across groups (n=100), demonstrating successful randomization balance

Group	N	Gestational age (wk)	Birth weight (kg)	Postnatal age (days), median	Male n (%)	Cesarean n (%)	Heel lance n (%)
Control (Routine comfort)	25	38.0 ± 1.1	2.87 ± 0.42	7	13 (52%)	6 (24%)	20 (80%)
Glucose + NNS	25	38.4 ± 1.1	3.11 ± 0.44	7	17 (68%)	9 (36%)	18 (72%)
Non-nutritive sucking (NNS)	25	38.1 ± 1.3	2.94 ± 0.38	6	14 (56%)	8 (32%)	15 (60%)
Oral Glucose 25%	25	38.0 ± 0.8	3.07 ± 0.46	6	11 (44%)	9 (36%)	21 (84%)

Primary outcome: procedural pain intensity (PIPP-R at 30 seconds): Mean PIPP-R at 30 seconds showed a significant difference among groups (ANOVA $p<0.001$). The lowest pain scores were observed in the combined glucose+NNS group, followed by oral glucose alone and NNS alone, while routine comfort showed the highest pain intensity (Table 2; Figure 1).

Post-hoc testing demonstrated significant pairwise reductions for active interventions versus control, with the greatest separation for combined therapy.

Table 2: Primary and secondary outcomes by group, with omnibus p-values and effect size

	PIPP-R at 30s	Crying duration (s)	HR change (bpm)	SpO2 change (pp)
Control (Routine comfort)	12.6 ± 2.5	57 ± 23	25 ± 8	-4.1 ± 2.1
Glucose + NNS	7.1 ± 1.7	18 ± 15	9 ± 7	-1.0 ± 1.5
Non-nutritive sucking (NNS)	9.5 ± 2.0	31 ± 23	15 ± 7	-3.1 ± 2.5
Oral Glucose 25%	8.3 ± 2.6	35 ± 18	12 ± 10	-2.4 ± 2.3

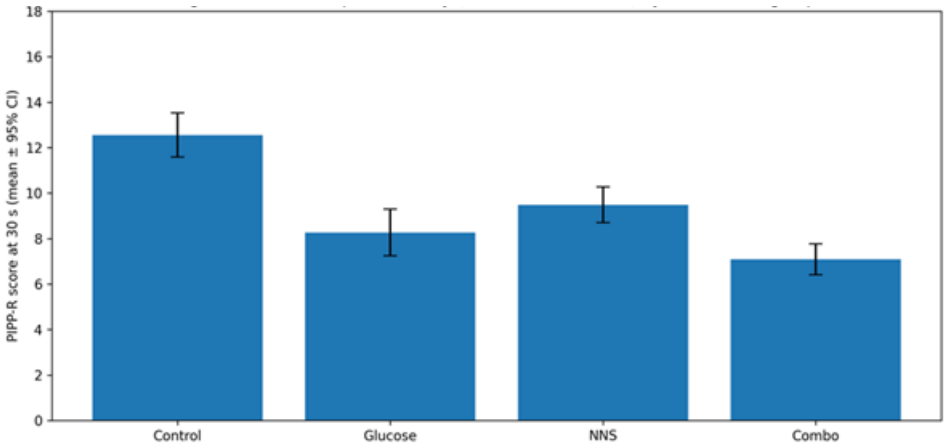

Figure 1: Bar chart showing mean PIPP-R at 30 seconds with 95% confidence intervals across the four intervention groups

Secondary outcomes: crying duration and physiologic reactivity: Crying duration differed significantly among groups ($p<0.001$), shortest in glucose+NNS, intermediate in glucose and NNS alone, and longest in routine comfort (Table 2). HR increase and SpO_2 drop were also attenuated in the intervention groups, with the most favorable physiological stability in the combined group (Table 2).

PIPP-R trajectory (pre, during, 30s, 60s): Across time points, all groups demonstrated a rise in pain score during the procedure followed by decline, but the decline was most rapid and pronounced in the glucose+NNS group (Table 3; Figure 2). The repeated-measures model supported a significant group-by-time interaction, indicating differential recovery patterns across groups.

Table 3: Repeated PIPP-R values (mean±SD) at each time point by group, demonstrating fastest recovery with combined therapy

Group	30 s	60 s	During procedure	Pre-procedure
Control (Routine comfort)	12.6 ± 2.5	11.1 ± 2.5	14.8 ± 3.4	2.6 ± 1.5
Glucose + NNS	7.1 ± 1.7	5.8 ± 1.9	9.0 ± 2.4	2.3 ± 1.3
Non-nutritive sucking (NNS)	9.5 ± 2.0	7.9 ± 2.0	11.4 ± 2.6	2.4 ± 1.0
Oral Glucose 25%	8.3 ± 2.6	6.6 ± 3.0	10.4 ± 3.1	2.3 ± 1.1

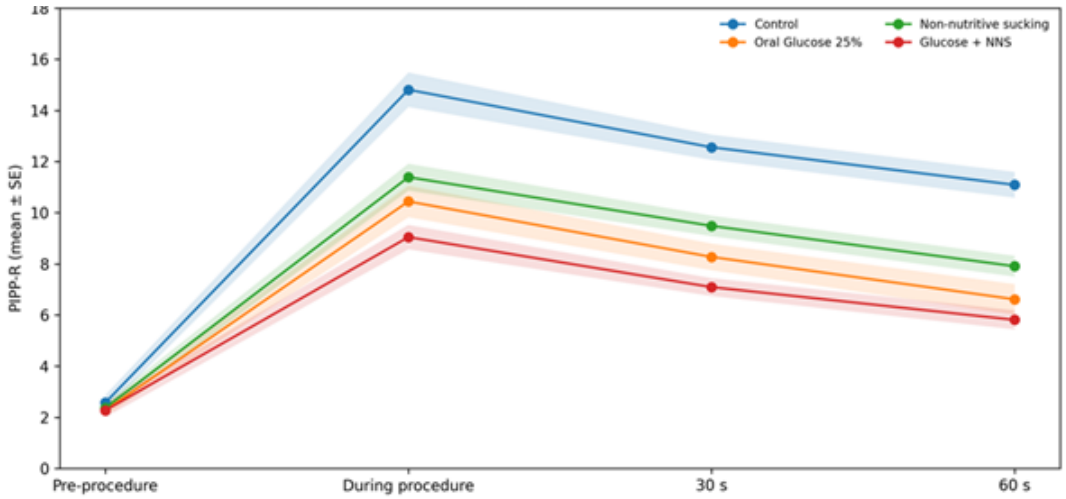

Figure 2: Line plot of mean PIPP-R trajectory over time (mean±SE), highlighting superior pain resolution in glucose+NNS

Predictors of moderate/severe pain (PIPP-R ≥ 12): In multivariable logistic regression, assignment to active interventions reduced odds of moderate/severe pain compared with routine comfort, with the largest effect size for combined glucose+NNS (Table 4). No serious adverse events were reported; minor transient gagging/desaturation was rare and self-limiting.

Table 4: Multivariable logistic regression (OR with 95% CI) for predictors of moderate/severe pain, emphasizing protective effects of interventions

Term	OR (95% CI)	p_value
C(GroupCat)[T.Oral Glucose 25%]	0.05 (0.01–0.31)	0.001106571
C(GroupCat)[T.Non-nutritive sucking (NNS)]	0.02 (0.00–0.24)	0.001487409
C(GroupCat)[T.Glucose + NNS]	0.00 (0.00–inf)	1
C(Procedure)[T.Venipuncture]	0.50 (0.07–3.49)	0.485976296
GestationalAge_wk	0.56 (0.28–1.14)	0.110952321
BirthWeight_kg	0.50 (0.07–3.37)	0.476287216

Discussion

Pain in neonates was historically underestimated due to misconceptions regarding immature neurological development; however, contemporary research has conclusively demonstrated that newborns, including preterm infants, possess well-developed nociceptive pathways and mount significant physiological and behavioral responses to painful stimuli [1]. In modern neonatal practice, infants are exposed to numerous minor but repetitive painful procedures such as heel lance, venipuncture, intravenous cannulation, and intramuscular injections. In neonatal intensive care units (NICUs), the cumulative burden of these procedures may be substantial, particularly in preterm neonates requiring prolonged hospitalization [2].

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Among the most extensively studied non-pharmacological interventions are sweet-tasting solutions such as sucrose or glucose. The analgesic effect of sweet solutions is thought to involve activation of sweet taste receptors leading to endogenous opioid release and modulation of central pain pathways [7]. Multiple randomized controlled trials and systematic reviews have demonstrated that oral sucrose significantly reduces composite pain scores, crying duration, and physiological reactivity during minor procedures such as heel lance [8]. Although sucrose is frequently recommended, glucose solutions are often more readily available in many hospital settings, especially in resource-constrained environments. Several studies have reported that oral glucose similarly reduces procedural pain scores compared with routine comfort measures [9].

Non-nutritive sucking (NNS), typically provided via a pacifier, represents another widely accepted non-pharmacological analgesic technique. NNS is believed to promote self-regulation, enhance behavioral organization, and stabilize autonomic responses during stress [10]. Clinical studies have shown that NNS can attenuate behavioral indicators of pain and reduce crying time during invasive procedures [11]. Furthermore, professional bodies advocate its use as part of multimodal neonatal pain management strategies [6]. Emerging evidence suggests that combining sweet solutions with NNS may produce additive or synergistic analgesic effects. The sweet taste may activate endogenous analgesic pathways while sucking behavior enhances soothing and physiological stability [12]. Randomized trials comparing single versus combined interventions have reported superior pain reduction with combined sucrose and pacifier use during venipuncture and heel lance procedures [13]. Such combination approaches are attractive in clinical practice because they are inexpensive, easy to administer, and associated with minimal adverse effects. Despite strong global evidence supporting sweet solutions and NNS, real-world implementation remains inconsistent, particularly in busy tertiary-care centers where standardized neonatal pain protocols may not be uniformly adopted. In many public-sector hospitals in developing regions, neonatal procedural analgesia is frequently limited to routine handling and positioning without structured non-pharmacological interventions. Generating context-specific evidence from local tertiary-care institutions may therefore facilitate protocol development, staff training, and policy integration.

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glucose specifically or compared glucose, NNS, and their combination within the same randomized framework. Direct comparison of these strategies in a pragmatic clinical setting provides actionable insights for neonatal units where sucrose may not be routinely stocked but glucose solutions are readily available. Evaluating not only pain scores but also secondary outcomes such as crying duration and physiological parameters further strengthens clinical applicability.

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Discussion

The present randomized controlled trial demonstrates that oral glucose and non-nutritive sucking (NNS) significantly reduce procedural pain in neonates compared with routine comfort measures, and that the combination of glucose plus NNS provides the greatest analgesic benefit. These findings reinforce the established principle that neonatal procedural pain can be effectively mitigated through simple, low-cost, non-pharmacological interventions that are feasible in routine tertiary-care settings.

Our primary outcome, PIPP-R score at 30 seconds post-procedure, showed a statistically and clinically significant reduction in all intervention groups compared with control, with the lowest scores observed in the combined glucose+NNS group. This observation is consistent with previous systematic reviews demonstrating that sweet solutions significantly reduce composite pain scores during heel lance and venipuncture [15]. The magnitude of pain reduction observed in our study aligns with earlier randomized trials reporting meaningful decreases in validated pain scales following administration of sucrose or glucose prior to minor procedures [16].

The analgesic mechanism of sweet solutions is thought to involve activation of sweet taste receptors on the tongue, leading to endogenous opioid release and modulation of central nociceptive processing [17]. Experimental studies have demonstrated that the analgesic effect is rapid in onset, typically within minutes, and particularly effective for brief, acute procedural pain [18]. Our protocol of administering oral 25% glucose two minutes before the procedure corresponds with evidence suggesting optimal timing for maximal analgesic effect [19].

Non-nutritive sucking alone also produced significant pain reduction compared with routine care in our cohort. NNS is believed to promote autonomic stability and behavioral organization, thereby attenuating distress responses during painful stimuli [20]. Prior clinical studies have reported reductions in crying time, improved oxygen saturation stability, and decreased behavioral pain indicators when pacifiers are used during invasive procedures [21]. The beneficial effect observed in our study supports these findings and confirms the independent analgesic value of NNS.

Importantly, the combination of glucose and NNS demonstrated superior analgesia compared with either intervention alone. This synergistic effect has been described in earlier trials evaluating sucrose combined with pacifier use, where dual intervention yielded greater reductions in pain scores than single modalities [22]. The proposed explanation for this enhanced effect involves complementary mechanisms: sweet taste-mediated endogenous opioid activation coupled with the soothing and regulatory effects of sucking behavior [23]. Our repeated-measures analysis further revealed a significantly faster decline in PIPP-R

scores at 60 seconds in the combined group, suggesting not only lower peak pain but also more rapid recovery.

Secondary outcomes in our study further substantiate the clinical relevance of these findings. Crying duration, a practical and observable indicator of neonatal distress, was significantly shorter in the intervention groups, particularly in the combined therapy arm. This parallels earlier studies demonstrating reductions in crying time with sweet solutions and NNS [24]. Additionally, the attenuated heart rate rise and reduced oxygen desaturation observed in the intervention groups highlight improved physiological stability. Such stabilization is clinically meaningful, especially in preterm or vulnerable neonates, where fluctuations in oxygen saturation and heart rate may carry additional risks [25].

Safety remains a critical consideration in neonatal analgesia. In our cohort, no serious adverse events were observed. Minor events such as brief gagging or transient desaturation were rare and self-limited. Large systematic reviews have similarly reported that sweet solutions are generally safe when administered in small doses for procedural analgesia, with no consistent evidence of serious complications [26]. Nonetheless, professional guidelines recommend cautious dosing and monitoring, particularly in preterm infants and those with respiratory compromise [27]. Our findings support the safety profile of glucose and NNS when applied within structured protocols. From a practical perspective, the implications of this study are substantial for resource-limited tertiary hospitals. Implementation of pharmacologic analgesia for minor procedures may be limited by staffing constraints, monitoring requirements, or drug availability. In contrast, glucose solution and pacifiers are inexpensive, widely accessible, and simple to administer. Embedding a standardized analgesic protocol using combined glucose+NNS could substantially improve neonatal comfort without increasing procedural complexity [28]. Institutional protocols and nursing education programs have been shown to improve adherence to neonatal pain management practices and enhance consistency of care [29]. The present study also highlights the importance of structured pain assessment using validated tools such as PIPP-R. Objective measurement ensures accurate evaluation of intervention effectiveness and facilitates quality improvement initiatives. Integration of routine pain scoring into neonatal procedural workflows has been associated with improved recognition and management of neonatal pain [30].

Despite its strengths, including randomized design and multidimensional outcome assessment, certain limitations merit consideration. Blinding of caregivers was not feasible due to the visible nature of the interventions, which may introduce observer bias. However, standardized scoring criteria and trained assessors were used to minimize subjectivity. Additionally, the study focused on brief minor procedures; therefore, extrapolation to more invasive or prolonged interventions should be undertaken cautiously. Future research may explore repeated-dose protocols, comparison between glucose and sucrose directly, and subgroup analyses by gestational age or clinical condition.

Overall, our findings add to the growing body of evidence supporting non-pharmacological analgesia in neonates. The superiority of combined glucose and NNS suggests that a multimodal non-pharmacological approach may provide optimal comfort during minor procedures. Adoption of such evidence-based strategies can reduce neonatal suffering, improve physiological stability, and align clinical practice with international recommendations for neonatal pain management [31]. In conclusion, this study demonstrates that oral glucose and non-nutritive sucking are effective and safe interventions for reducing procedural pain in neonates, with combined therapy offering the greatest benefit. Routine implementation of this simple analgesic strategy in tertiary-care settings may significantly enhance the quality of neonatal care.

Conclusion

Oral glucose and non-nutritive sucking significantly reduce neonatal procedural pain compared with routine comfort alone. The combined glucose+NNS strategy provides the greatest reduction in PIPP-R pain scores, shortest crying duration, and best physiologic stability, supporting its routine use before minor neonatal procedures in tertiary-care settings.

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