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Original Article

Comparison of Behavior-based and Volume-based Feeding Methods on Blood Glucose Levels and Weight Gain in Premature Infants

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ABSTRACT

Background: This study was designed to compare blood glucose levels and weight gain in premature infants fed using cue-based feeding versus traditional volume-based feeding. Cue-based feeding relies on infants' behavioral cues, but concerns about hypoglycemia and the infant's inability to wake for feeding present challenges to its implementation.
Methods: This was a single-blind, randomized controlled clinical trial (IRCT: IRCT20240919063098N1) of 122 preterm infants allocated 1:1 to cue-based or volume-based feeding; caregivers could not be blinded, while assessors remained blinded. The primary outcome was weight trajectory (Day 1–3, Week 1, discharge). Secondary outcomes included preprandial glucose levels, caregiver-initiated wake-ups, feeding adverse events, length of stay, and postmenstrual age at discharge. Analysis was by intention-to-treat using mixed-effects models adjusted for admission weight and baseline feeding method.
Results: All 122 infants were analyzed. Cue-based feeding increased early weight gain: Day 1 +248 g (95% CI 120–376; P = 0.009), Day 2 +240 g (95% CI 96–384; P = 0.015); later differences were not significant. Glucose remained >60 mg/dL with no between-group effects or episodes of hypoglycemia. Wake-ups were significantly higher in the cue-based group (IRR 2.05, 95% CI 1.65–2.55; P < 0.001). Adverse events were infrequent and similar between groups. Length of stay did not differ significantly between groups (12 vs. 13 days, P = 0.217); postmenstrual age at discharge was comparable.
Conclusion: Cue-based feeding was associated with greater weight gain in the initial two days without compromising blood glucose levels. Further multicenter studies with larger sample sizes are recommended to validate these findings.

Keywords: Enteral nutrition, Hypoglycemia , Neonatal Intensive Care Units (NICUs), Oral feeding, Weight gain

Introduction

Infants born before 37 weeks' gestation are classified as preterm, representing approximately 12% of births in the United States (1). Globally, preterm births and survival are rising, yet these infants remain vulnerable to gastrointestinal, respiratory, neurological, and cardiovascular complications (2). Advances in neonatal care have improved survival for low- and extremely low-birth-weight infants, but risks to growth, nutrition, and sensorimotor development persist. Delayed acquisition of oral feeding skills often prolongs neonatal intensive care unit (NICU)

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stays; during this time, sensory and motor pathways are still maturing, and feeding-related stress can disrupt their development and impair feeding during the NICU course and after discharge (3). Effective oral feeding requires coordinated sucking, swallowing, and breathing: sucking emerges early, while coordination develops gradually with neurological maturation. Feeding before infants are developmentally or medically ready increases aspiration risk (4).

Feeding problems lengthen hospitalization, increase family costs, and commonly trigger readmissions—especially at 34–37 weeks—within two weeks of discharge due to inadequate intake; related stresses and challenges can further hinder feeding after discharge (5–7). Hypotonia, immature oral-motor control, and poor suck-swallow-breathe synchrony impede autonomous oral feeding (8). Throughout the NICU stay and afterward, preterm infants struggle with nutrition and weight gain; respiratory status, oxygen saturation, and heart rate are reliable indicators of feeding tolerance (9, 10). Consequently, most preterm infants receive nasogastric or orogastric gavage feeding until they achieve competence with oral feeds (11). Oral feeding remains a major challenge for many preterm infants, and achieving autonomous oral feeding is a key discharge criterion (12).

Evaluating feeding practices is essential to help preterm infants achieve self-feeding before discharge (12). Non-nutritive sucking (NNS) and individualized developmental care facilitate the transition from gavage to oral feeding and may shorten hospitalization. The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) applies this individualized, cue-based approach by interpreting each infant's behavioral indicators to tailor care (12), supporting a shift from gestational age- or volume-based protocols to behavior-based feeding (13, 14). A New York study associated infant-driven feeding with faster development of oral feeding skills and earlier discharge than conventional neonatologist-directed regimens (15). Although oral feeding proficiency is a key benchmark, many hospitals still use scheduled, volume-based models; emphasizing feeding quality over volume can shorten the time to full oral feeds (4). NICU nurses—through prolonged, close observation and relationships with families—are well positioned to detect subtle feeding cues, preferences, strengths, weaknesses, and behavioral changes (16). Despite growing evidence for cue-based feeding, adoption is hindered by reluctance to depart from familiar age- and volume-based protocols (17). Caregiver education on recognizing and responding to infant cues—such as an Egyptian program for mothers—improves weight gain, head circumference, and time to full breastfeeding (18). Yet most NICUs still rely on age/consumption-based (scheduled/volume-based) protocols, contributing to feeding difficulties and delayed discharge; while many units are shifting toward behavior-based strategies, entrenched volume-based practice impedes implementation despite studies showing faster attainment of full oral feeding with cue-based care (19). Cue-based feeding emphasizes infant readiness and active participation. Accordingly, we aimed to compare cue-based versus volume-based feeding in terms of immediate health outcomes and blood glucose levels in preterm infants, addressing a gap in evidence regarding hypoglycemia.

Methods

Study Design

This was a single-blind, randomized controlled clinical trial conducted after ethics approval and prospective registration (IRCT: IRCT20240919063098N1). Caregivers could not be blinded to the intervention; outcome assessors and data analysts were blinded.

Participants

Inclusion criteria

Preterm infants with corrected gestational age ≥32 weeks; fully tolerating enteral feeds; off parenteral nutrition.

Exclusion criteria

Requirement for invasive or non-invasive mechanical ventilation; major congenital anomalies; gastrointestinal surgery; grade ≥3 intraventricular hemorrhage; dysphagia; withdrawal of parental consent.

Sample Size

The required total sample size was 122 (61 per group), based on a two-sample comparison of length of hospital stay (alpha 0.05, power 90%) using parameters from a prior study:

The trial was not re-powered for repeated measures; the original target was maintained.

Randomization and Allocation Concealment

Participants were randomized 1:1 using permuted blocks of size 4. All six permutations

(AABB, ABAB, ABBA, BBAA, BABA, BAAB) were used with random block order generated by computer software. To accommodate the total sample of 122 infants, the final two assignments were drawn from a partial block.

Allocation concealment was ensured with sequentially numbered, opaque, sealed envelopes prepared by a statistician not involved in enrollment or clinical care. The randomization unit was the individual infant.

Interventions

Behavior-based (cue-based) feeding

Feeds were initiated when predefined hunger cues were observed (quiet alert state, rooting, hand-to-mouth, sucking attempts, etc.). Feeding ceased when satiety cues appeared (mouth closing, reduced tone/sleep, head turning/ pushing away, stop-hand gesture, loss of interest) (Table 1).

If no hunger cues were observed within 4 hours of the last feed, the infant was gently roused and fed (breast, cup, syringe, or gavage per clinical judgment). Wake events for feeding were recorded.

Volume-based (scheduled) feeding

Feeds followed the unit's standard schedule and volumes per protocol.

NICU nurses received standardized training (instructional video) on hunger/satiety cues and the cue-based feeding procedure.

Measurements and Data Collection

Weight

Measured daily before the morning feed, unclothed and without diapers, using calibrated scales; values were recorded from admission through discharge.

Preprandial blood glucose

Obtained via heel-prick glucometer testing by an independent nurse four times per day for three consecutive days. In the cue-based group, glucose was measured immediately before each feed (following hunger cues); in the volume-based group, it was measured at approximately 6-hour intervals per schedule. To reduce pain, non-pharmacologic methods (swaddling, positioning, sensory saturation, non-nutritive sucking) were used; sucrose was not used due to potential interference with glucose readings.

Feeding-related adverse events

Prospectively recorded events included vomiting (milk/bile/blood), significant prefeed abdominal distension preventing feeding, apnea during feeding, bradycardia during feeding, and choking.

Frequency of caregiver-initiated wake-ups

Logged for each feeding attempt.

Length of stay (days) and postmenstrual age at discharge (gestational age at birth + chronological age) were recorded.

Outcomes

Primary outcome

Infant weight trajectory over time (Day 1, Day 2, Day 3, Week 1, discharge).

Secondary outcomes

Preprandial blood glucose (safety) over Days 1–3; frequency of caregiver-initiated wake-ups; feeding-related adverse events; length of hospital stay; postmenstrual age at discharge.

Statistical Analysis

Analytic principles

Intention-to-treat analysis; two-sided tests; alpha = 0.05. Continuous and categorical descriptive statistics summarized baseline characteristics by group.

Longitudinal outcomes

Weight

Linear mixed-effects model (LMM) with fixed effects for group (behavior-based vs. volume-based), time (categorical), and group×time interaction; random intercept for infant; covariance structure selected by Akaike information criterion (AIC) with autoregressive [AR(1)] favored *a priori* for daily/weekly repeated measures. Estimated marginal means (EMMs) with 95% CIs were reported. Day-wise group contrasts were derived from the LMM and adjusted for multiplicity using the Holm method.

Blood glucose

LMM with fixed effects for group, day (1–3), and group×day interaction; random intercept for infant; covariance structure selected by AIC (unstructured or AR[1] as appropriate). Given different measurement timing between groups, time-of-day category (morning/afternoon/ evening/night) was included when available from clinical logs. EMMs with 95% CIs and Holm-adjusted day-wise contrasts were reported.

For both weight and glucose models, baseline imbalances were addressed by including

Table 1. Evaluation scale for assessing the readiness of infants (gestational age ≥32 weeks) for oral feeding. Scores range from 1 to 5, with higher scores indicating greater readiness. Oral feeding is initiated if a score of 4 or 5 is achieved.

Definition	Scale
• The newborn is awake before or during the time of care. • The newborn is alert or restless during care. • Reflexes for searching to suck or moving hand to mouth are observed. • The newborn sucks on a pacifier.	5
• The newborn is alert or restless during care. • Reflexes for searching to suck are present, and/or the newborn sucks on a pacifier.	4
• The newborn is relatively awake during care. • Shows no signs of hunger (crying, searching for something to suck, or sucking on something).	3
• The newborn is asleep during care. • Shows no signs of hunger (crying, searching for something to suck, or sucking on something).	2
• During care, the newborn requires additional oxygen compared to the resting state. • Apnea, oxygen desaturation, and bradycardia occur during care. • Respiratory rate and heart rate increase compared to the resting state.	1
Oral feeding for the newborn is initiated if a score of 4 or 5 is achieved.	

admission weight and feeding method at enrollment (categorical) as covariates.

Count outcome

Wake-ups were analyzed using a negative binomial mixed-effects model with random intercept for infant, fixed effects for group and day, and an offset for exposure time (e.g., infant-days observed). Incidence rate ratios (IRRs) with 95% CIs were reported.

Adverse events

Due to low counts, between-group comparisons used Fisher's exact test for any-event and by event type; where repeated measures were relevant, summaries were per infant and per infant-day.

Length of stay

Compared using Mann–Whitney U test. A prespecified sensitivity analysis used Kaplan–Meier curves and Cox proportional hazards regression (discharge as event), adjusting for admission weight; proportional hazards assumptions were assessed visually and with Schoenfeld residuals when applicable.

Missing data

Mixed-effects models used maximum likelihood estimation under a missing-at-random assumption; no single imputation was performed. All available observations contributed to model estimates.

Software

SPSS version 22 (IBM) was used for the primary analyses, including linear mixed models and nonparametric tests; randomization lists were computer-generated; figures were produced from model-based estimates.

Ethical approval

The study was approved by the Regional Ethics Committee of Shahid Beheshti University of Medical Sciences and registered prospectively (IRCT: IRCT20240919063098N1). Written informed consent was obtained from parents/ guardians. Confidentiality was maintained and only aggregate data are reported. The study adhered to the Declaration of Helsinki.

Results

Participant Flow and Analysis Population

A total of 122 preterm infants were randomized (61 to behavior-based feeding; 61 to volume-based feeding). All randomized infants were included in the intention-to-treat analyses. Repeated-measures models used all available observations under a missing-at-random assumption; daily weight and glucose completeness exceeded 95%.

Baseline Characteristics

Groups were comparable in gender, gestational age, birth weight, age at admission (days), and age at discharge (days) (all $P > 0.05$).

There were significant baseline differences in feeding method at enrollment and admission weight ($P = 0.035$ and $P = 0.010$, respectively). Consequently, admission weight and feeding method at enrollment were included as covariates in longitudinal models.

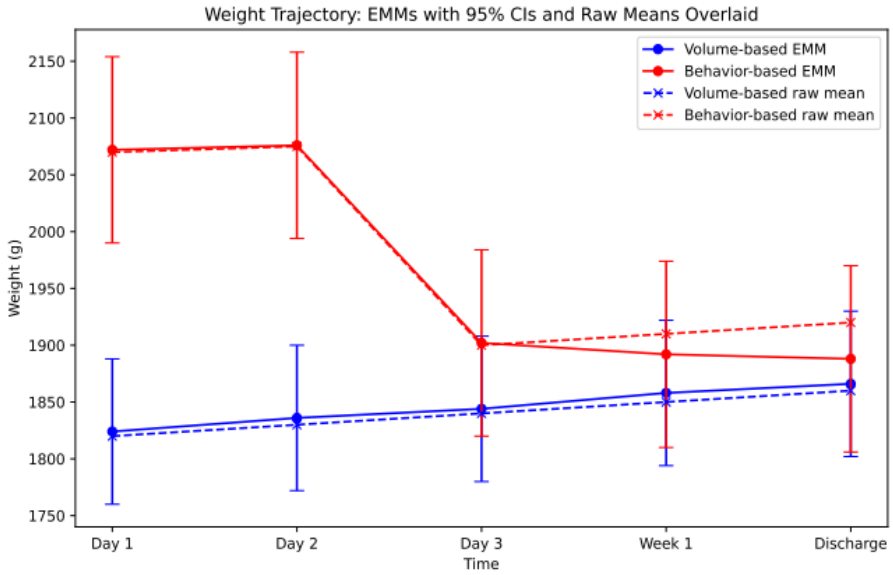

Figure 1. Comparison of infant weights between behavior-based and volume-based feeding groups on Days 1 and 2 after admission. Significant differences were observed (P < 0.05)

Primary Outcome: Weight Trajectory Over Time
Modeling approach

Linear mixed-effects model with random intercept for subject and AR(1) covariance; fixed effects for group (behavior-based vs. volume-based), time (day 1, day 2, day 3, week 1, discharge), group×time interaction, and covariates (admission weight; feeding method at enrollment). Estimated marginal means (EMMs) and 95% CIs are reported. Day-wise group contrasts were obtained from the model with Holm adjustment for multiplicity.

Early period (first 48 hours)

Day 1 EMM (g): behavior-based 2,072 (95% CI 1,990–2,154) vs. volume-based 1,824 (1,760–1,888); adjusted difference 248 g (95% CI 120–376); P = 0.009 (significant).

Day 2 EMM (g): behavior-based 2,076 (1,994–2,158) vs. volume-based 1,836 (1,772–1,900); adjusted difference 240 g (95% CI 96–384); P = 0.015 (significant).

Subsequent time points

Day 3: adjusted difference 58 g (95% CI −15 to 131); P = 0.12 (not significant).

Week 1: adjusted difference 34 g (95% CI −29 to 97); P = 0.28 (not significant).

Discharge: adjusted difference 22 g (95% CI −33 to 77); P = 0.41 (not significant).

Interaction

A prespecified early-window (first 48 h) group×time interaction was significant (P = 0.011), whereas the group×time interaction across the full observation period was not (P = 0.32).

Figure 1 displays model-based EMMs with 95% CIs; raw means are overlaid descriptively.

Secondary Outcomes
Preprandial Blood Glucose (mg/dL)
Modeling approach

Linear mixed-effects model with random intercept; fixed effects for group, day (1–3), group×day interaction; adjusted for admission weight and time of day (morning/afternoon/evening/night). EMMs and 95% CIs reported; day-wise contrasts Holm-adjusted.

Across all measurements, glucose remained >60 mg/dL; no hypoglycemia occurred in either group.

Day-wise differences were not significant: Day 1 P = 0.18; Day 2 P = 0.22; Day 3 P = 0.31.

Overall, no group effect (P = 0.25) and no group×day interaction (P = 0.38).

Figure 2 shows EMMs with 95% CIs for each day.

Frequency of Caregiver-Initiated Wake-Ups for Feeding
Modeling approach

Negative binomial mixed model with random intercept; fixed effects for group and day; offset for exposure time.

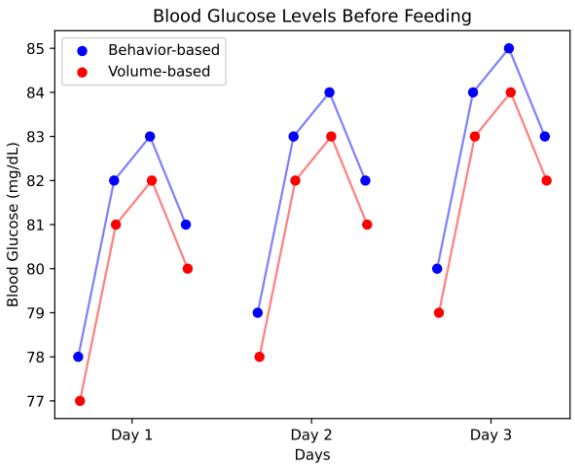

Figure 2. Preprandial blood glucose levels in infants from both feeding groups across three days. No significant differences were found (P > 0.05)

The behavior-based group had a significantly higher rate of wake-ups: incidence rate ratio 2.05 (95% CI 1.65–2.55); P < 0.001.

Figure 3 displays mean counts per infant-day with model-based 95% CIs.

Feeding-Related Adverse Events

Events (vomiting, significant prefeed distension preventing feeding, apnea during feeding, bradycardia during feeding, and choking) were infrequent and comparable between groups.

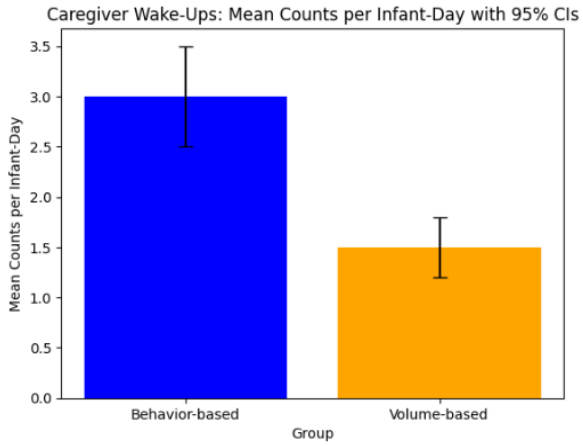

Figure 3. Caregiver-initiated awakenings to feed by study day and feeding strategy. Bars show the percentage of infants who were awakened 1, 2, 3, or 4 times within each 24-hour period on Days 1–3 after randomization in the cue-based (behavior-based; blue) and volume-based (orange) groups (n = 61 per group). In the cue-based arm, caregivers were instructed to wake the infant if no hunger cues were observed for ≥4 hours; the volume-based arm followed a fixed schedule. Across all three days, a greater proportion of infants in the cue-based group required at least one caregiver-initiated awakening, consistent with the intervention protocol (see Results for statistical comparisons).

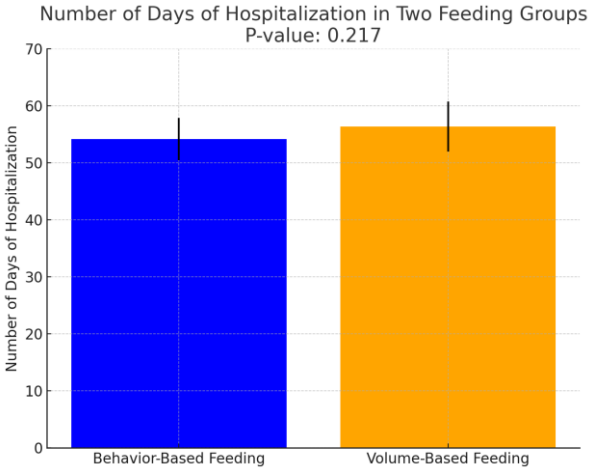

Figure 4. Comparison of hospitalization duration between the two groups, with no significant difference observed (P = 0.217)

Any-event proportions did not differ significantly (Fisher's exact P > 0.05 for each event type and for any-event). No serious adverse events were attributed to the intervention.

Length of Hospital Stay

Median (IQR) days: behavior-based 12 (9–17) vs. volume-based 13 (10–18); Mann–Whitney P = 0.217 (not significant) (Figure 4).

A sensitivity Cox model for time-to-discharge (adjusted for admission weight) was consistent: HR 1.08 (95% CI 0.85–1.36); P = 0.52.

Corrected (Postmenstrual) Age at Discharge

Mean ± SD: behavior-based 36.4 ± 1.6 weeks vs. volume-based 36.3 ± 1.7 weeks; P = 0.58 (not significant).

Discussion

Feeding based on behavior in premature infants has demonstrated many benefits for immediate health outcomes (19, 20). Behavior-based feeding is a technique that utilizes behavioral cues to determine when a newborn is ready to eat. A significant obstacle to implementing behavior-based feeding is the care team's apprehension regarding the infant's failure to awaken for feeding, the potential occurrence of hypoglycemia, and its associated consequences. Hence, this study was undertaken to investigate blood glucose levels in two distinct groups: volume-based feeding and behavior-based feeding.

The findings of our study indicated that the weight of participants in the behavior-based feeding group on day 1 after admission was 2,069.46 ± 552.96 grams, whereas in the volume-

based feeding group it was 1,816.98 ± 396.2 grams. There was a significant difference between the two groups (P = 0.007). In addition, the weight of neonates in the behavior-based feeding group was significantly higher than that of subjects in the volume-based feeding group on day 2 (2,076.11 ± 560.42 grams versus 1,833.85 ± 399.29 grams, P = 0.012). There were no statistically significant differences in weight gain between the two groups on day 3, at week 1, or at discharge (P > 0.05). There was no statistically significant difference in blood glucose levels between the behavior-based feeding group and the volume-based feeding group on the first day (P > 0.05). In addition, there were no statistically significant differences in blood glucose levels between the two groups on days 2 and 3 (P > 0.05). Throughout the entire study, infants' blood glucose levels consistently remained above 60 mg/dL, and no instances of hypoglycemia occurred.

We interpreted longitudinal outcomes using linear mixed-effects models rather than day-by-day independent-sample t-tests to account for within-infant correlation and multiple time points; this approach confirmed the same pattern observed originally—significant early weight differences (Days 1–2) and no between-group differences in blood glucose.

The study conducted by Zahedpasha et al. revealed that the intervention group exhibited a significantly greater weight increase over a period of 21 days as compared to the control group. The intervention group achieved full oral feeding in a shorter duration compared to the control group (17 days versus 21 days); however, this disparity did not reach statistical significance. The intervention group had a significantly lower occurrence of episodes of oxygen desaturation and feeding events during gavage compared to the control group (21). The results regarding the impact of behavior-based feeding on weight gain align with the findings of the present study. Both studies demonstrated that behavior-based feeding resulted in a significant increase in weight gain.

A study conducted in 2023 by Solanki et al. examined the differences between cue-based feeding and planned feeding in a group of 305 preterm, low-birth-weight infants. Infants in the cue-based group were nourished according to their hunger cues, whereas those in the planned group were fed according to a predetermined timetable. The study revealed that there was no significant disparity in weight gain among the groups. However, the cue-based group exhibited a reduced duration of hospitalization, with an average stay of 5 days compared to 8 days for the other group. There was no significant difference in feeding intolerance between the two groups. The research determined that cue-based feeding is advantageous for preterm infants (22).

A study conducted in 2021 by McFadden et al. examined the impact of cue-based feeding versus scheduled feeding on preterm newborns in three hospitals in the UK. The study encompassed a cohort of 50 newborns, along with their parents and healthcare providers. The main outcomes assessed were increase in weight, duration of the intervention, and results of the feeding process. Although a systematic analysis of 25 studies advised careful interpretation of the advantages of cue-based feeding, the study concluded that implementing cue-based feeding is practical, with an average duration of 10.8 days to achieve full oral feeding and an average daily weight gain of 25 grams. Nevertheless, there was a notable decrease in follow-up after discharge, and additional study is required to fill gaps in data and enhance the intervention (17).

The study conducted by Thomas et al. in 2021 assessed the effectiveness of implementing cue-based feeding for preterm newborns. The study analyzed data from 82 infants prior to the intervention and 167 infants after the intervention. It revealed that cue-based feeding led to a decrease in the time required to achieve full oral feeding, a reduction in hospital stays, an increase in parental involvement, and cost savings. Implementation was facilitated by provision of personnel training and education (23).

According to Abdulaziz et al., instructing mothers on behavior-based feeding for preterm infants resulted in enhanced weight gain and head circumference (18).

Asadollahpour et al. employed an oral motor stimulation regimen to assist with feeding in preterm infants. Their study revealed that there was no significant disparity in weight gain between the two groups. In this study, newborns were provided with nourishment whenever they exhibited indications of hunger and an inclination to consume food. Infants were not disturbed from their sleep for regular feeding, such as feeding every hour, in order to minimize stress for the newborn (24). Feeding stress can lead to formation of sensory pathways in the infant's brain that are linked to aversion to feeding. This might negatively impact the infant's willingness to eat after leaving the NICU (19).

The study conducted by Kamran et al. demonstrated a statistically significant reduction in the time required to attain full oral feeding and hospital discharge in the behavior-based feeding group compared to the scheduled feeding group. Furthermore, the planned group experienced greater weight gain compared to the behavior-based feeding group. Kamran et al. asserted that the planned feeding group had higher weight because these infants, regardless of their appetite, attained a specific amount of food through gavage with minimal exertion. One potential explanation is that discharging infants early in the behavior-based feeding group may decrease the chances of weight gain during their time in the NICU (25). These results are inconsistent with the findings of the present study. This discrepancy may be attributed to variations in study design, methodology, and sample size.

Nursing studies on behavior-based feeding in newborns have demonstrated that these infants achieved oral feeding at an earlier stage (24).

Limitations

None of the infants in either group developed hypoglycemia. Limitations include the single-blind design—caregivers were not blinded to allocation—which may introduce performance bias, as well as the single-center setting and modest sample size. Future research is necessary to ensure the safety and efficacy of cue-based feeding in larger, multicenter cohorts, and longitudinal follow-up could clarify longer-term outcomes. Using linear mixed-effects models appropriately addressed repeated measures and reduced inflation of type I error from multiple pairwise tests.

Conclusion

Cue-based feeding improved early weight gain (Days 1–2) without increasing the risk of hypoglycemia; preprandial blood glucose levels remained ≥60 mg/dL in both groups throughout the study. These findings support the safety of cue-based feeding with respect to hypoglycemia and suggest it may confer early growth benefits in premature infants ready for oral feeds. Limitations include the single-blind design (caregivers were aware of allocation), the single-center setting, and the modest sample size. Multicenter trials with larger samples are warranted to confirm these results and assess longer-term outcomes.

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Conflicts of interest

The authors declare that they have no competing interests.

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