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Impact of Oropharyngeal Colostrum Therapy on Early Nutritional Maturation, Enteral Transition, and NICU Recovery Outcomes in Very Preterm Infants: A Randomized Controlled Trial

Niayesh Tahmasebi Nezhad
Dezful University of Medical Sciences
Ali Khosravi
Dezful University of Medical Sciences
Sara Kord
bahare.kord132@gmail.com
Dezful University of Medical Sciences
Azam Jahangirimehr

Short Report

Keywords: Colostrum, Premature infant, Enteral nutrition, Growth, Necrotizing enterocolitis

Posted Date: August 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10495241/v1

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Additional Declarations: No competing interests reported.

Abstract

Objective:

Very preterm infants often experience delayed nutritional maturation and prolonged dependence on parenteral nutrition, increasing the risk of sepsis, necrotizing enterocolitis (NEC), and impaired early growth. Oropharyngeal administration of maternal colostrum (OAC) has been proposed as an early immunopurified strategy to support gastrointestinal adaptation. This randomized controlled trial evaluated whether a standardized 8-day OAC protocol could accelerate enteral feeding progression, enhance early growth efficiency, and improve short-term NICU recovery outcomes in very preterm infants.

Results:

A total of 91 infants were randomized (45 OAC; 46 control). Infants receiving OAC initiated enteral feeding earlier (median 6 vs. 12 days) and achieved full enteral feeding sooner (median 18 vs. 25.5 days). Growth velocity was significantly higher in the OAC group (9.51 vs. 5.12 g/kg/day). OAC was associated with markedly lower rates of culture-proven sepsis (31.7% vs. 78.9%) and NEC (7.3% vs. 31.6%), although these secondary outcomes were exploratory and not adjusted for multiple comparisons. Duration of antibiotic therapy was shorter in the OAC group (median 10 vs. 18 days). No intervention-related adverse events occurred. Overall, OAC may support earlier nutritional maturation and short-term recovery in very preterm infants, warranting confirmation in larger multicenter trials.

Trial registration

IRCT20240501061616N1. Registered prospectively on 20240730

Introduction

Preterm birth, particularly at gestational ages below 33 weeks, remains a major contributor to neonatal morbidity and mortality worldwide(1, 2). Very preterm infants experience substantial gastrointestinal and physiological immaturity, predisposing them to complications such as necrotizing enterocolitis (NEC), late-onset sepsis (LOS), feeding intolerance, bronchopulmonary dysplasia, and postnatal growth failure (3–7). Despite advances in neonatal intensive care, achieving early nutritional maturation and safely progressing toward full enteral feeding continues to be a clinical challenge. Delayed initiation of enteral feeding, slow advancement of feeding volumes, and frequent episodes of feeding intolerance often prolong dependence on parenteral nutrition(8). Extended parenteral nutrition increases infection risk, metabolic complications, and length of hospitalization, while early nutritional instability is strongly associated with impaired growth and adverse long-term neurodevelopmental outcomes (6, 9). These challenges highlight the need for strategies that support safe and timely enteral feeding progression.

Colostrum, the earliest postpartum milk, contains high concentrations of immunomodulatory and growth-promoting bioactive components, including secretory immunoglobulin A, lactoferrin, oligosaccharides, antimicrobial peptides, anti-inflammatory cytokines, leukocytes, and growth factor-β (TGF-β) (5, 11, 12) Colostrum produced by mothers of preterm infants contains even higher levels of protective immunological factors, reflecting a biological adaptation to the heightened vulnerability of premature neonates (13, 14) However, early enteral exposure to colostrum is often limited due to respiratory instability or gastrointestinal immaturity, and gavage feeding bypasses the oropharyngeal mucosa, reducing stimulation of oropharyngeal-associated lymphoid tissue (OFALT), an important component of neonatal mucosal immunity (14–16).

Oropharyngeal administration of colostrum (OAC) has emerged as a feasible strategy to restore early mucosal exposure by applying small volumes of maternal colostrum directly to the buccal mucosa. This approach allows bioactive molecules to interact with OFALT and may support gastrointestinal adaptation and safer advancement of enteral feeding(12, 13, 15–20). Previous randomized trials and meta-analyses have reported improvements in feeding tolerance and reductions in LOS and NEC; however, findings related to nutritional maturation, growth velocity, and early enteral transition remain inconsistent across studies, partly due to variability in feeding protocols and NICU practices(4, 14, 21–23) Most prior studies have

focused primarily on infectious or gastrointestinal outcomes, leaving the specific effects of OAC on early nutritional maturation insufficiently characterized.

Given the clinical importance of early nutritional stability, this randomized controlled trial evaluated whether a standardized 8-day OAC protocol could accelerate enteral feeding progression, enhance early growth efficiency, and improve short-term NICU recovery outcomes in very preterm infants.

Methods

Study Design and Setting

This prospective, single-center, parallel-group randomized controlled trial was conducted in the Level III NICU of Al-Hadi Educational and Medical Center, Shushtar, Iran, between January 2025 and March 2026. The NICU provides advanced respiratory support, parenteral nutrition, and comprehensive care for very preterm infants. The protocol adhered to CONSORT guidelines and was prospectively registered in the Iranian Registry of Clinical Trials (IRCT20240501061616N1). All procedures followed the preregistered protocol.

Participants

Infants were eligible if born at < 33 weeks' gestation, weighed < 1800 g, and were admitted within 24 hours of birth. Exclusion criteria included major congenital or gastrointestinal anomalies, chromosomal abnormalities, TORCH infections, maternal contraindications to breastfeeding, and early neonatal death or transfer before completion of the intervention period. Parents provided written informed consent. Of 104 screened infants, 91 met eligibility criteria and were randomized. The Fig. 1 shows CONSORT flow diagram showing enrollment, allocation, follow-up.

Randomization, Allocation, and Participant Flow

Infants were randomized 1:1 to the intervention (n = 45) or control group (n = 46) using a computer-generated sequence prepared by an independent researcher. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. Outcome assessors and statisticians were blinded. Caregivers could not be blinded due to the nature of the intervention; no sham stimulation was used.

Intervention protocol

Maternal colostrum was expressed within 6–8 hours after birth using aseptic technique and stored in sterile syringes. Oropharyngeal colostrum administration was initiated within the first 72 hours of life. At each session, 0.2 mL of colostrum was applied to the buccal mucosa (0.1 mL per side) and gently spread for at least 2 minutes. The procedure was repeated every 6 hours for 8 consecutive days (32 doses total). Heart rate, respiratory rate, and oxygen saturation were continuously monitored. The intervention was paused if apnea, bradycardia (< 90 bpm), tachycardia (> 180 bpm), or desaturation (< 88%) occurred. Control infants received routine NICU care without colostrum or sham stimulation.

Routine care and nutritional protocol

All infants were managed according to standardized NICU protocols. Enteral feeding was initiated based on clinical stability, with maternal breast milk prioritized. Feeding volumes were advanced by 15–20 mL/kg/day as tolerated. Premature Infant Oral Motor Intervention (PIOMI) was implemented once infants reached readiness for oral feeding. Full enteral feeding (FEF) was defined as tolerance of 150 mL/kg/day.

Outcome Measures

Primary Outcome Time to full enteral feeding (days) was prespecified as the single primary outcome to avoid multiplicity and ensure adequate statistical power.

Secondary Outcomes Secondary outcomes included:

Day of enteral feeding initiation

Feeding intolerance (gastric residuals > 50%, vomiting, abdominal distension requiring feed reduction, or ≥ 24-hour delay in feed advancement)

PIOMI requirement

Growth velocity (g/kg/day) and discharge weight

Duration of antibiotic therapy

Blood transfusion requirement

Rehospitalization within 60 days

Culture-proven sepsis

NEC

In-hospital mortality

Safety monitoring included predefined events: apnea, bradycardia, tachycardia, desaturation, and mucosal injury.

Data collection procedures

Data were collected prospectively using a predefined case-report form. Baseline demographic and perinatal characteristics were recorded at enrollment. Nutritional, growth, recovery, and morbidity data were extracted from medical records by trained staff blinded to group allocation. Data were checked for completeness and internal consistency.

Sample Size

Sample size was calculated to detect a 5-day reduction in time to full enteral feeding, assuming SD = 7 days, $\alpha = 0.05$, and power = 80%. A minimum of 40 infants per group was required. To account for attrition, the target sample size was increased to 45 per group. Ultimately, 91 infants were randomized. Secondary outcomes were exploratory because the trial was powered only for the primary endpoint.

Statistical Analysis

Analyses followed an intention-to-treat (ITT) approach for mortality. Infants who died before achieving feeding milestones were excluded from feeding and growth analyses because these outcomes were not measurable; this constituted a per-protocol analysis. Continuous variables were expressed as median (Q1–Q3) and compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Effect sizes were reported as median differences or odds ratios with 95% confidence intervals.

Multivariate logistic regression with forward stepwise selection was used to identify predictors of mortality, sepsis, and NEC. Candidate variables included study group, gestational age, birth weight, Apgar scores, sex, and delivery mode. Model

performance was assessed using Nagelkerke R^2 and classification accuracy. No correction for multiple comparisons was applied due to the exploratory nature of secondary outcomes.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of Shoushtar University of Medical Sciences (IR.SHOUSHTAR.REC.1403.008). The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki. Parents or legal guardians of all participating infants were fully informed about the study objectives, intervention protocol, potential risks, and their right to withdraw at any time without affecting the quality of routine care. Written informed consent was obtained prior to enrollment. Participant confidentiality was ensured by anonymizing personal data and using unique coded identifiers for data storage and analysis.

Results

Participant Flow

During the study period, 104 very preterm infants were assessed for eligibility. Thirteen infants were excluded (nine did not meet inclusion criteria and four declined participation). A total of 91 infants were randomized (45 to the OAC group and 46 to the control group). All infants in the intervention group completed the 8-day protocol. In the control group, eight infants died before achieving enteral feeding milestones; these infants were included in the ITT mortality analysis but excluded from feeding and growth analyses because these outcomes were not measurable. Thus, 41 infants in the intervention group and 38 infants in the control group were included in per-protocol analyses. No infants were withdrawn or lost to follow-up.

Baseline Characteristics

Maternal, perinatal, and neonatal baseline characteristics were comparable between groups, indicating successful randomization. No significant differences were observed in gestational age, birth weight, Apgar scores, sex distribution, delivery mode, antenatal corticosteroid exposure, or umbilical catheterization (all $p > 0.05$). These findings confirm that groups were similar at baseline and that observed differences in outcomes are unlikely to be attributable to confounding. Baseline characteristics are summarized in Tables 1 and 2.

Table 1
Maternal Baseline Characteristics

Variable	Intervention (n = 45)	Control (n = 46)	p-value
Maternal age (years)	29.8 ± 5.2	30.1 ± 5.5	0.72
Antenatal corticosteroid (complete course)	57%	52%	0.64
Antenatal antibiotics	24%	28%	0.81
PROM > 18 hrs	21%	25%	0.67
Cesarean delivery	83%	79%	0.59
NOTE: PROM = premature rupture of membranes.			

Table 2
Neonatal Baseline Demographic and Clinical Characteristics

Characteristic	Total (N = 91)	intervention (N = 45)	Control (N = 46)	OR (95% CI)	Test statistic	P-value
Gestational age (weeks)	28.60 (27.50–30.00)	28.60 (27.50–30.00)	29.00 (28.00–30.00)	—	U = 956.0	0.522
Birth weight (grams)	1150.0 (1000.0–1350.0)	1100.0 (940.0–1250.0)	1275.0 (1037.5–1385.0)	—	U = 826.0	0.097
Apgar 1 min	7.00 (6.00–8.00)	7.00 (6.00–8.00)	7.00 (6.00–8.00)	—	U = 1016.0	0.876
Apgar 5 min	8.00 (7.00–8.00)	8.00 (7.00–8.00)	8.00 (8.00–9.00)	—	U = 841.0	0.106
Gender, n (%)					χ^2 = 0.093	0.760
Girl	41 (45.1%)	21 (46.7%)	20 (43.5%)	1.14 (0.50–2.60)		
Boy	50 (54.9%)	24 (53.3%)	26 (56.5%)	Reference		
Delivery mode, n (%)					χ^2 = 2.462	0.117
NVD	43 (47.3%)	25 (55.6%)	18 (39.1%)	1.94 (0.84–4.47)		
Cesarean section	48 (52.7%)	20 (44.4%)	28 (60.9%)	Reference		
Umbilical catheter, n (%)					χ^2 = 2.098	0.148
Yes	83 (91.2%)	43 (95.6%)	40 (87.0%)	3.23 (0.62–16.82)		
No	8 (8.8%)	2 (4.4%)	6 (13.0%)	Reference		
BLES received (score 0–3)	2.00 (1.00–2.00)	2.00 (1.00–2.00)	2.00 (1.00–2.00)	—	U = 973.0	0.589
Caffeine use, n (%)					χ^2 = 0.105	0.746
Yes	47 (52.8%)	23 (51.1%)	24 (54.5%)	0.87 (0.38–2.02)		
No	42 (47.2%)	22 (48.9%)	20 (45.5%)	Reference		
Aminophylline use, n (%)					χ^2 = 0.105	0.746
Yes	42 (47.2%)	22 (48.9%)	20 (45.5%)	1.15 (0.50–2.64)		
No	47 (52.8%)	23 (51.1%)	24 (54.5%)	Reference		

Note: Continuous variables presented as median (Q1–Q3). Mann-Whitney U test. Categorical variables presented as n (%) with Chi-square test. P-values < 0.05

Primary Outcomes

Oropharyngeal colostrum therapy was associated with significantly accelerated nutritional maturation.

Earlier initiation of enteral feeding

Infants receiving OAC initiated enteral feeding earlier than controls:

Median 6.0 days (Q1–Q3: 5–7) vs. 12.0 days (7–17)

Median difference: −4.99 days (95% CI: −7.12 to − 2.87)

$p < 0.001$

Shorter time to full enteral feeding

OAC infants achieved full enteral feeding substantially sooner:

Median 18.0 days (15–21) vs. 25.5 days (22–35)

Median difference: −7.93 days (95% CI: −11.18 to − 4.68)

$p < 0.001$

These findings remained consistent across sensitivity analyses. The Table 3 shows Feeding and Growth Outcomes.

Table 3
Feeding and Growth Outcomes

Outcome	Intervention (n = 41)	Control (n = 38)	Effect Size (95% CI)	Test Statistic	p-value
Day of enteral feeding start	6.0 (5–7)	12.0 (7–17)	MD − 4.99 (− 7.12 to − 2.87)	U = 312.0	0.00021
Day of full enteral feeding	18.0 (15–21)	25.5 (22–35)	MD − 7.93 (− 11.18 to − 4.68)	U = 334.0	0.00019
PIOMI sessions (0–6)	2.0 (0–2)	4.0 (3–5)	MD − 2.02 (− 2.66 to − 1.38)	U = 256.0	0.00003
Discharge weight (g)	1500 (1430–1640)	1575 (1450–1650)	MD − 2.78 (− 64.19 to 69.75)	U = 738.0	0.687
Growth velocity (g/kg/day)	9.51 (5.43–11.23)	5.12 (3.69–6.97)	MD + 4.39 (2.17 to 6.61)	U = 341.0	0.00014

Note:

Continuous variables: median (IQR).

Test: Mann–Whitney U.

Effect size: Median Difference (MD) with 95% CI.

Infants who died before achieving feeding milestones were excluded from feeding/growth analyses (ITT applied for mortality only).

Secondary Outcomes

Feeding Progression

OAC infants required fewer PIOMI sessions:

Median 2.0 (0–2) vs. 4.0 (3–5)

Median difference: −2.02 (95% CI: −2.66 to − 1.38)

p < 0.001

Feeding intolerance was less frequent in the OAC group, although the study was not powered for definitive comparison.

Growth Outcomes

Growth velocity was significantly higher in the OAC group:

9.51 g/kg/day (5.43–11.23) vs. 5.12 g/kg/day (3.69–6.97)

Median difference: +4.39 g/kg/day (95% CI: 2.17 to 6.61)

p < 0.001

Discharge weight did not differ significantly between groups (p = 0.687).

NICU Recovery Outcomes

Duration of antibiotic therapy was markedly shorter in the OAC group:

10 days (7–14) vs. 18 days (12–22)

Median difference: −8.0 days (95% CI: −10.9 to − 5.1)

p < 0.001

Blood transfusion and rehospitalization rates showed no significant differences.

Clinical Morbidity

OAC was associated with substantially lower rates of major morbidities:

Culture-proven sepsis:

31.7% vs. 78.9%

OR 8.08 (95% CI: 2.91–22.41)

p < 0.001

NEC:

7.3% vs. 31.6%

OR 5.85 (95% CI: 1.50–22.78)

p = 0.006

Mortality (ITT) Mortality was lower in the OAC group:

0/45 (0%) vs. 8/46 (17.4%)

RR 0.08 (95% CI: 0.00–1.30)

p = 0.004 (Fisher) This outcome was not powered for definitive comparison.

Multivariate Analyses

Multivariate logistic regression identified OAC as an independent predictor of reduced sepsis and NEC after adjusting for gestational age, birth weight, Apgar scores, sex, and delivery mode.

Sepsis Model

OAC group: OR 0.05 (95% CI: 0.012–0.203), $p < 0.001$

Apgar 1 min: OR 0.316 (95% CI: 0.167–0.598), $p < 0.001$

Delivery mode: OR 4.06 (95% CI: 1.04–15.90), $p = 0.044$

Nagelkerke $R^2 = 0.535$; classification accuracy = 77.2%

NEC Model

OAC group: OR 0.004 (95% CI: 0.000–0.118), $p = 0.002$

Gestational age: OR 0.137 (95% CI: 0.049–0.386), $p < 0.001$

Male sex: OR 12.33 (95% CI: 1.56–97.73), $p = 0.017$

Nagelkerke $R^2 = 0.636$; classification accuracy = 84.8%

Mortality Model

Gestational age: OR 0.09 (95% CI: 0.023–0.352), $p = 0.001$

Nagelkerke $R^2 = 0.763$; classification accuracy = 94.5%

Secondary outcomes were exploratory and not adjusted for multiple comparisons.

Secondary outcomes are summarized in Table 4 and Table 5. The Table 6 shows Multivariate logistic regression analysis for mortality, sepsis, and necrotizing enterocolitis. No intervention-related adverse events were observed, and continuous monitoring during OAC sessions revealed no episodes of apnea, bradycardia, tachycardia, desaturation, or mucosal injury attributable to the intervention.

Table 4
Summary Table of Key Clinical Effects

Outcome	Intervention (n = 41)	Control (n = 38)	Effect Size (95% CI)	p-value
Day of enteral feeding start	6.0 (5–7)	12.0 (7–17)	MD − 4.99 (− 7.12 to − 2.87)	0.00021
Day of full enteral feeding	18.0 (15–21)	25.5 (22–35)	MD − 7.93 (− 11.18 to − 4.68)	0.00019
Growth velocity (g/kg/day)	9.51 (5.43–11.23)	5.12 (3.69–6.97)	MD + 4.39 (2.17 to 6.61)	0.00014
Sepsis (culture-proven)	**13/41 (31.7%)**	**30/38 (78.9%)**	OR 8.08 (2.91–22.41)	0.00004
NEC	**3/41 (7.3%)**	**12/38 (31.6%)**	OR 5.85 (1.50–22.78)	0.0061

NOTE: Binary outcomes: n/N (%).

Test: Chi-square.

Effect size: Odds Ratio (OR) with 95% CI.

Denominator includes all surviving infants; mortality included only in mortality analysis.

Table 5
Secondary Outcomes- In-hospital outcomes

Outcome	Intervention (n = 41)	Control (n = 38)	Effect Size (95% CI)	p-value
Antibiotic duration (days)	10 (7–14)	18 (12–22)	MD − 8.0 (− 10.9 to − 5.1)	0.00011
Blood transfusion	6/41 (14.6%)	7/38 (18.4%)	OR 1.32 (0.41–4.21)	0.62
Rehospitalization (60 days)	4/41 (9.7%)	5/38 (13.1%)	OR 1.40 (0.36–5.40)	0.64
Mortality (ITT)	0/45 (0%)	8/46 (17.4%)	RR 0.08 (0.00–1.30)	0.004 (Fisher)

Note:

Continuous variables: median (IQR), Mann–Whitney U.

Binary variables: n/N (%), Chi-square or Fisher's exact test.

Effect sizes: MD or OR/RR with 95% CI.

Mortality analyzed using ITT (all randomized infants included).

Table 6
– Multivariate logistic regression analysis for mortality, sepsis, and necrotizing enterocolitis

Outcome	Variable	B (β)	S.E.	Wald	P-value	Exp(B)	95% CI for Exp(B)	Nagelkerke R^2	Correct classification %
Mortality (Expire)	Gestational age (per week)	–2.406	0.695	12.002	**0.001**	0.090	0.023–0.352	**0.763**	**94.5%**
	Apgar 5 (per score)	0.695	0.377	3.405	0.065	2.004	0.956–4.200		
	Constant	57.556	16.611	12.006	0.001	—	—		
Sepsis	Group (intervention vs. control)	–2.986	0.718	17.282	**< 0.001**	0.050	0.012–0.203	**0.535**	**77.2%**
	Apgar 1 (per score)	–1.152	0.324	12.615	**< 0.001**	0.316	0.167–0.598		
	Delivery (NVD vs. cesarean)	1.402	0.696	4.053	**0.044**	4.063	1.038–15.902		
	Constant	10.554	2.735	14.892	< 0.001	—	—		
Necrotizing enterocolitis	Group (intervention vs. control)	–5.532	1.757	9.914	**0.002**	0.004	0.000–0.118	**0.636**	**84.8%**
	Gestational age (per week)	–1.986	0.528	14.156	**< 0.001**	0.137	0.049–0.386		
	Gender (male vs. female)	2.513	1.056	5.657	**0.017**	12.336	1.557–97.733		
	Constant	58.076	15.586	13.885	< 0.001	—	—		

Note: Variables entered into each model: group, gestational age, birth weight, Apgar 1, Apgar 5, gender, and delivery mode. Forward stepwise (conditional) method was used with entry criterion $P < 0.05$ and removal criterion $P > 0.10$. Only variables that remained in the final model are shown. B: regression coefficient (β); S.E.: standard error; Wald: Wald chi-square statistic; Exp(B): odds ratio; CI: confidence interval; NVD: normal vaginal delivery. For sepsis and NEC analyses, due to missing data in some variables, 79 cases were included (86.8% of the total).

Study Strengths and Limitations

This randomized controlled trial used a standardized 8-day OAC protocol and incorporated multiple clinically relevant nutritional and recovery outcomes, strengthening internal validity. Blinded outcome assessment and prospective data collection further enhanced methodological rigor. However, the single-center design limits generalizability, and the study was powered only for the primary outcome; therefore, reductions in sepsis and NEC should be interpreted cautiously. Feeding and growth outcomes could not be measured in infants who died, resulting in a per-protocol analysis for these endpoints. Caregivers were not blinded, and no sham stimulation was used, introducing potential performance bias. Long-term outcomes were not assessed. Larger multicenter trials with standardized protocols and extended follow-up are needed to confirm these findings.

Conclusion

Oropharyngeal administration of maternal colostrum was associated with earlier initiation of enteral feeding, faster achievement of full enteral nutrition, and improved early growth velocity in very preterm infants. These findings suggest that early mucosal exposure to colostrum may support gastrointestinal adaptation and enhance nutritional stability during the neonatal period. Favorable trends in secondary outcomes—including reduced culture-proven sepsis, NEC, and shorter antibiotic duration—are encouraging but should be interpreted cautiously, as the trial was powered only for the primary endpoint and secondary analyses were exploratory without adjustment for multiple comparisons. No intervention-related adverse events were observed, confirming the feasibility and safety of the standardized 8-day OAC protocol. Given the single-center design and limited sample size, larger multicenter trials with harmonized feeding protocols and extended follow-up are needed to validate these results and determine whether early nutritional benefits translate into sustained improvements in long-term clinical outcomes.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shoushtar University of Medical Sciences (IR.SHOUSHTAR.REC.1403.008). Written informed consent was obtained from all parents or legal guardians prior to enrollment. Participation was voluntary, and families were assured that refusal to participate would not affect the quality of clinical care provided to their infants. All collected data were anonymized and handled confidentially.

Consent for publication

Not applicable. No identifiable personal or clinical images of participants are included in this manuscript.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to institutional data protection policies. Data may be made available from the corresponding author upon reasonable request and with appropriate ethical approvals.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

SK conceptualized and designed the study. NT and AKH coordinated patient recruitment, intervention delivery, and data collection. AJ supervised clinical procedures, ensured adherence to NICU protocols, and contributed to methodological oversight. AJ performed statistical analysis and assisted with data interpretation. NT drafted the initial manuscript, and SK contributed to data curation, manuscript refinement, and quality control. All authors reviewed, revised, and approved the final manuscript.

Acknowledgements

The authors express their sincere appreciation to the NICU nursing staff of Al Hadi Educational and Medical Center for their invaluable support in implementing the intervention protocol and ensuring high-quality clinical monitoring. We also thank the participating families for their cooperation and trust. The authors gratefully acknowledge the support of Dezful University of Medical Sciences and the Student Research Committee for facilitating the conduct of this study.

Use of artificial intelligence tools

Artificial intelligence tools were used solely to assist with language refinement, structural editing, and improvement of clarity during manuscript preparation. No AI system was involved in study design, data collection, statistical analysis, interpretation of results, or formulation of scientific conclusions. All AI-assisted edits were reviewed and approved by the authors to ensure accuracy and integrity of the scientific content.

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Figures

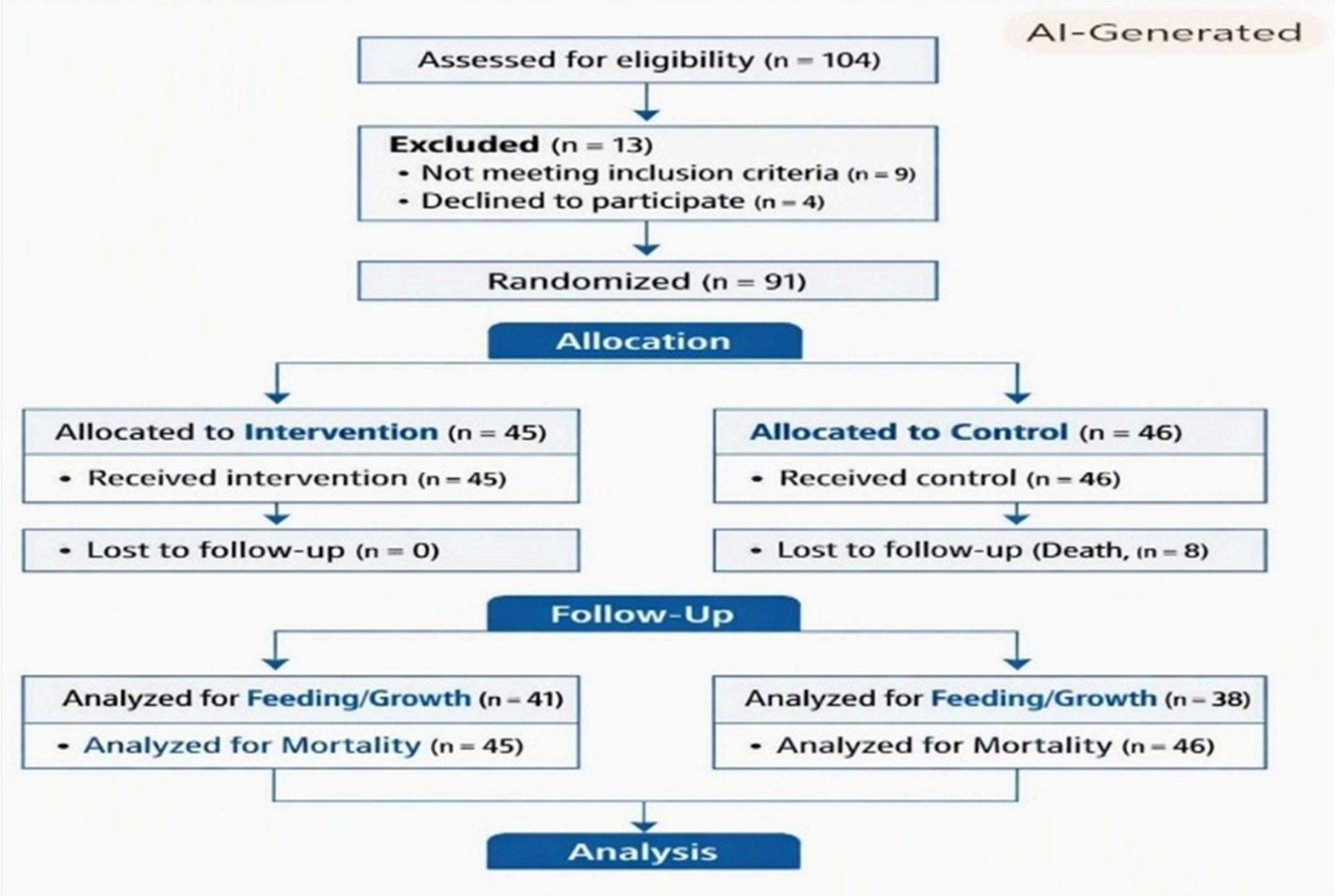


Figure 1

CONSORT flow diagram showing enrollment, allocation, follow-up, and analysis of very preterm infants (n = 91 randomized).”