Oropharyngeal Colostrum Administration in Extremely Premature Infants: An RCT

Juyoung Lee, MD, Han-Suk Kim, MD, PhD, Young Hwa Jung, MD, Ka Young Choi, MD, Seung Han Shin, MD, Ee-Kyung Kim, MD, PhD, Jung-Hwan Choi, MD, PhD

abstract

OBJECTIVE: To determine the immunologic effects of oropharyngeal colostrum administration in extremely premature infants.

METHODS: We conducted a double-blind, randomized, placebo-controlled trial involving 48 preterm infants born before 28 weeks' gestation. Subjects received 0.2 mL of their mother’s colostrum or sterile water via oropharyngeal route every 3 hours for 3 days beginning at 48 to 96 hours of life. To measure concentrations of secretory immunoglobulin A, lactoferrin, and several immune substances, urine and saliva were obtained during the first 24 hours of life and at 8 and 15 days. Clinical data during hospitalization were collected.

RESULTS: Urinary levels of secretory immunoglobulin A at 1 week (71.4 vs 26.5 ng/g creatinine, \( P = .04 \)) and 2 weeks (233.8 vs 48.3 ng/g creatinine, \( P = .006 \)), and lactoferrin at 1 week (3.5 vs 0.9 \( \mu \)g/g creatinine, \( P = .01 \)) were significantly higher in colostrum group. Urine interleukin-1\( \beta \) level was significantly lower in colostrum group at 2 weeks (55.3 vs 91.8 \( \mu \)g/g creatinine, \( P = .01 \)). Salivary transforming growth factor-\( \beta \)1 (39.2 vs 69.7 \( \mu \)g/mL, \( P = .03 \)) and interleukin-8 (1.2 vs 4.9 ng/mL, \( P = .04 \)) were significantly lower at 2 weeks in colostrum group. A significant reduction in the incidence of clinical sepsis was noted in colostrum group (50% vs 92%, \( P = .003 \)).

CONCLUSIONS: This study suggests that oropharyngeal administration of colostrum may decrease clinical sepsis, inhibit secretion of pro-inflammatory cytokines, and increase levels of circulating immune-protective factors in extremely premature infants. Larger studies to confirm these findings are warranted.

WHAT'S KNOWN ON THIS SUBJECT: Immune-related bioactive proteins are highly concentrated in the colostrum of mothers who deliver preterm infants. Oropharyngeal administration was proposed as a safe and feasible alternative method of providing colostrum to immunocompromised premature infants.

WHAT THIS STUDY ADDS: Oropharyngeal administration of colostrum during the first few days of life increased urinary secretory immunoglobulin A and lactoferrin, decreased urinary interleukin-1\( \beta \), reduced salivary transforming growth factor-\( \beta \)1 and interleukin-8, and reduced the occurrence of clinical sepsis in extremely premature infants.
During the first few days after birth, open tight junctions of the mammary epithelium allow for paracellular transport of many bioactive immune substances from the mother’s circulation into the colostrum. This small volume of breast milk contains increased concentrations of secretory immunoglobulin A (sIgA), growth factors, lactoferrin, anti-inflammatory cytokines, pro-inflammatory cytokines, and other protective components, compared with mature breast milk. Several studies indicate that immunoprotective factors are more highly concentrated in the colostrum of mothers who deliver preterm infants than those who give birth at term. Similarly, studies suggest that closure of the tight junctions in the mammary epithelium might be delayed after preterm compared with term birth. However, many preterm infants cannot tolerate enteral feedings because of clinical instability and therefore do not receive maternal colostrum, possibly resulting in increased susceptibility to various infections and inflammatory conditions.

Recently oropharyngeal administration of colostrum (so-called oral immune therapy) has been advocated for preterm infants. Oropharyngeal administration does not involve the infant’s swallowing of milk. During this intervention, a small amount of colostrum is placed directly onto the oropharyngeal mucosa in the buccal cavity for absorption. In theory, the abundant immune factors in colostrum interact with lymphoid tissues in the oropharynx and stimulate the immature neonatal immune system when administered via the oropharyngeal route. Although theoretical and preclinical support for this practice exists, there is insufficient evidence that oropharyngeal administration of colostrum is beneficial to date.

We aimed to evaluate the immunologic effects of oropharyngeal colostrum administration in extremely premature infants.

**METHODS**

**Study Design**

A randomized, double-blind, placebo-controlled, intervention trial was conducted from January 2012 to December 2013 in the NICU of Seoul National University Children’s Hospital in Seoul, Korea. The local institutional review board approved the protocol. The entirety of this study was conducted in accordance with the current revisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

**Participants**

Neonates born before 28 weeks’ gestation were enrolled. Infants with congenital gastrointestinal or renal anomalies or a maternal history of substance abuse or HIV infection were excluded. After informed parental consent was obtained, regardless of twin or higher-order multiples, each neonate was randomly assigned independently to the colostrum or placebo group in a 1:1 ratio on the randomization Web site of Medical Research Collaborating Center of Seoul National University Hospital. Randomization was conducted using a computer-generated allocation sequence (block sizes of 8). Allocation was concealed from all investigators, nurses, doctors, and parents, with the exception of 1 independent research staff member, who prepared the colostrum and placebo syringes. The feeding status of each patient was decided by the attending physicians under the principle that trophic feeding should be started as soon as possible if no contraindication was found (eg, bilious gastric remain, fixed dilated bowel loop on radiograph, severe hemodynamic instability). Both groups of neonates were fed breast milk or preterm formula, whichever was prepared first. The probiotic Duolac Baby (Cell Biotech, Seoul, Korea) was added according to the local practice protocol when the amount of each feeding was >2 mL.

**Intervention**

Investigators who qualified as international board-certified lactation consultants met the mothers of each enrolled neonate within 24 hours of delivery and educated them about hand-expression and electric pumping of breast milk every 2 to 3 hours. Mothers were given prelabeled sterile milk collection bags and instructed to collect their colostrum by using a sanitary hand-expression method and then to send the colostrum to the NICU immediately for refrigeration.

Tuberculin syringes were used to administer colostrum or placebo via the oropharyngeal route. One unblinded investigator prepared 48 syringes with 0.1 mL of mother’s colostrum or sterile distilled water using aseptic techniques. These syringes were then labeled and wrapped with opaque covers to maintain blinding. The syringes were placed in prelabeled plastic cups and stored at 4°C in a specified milk refrigerator.

Beginning at 48 to 96 hours after birth, each neonate received 0.2 mL of his or her mother’s colostrum or sterile water every 3 hours for 72 consecutive hours, regardless of whether the infant was being fed enteraly. At each session, 2 prefilled syringes with 0.1 mL of colostrum or sterile water were warmed in the infant’s incubator for 5 minutes. One syringe was placed on the patient’s right or left buccal mucosa, and the colostrum or placebo drops were administered toward the posterior oropharynx for at least 10 seconds (Fig 1 and Supplemental Video). The same process was repeated on the opposite site, as described in a previous study. Heart rate (HR), respiratory rate (RR), blood pressure, and pulse oxygen saturation (SpO₂)
signs of pneumonia combined with
mortality. We de
hospitalization duration, and
or proven sepsis, time to reach full
intraventricular hemorrhage, clinical
(VAP), retinopathy of prematurity,
ventilator-associated pneumonia
enterocolitis (NEC),
of prematurity, such as necrotizing

tachypnea (RR
bradycardia (HR
increase in fraction of inspiratory
oxygen >0.1 to maintain a SpO2 >85%,
bradycardia (HR <100/minute) or
tachycardia (HR >200/minute), and
tachypnea (RR >80/minute).

Assessments and Monitoring

To evaluate the salivary production of
bioactive proteins after activation of
oropharyngeal mucosa-associated
lymphoid tissue (MALT) and the
urinary excretion of bioactive
proteins after systemic circulation, we
measured the concentrations of
immunologic factors in saliva and
urine. We also looked at the incidence
of late-onset sepsis and other
inflammatory medical comorbidities
of prematurity, such as necrotizing
enterocolitis (NEC),
bronchopulmonary dysplasia,
ventilator-associated pneumonia
(VAP), retinopathy of prematurity,
intraventricular hemorrhage, clinical
or proven sepsis, time to reach full
feeding (100 mL/kg/day),
hospitalization duration, and
mortality. We defined VAP as clinical
signs of pneumonia combined with
pneumonic infiltration on ≥2 serial
chest radiographs in patients
receiving mechanical ventilation for
>48 hours. Clinical signs of
pneumonia included worsening gas
exchange, increased oxygen
requirements, increased ventilator
demand, and ≥1 clinical symptoms
(new onset of purulent sputum,
temperature instability, leukopenia/
leukocytosis with left shift, apnea/
tachypnea, or bradycardia/
tachycardia). Clinical sepsis was
defined as clinical signs of infection
accompanied by concurrent antibiotic
treatment of >3 days. Clinical signs of
infection included all 3 of the
following categories and at least 1 sign
in each of the 3 categories: general
signs (fever, apnea/tachypnea,
respiratory distress, positive fluid
balance), laboratory results
(leukopenia/leukocytosis, increased
C-reactive protein), and hemodynamic
alterations (hypotension, tachycardia,
altered skin perfusion, decreased
urine output, increased base deficit).17
Proven sepsis was defined as bacterial
growth in at least 1 blood culture and
fulfillment of clinical sepsis.

Vital signs were monitored
throughout the study, and any
occurrence of adverse events was
recorded. Clinical data from each
patient’s hospitalization were
collected at discharge from the NICU.
An independent data and safety-
monitoring board supervised the
investigation and reviewed the data
from the first 3 patients and after
completion of the study. The board
had access to all data, and none of
their analyses resulted in
modifications or termination of this
study.

Specimen Collection and Assays

To measure the concentrations of
immunologic factors, urine and saliva
were collected during the first 24
hours and at 8 and 15 days of life.
Urine was obtained by using a sterile
attachable urine bag for neonates.
Unstimulated whole saliva was
collected in a sterile container using
weak suction. All specimens were
centrifuged, aliquoted, and stored at
−70°C until biochemical analysis.
The concentrations of slgA,
lactoferrin, transforming growth
factor (TGF)-β1, and interleukin
(IL)-10 from the urine and saliva
specimens were measured using
enzyme-linked immunosorbent assay
kits (slgA: USCN Life Science, Wuhan,
China; lactoferrin: EMD Millipore,
Billerica, MA; TGF-β1 and IL-10: R&D
Systems, Minneapolis, MN) according
to the manufacturer’s protocols.
Epidermal growth factor (EGF),
tumor necrosis factor–α, interferon-γ,
IL-1β, IL-2, IL-4, IL-6, and IL-8 were
measured using luminex fluorescent
bead human cytokine immunoassays
(MILLIPLEX MAP, Millipore).

Sample Size Calculation and
Statistical Analysis

On the basis of results from
a previous study,18 we assumed
a mean difference in urinary slgA of
29.75 µg/mL between the 2 groups,
and the SDs were 41.55 µg/mL for
the colostrum group and 29.75
µg/mL for the placebo group. Given an
asymptotic relative efficacy on the
80% power and a 5% significance
level with the independent t test, the
required sample size for the Mann-
Whitney U test was calculated as 21
infants for each group. Therefore,
assuming a 10% dropout rate, we
estimated that 48 subjects were
needed.

Analysis of the clinical data was
performed on an intention-to-treat
basis, and the biochemical data of
specimens from subjects who
completed the protocol were analyzed. Statistical analyses were performed by using SPSS version 21.0 (SPSS, Chicago, IL). Mann-Whitney U tests or Fisher’s exact tests and regression analyses were used for group comparisons.

RESULTS

Of 75 extremely premature infants born <28 weeks’ gestation from January 2012 to December 2013, 48 were included and randomly assigned to the placebo or colostrum group (Fig 2). Two of 24 infants were excluded from the placebo group because of death before study initiation, and 1 infant was withdrawn from the study due to parental wishes. Three infants were excluded from the colostrum group: 2 due to the absence of colostrum until 96 hours after birth, and 1 due to death before study initiation. Forty-two of 48 infants completed the protocol. The median number of received doses was 24 (interquartile range [IQR]: 23–24) in both groups. Fifteen and sixteen infants received all 24 doses for the placebo and colostrum group, respectively. The median gestational age of the population was 26+5 weeks (range: 23+1–27+6 weeks), and the median birth weight was 815 g (range: 400–1450 g).

Table 1 shows no differences in the baseline characteristics of the study population or in the number that received formula before starting the protocol, during 3 days of intervention, and during a 2-week period after birth. Approximately half of the enrolled infants were nil per os (NPO) before the study, and 18 (37.5%) infants did not start enteral feeding during the first week of life. Figure 3 demonstrates urine levels of immune substances based on creatinine concentrations. The urinary sIgA level at 1 week was significantly increased in the colostrum group (71.4 vs 26.5 ng/g creatinine, P = .04), and remained elevated at 2 weeks (233.8 vs 48.3 ng/g creatinine, P = .06). Urinary lactoferrin level was also significantly increased at 1 week in the colostrum group (3.5 vs 0.9 µg/g creatinine, P = .01). Among the interleukins, urinary

<table>
<thead>
<tr>
<th>Table 1 Patient Demographics and Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Group (N = 24)</td>
</tr>
<tr>
<td>Gestational age, wk</td>
</tr>
<tr>
<td>Birth wt, g</td>
</tr>
<tr>
<td>Male/female ratio</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
</tr>
<tr>
<td>Multiple gestation</td>
</tr>
<tr>
<td>Vaginal delivery</td>
</tr>
<tr>
<td>Antenatal steroid use</td>
</tr>
<tr>
<td>Histologic chorioamnionitis*</td>
</tr>
<tr>
<td>Surfactant use</td>
</tr>
<tr>
<td>Feeding before the protocol</td>
</tr>
<tr>
<td>Feeding during the protocol</td>
</tr>
<tr>
<td>Breast milk</td>
</tr>
<tr>
<td>Preterm formula</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Feeding for 2 wk after birth</td>
</tr>
<tr>
<td>Breast milk</td>
</tr>
<tr>
<td>Preterm formula</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Mechanical ventilation at randomization</td>
</tr>
<tr>
<td>≥1 transfusion during 2 wk after birth</td>
</tr>
<tr>
<td>Prostaglandin inhibitor use</td>
</tr>
<tr>
<td>Postnatal steroid use</td>
</tr>
<tr>
<td>H2 blocker use</td>
</tr>
<tr>
<td>Probiotic use</td>
</tr>
</tbody>
</table>

Values are median (IQR) or number (%).
* Presence of acute inflammatory changes on fetal membranes (subchorion, chorion, amnion, or umbilicus).
FIGURE 3
Urinary levels of immune substances based on creatinine concentrations on days 1, 8, and 15, from 42 infants who completed the protocol. Each error bar represents 1 SE. Mann-Whitney U tests were used for group comparisons, * P < .05 versus placebo group.
IL-1β level was significantly reduced at 2 weeks in the colostrum group (55.3 vs 91.8 μg/g creatinine, \(P = .01\)). Regarding the immune substances in saliva (Fig 4), the concentrations of sIgA (5.4 vs 2.1 μg/mL, \(P = .02\)) and EGF (464.3 vs 258.4 pg/mL, \(P = .04\)) were significantly increased at 1 week in the colostrum group but were decreased to levels similar to that of the placebo group at 2 weeks. Salivary TGF-β1 (39.2 vs 69.7 μg/mL, \(P = .03\)) and IL-8 (1.2 vs 4.9 ng/mL, \(P = .04\)) were significantly reduced in the colostrum group at 2 weeks compared with the placebo group. The colostrum group had less clinical sepsis (50% vs 92%, \(P = .003\)) and shorter total antibiotic duration (6 [IQR: 3.8–8.5] vs 9.5 [IQR: 7–19] days, \(P = .014\)), but no difference in culture-proven sepsis (46% vs 58%, \(P = .56\)) (Table 2). The significant effect of colostrum administration on clinical sepsis was also validated in a regression analysis with all possible confounders, including mechanical ventilation, H2 blocker use, probiotic use, postnatal steroid use, feeding status and types (\(\exp [B] = 67.3, 95%\) confidence interval: 3.8–1186.9, \(P = .004\)). No differences in NEC, bronchopulmonary dysplasia, VAP, grade ≥3 intraventricular hemorrhage, retinopathy of prematurity that required laser surgery, time to reach full enteral feeding, hospitalization duration, or mortality were noted. Blood pressure, HR, RR, and \(SPO_2\) remained stable during each administration session. No episodes of agitation, aspiration events, bradycardia or tachycardia, hypotension, or other acute adverse events were noted in any of the infants during the interventions.

**DISCUSSION**

To the best of our knowledge, this is the first double-blind, randomized, placebo-controlled trial to provide immunologic and clinical evidence regarding the advantages of oropharyngeal colostrum administration in extremely premature infants. A prospective study of 15 extremely low birth weight infants demonstrated that the time to reach full enteral feeding was reduced,\(^{15}\) and 1 retrospective study reported that oropharyngeal administration of colostrum resulted in starting feeding earlier and reaching birth weight sooner.\(^{16}\) However, no published data have illustrated the clinical advantages of oropharyngeal colostrum administration in relation to the immune system.

Colostrum contains higher concentrations of immunoprotective agents compared with mature human milk,\(^{5}\) and these agents are believed to compensate for the delayed immune system development of premature infants by conducting immunomodulatory reactions at mucosal and systemic sites.\(^{12}\) Despite the theoretical advantages, providing maternal colostrum to extremely premature infants in the early postnatal period presents a variety of challenges. During this time, enteral feedings are frequently disturbed by immature gastrointestinal function and comorbidities that compromise splanchnic perfusion, such as patent ductus arteriosus, umbilical catheterization, or hypotension.\(^{19}\)

The oropharyngeal mucosal route was recently proposed as a solution for providing maternal colostrum to the sickest infants during the early postnatal period.\(^{11–14,16}\) Rodriguez et al\(^{12}\) described the expected mechanisms through which cytokines and other immunologic factors in colostrum stimulate the immature neonatal immune system via lymphoid tissues in the oropharynx and gut, resulting in the development of a protective mucosal immune barrier.

We observed that urinary excretion of sIgA and lactoferrin was significantly increased by oropharyngeal colostrum administration in extremely premature infants (Fig 3). This result could be interpreted mainly as excretion after their passage through the systemic circulation after being absorbed by the oral or gastrointestinal mucosa. The half-lives of sIgA and lactoferrin are 3 to 6 days, and their uptake from breast milk via neonatal gut mucosa with subsequent excretion of their intact maternal forms in the urine were well demonstrated in previous studies.\(^{7,20–22}\) This exceptional mucosal absorption might be expected to occur only in preterm infants, particularly before ‘gut closure,’ and our findings support this hypothesis.\(^{23,24}\) On the other hand, in addition to mucosal absorption, the result of continued increase of urinary sIgA at 2 weeks of age might be reflective that oropharyngeal stimulation by colostrum enhances endogenous production and/or excretion of sIgA.

Interestingly, the urinary excretion of IL-1β was significantly decreased by oropharyngeal administration of colostrum (Fig 3). Cytokines have short half-lives of several hours and are known to be involved in mucosal immunity mainly by binding to cellular receptors.\(^{2}\) Because the passive uptake of cytokines by mucosal barriers during the neonatal period has not been elucidated, urinary levels of cytokines might reflect endogenous production by immune systems. Contrary to evidence suggesting that the production of several cytokines by neonatal T cells are either slightly (tumor necrosis factor-α)\(^{25}\) or markedly reduced (IL-4, IL-6, IL-8, IL-10, and interferon-γ),\(^{26–29}\) IL-1β is known to be overproduced in preterm neonates and to be involved in excessive intestinal and systemic inflammation.\(^{30}\) It has been noted that IL-1β initiates inflammatory cascades and enhances the expression of a powerful chemokine, IL-8, in immature intestinal cells.\(^{30–32}\) In this regard, our data suggest the hypothesis that oropharyngeal
FIGURE 4
Salivary levels of immune substances on days 1, 8, and 15 from 42 infants who completed the protocol. Each error bar represents 1 SE. Mann-Whitney U tests were used for group comparisons, * P < .05 versus placebo group.
colostrum administration downregulates production and/or excretion of IL-1β, which in turn decreases the production of IL-8. Significantly decreased salivary levels of TGF-β1 and IL-8 in the colostrum group could be interpreted in a similar manner (Fig 4). TGF-β1 is the predominant isoform of TGF-β produced by immune cells within the mucosal lamina propria, and the salivary secretion of TGF-β1 is known to play a key role in active inordinate mucosal inflammation.33−35 IL-8, an important chemotactic factor for neutrophils, is a known initiator of excessive intestinal inflammatory responses in preterm NEC models.2,30,31,36 Evidence suggests that human milk factors suppress the induction of IL-8 expression in cultured mucosal epithelial cells; this suppression is more pronounced in immature cells.37

Abrupt increases in salivary sIgA and EGF concentrations in the colostrum group at 1 week were potentially influenced by orally administered colostrum (Fig 4). Because the protocol had been performed for 3 days, from the second to fourth postnatal day, a large amount of sIgA and EGF included in colostrum could remain in the oral cavity and might be subsequently collected with saliva at 1 week.

Our results demonstrate a significant reduction in the incidence of clinical but not proven sepsis in the colostrum group (Table 2). Because we confined proven sepsis to bacterial growth in any blood culture, viral infection or other systemic inflammatory responses precluded a diagnosis of proven sepsis. However, the results of several studies support that abundant immunomodulatory molecules in colostrum seem to have the capacity to decrease infection caused by bacteria, viruses, and possibly fungi without the use of inflammatory mechanisms.32,36,38,39 If the main immunologic effect of colostrum is to suppress mucosal and systemic inflammatory responses, the significant reduction of clinical sepsis by colostrum might reflect its capacity to downregulate immature, excessively exaggerated inflammatory responses to a variety of stimuli in newborns. In this sense, oropharyngeal administration of colostrum might be beneficial in preventing NEC or VAP. However, the number of infants in our study was too small to draw any conclusion about decreased risk of NEC or VAP.

Our trial had several other limitations. There was a high incidence of clinical and proven sepsis. The incidence of NEC was also relatively high, despite probiotic use. Furthermore, breastfeeding rates during postnatal 2 weeks were as low as ∼35%; however, there was no difference in the pattern of feeding or other factors that could affect the immune response, including chorioamnionitis, transfusion, and the use of postnatal steroids, H2 blockers, and probiotics, between the 2 groups. Although this small study cannot draw a conclusive statement about the clinical benefit of colostrum, it provides evidence suggesting that oropharyngeal administration of colostrum during the first few days of life can potentially enhance immune function in the sickest premature infants. Additionally, our findings suggest the possible usefulness of colostrum as an oropharyngeal immune-boosting agent to prevent sepsis and excessive mucosal inflammation in the preterm population. Larger-scale studies are needed to prove these effects.

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**TABLE 2 Clinical Outcomes at the Time of Discharge**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo Group (N = 24)</th>
<th>Colostrum Group (N = 24)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC, Bell stage ≥2</td>
<td>6 (25)</td>
<td>4 (17)</td>
<td>.72</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasiab</td>
<td>14 (58)</td>
<td>15 (63)</td>
<td>.58</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>8 (33)</td>
<td>3 (12.5)</td>
<td>.17</td>
</tr>
<tr>
<td>Proven sepsis</td>
<td>14 (58)</td>
<td>11 (46)</td>
<td>.56</td>
</tr>
<tr>
<td>Clinical sepsis</td>
<td>22 (92)</td>
<td>12 (50)</td>
<td>.003</td>
</tr>
<tr>
<td>Total antibiotic days</td>
<td>9.5 (7–19)</td>
<td>6 (5.8–8.5)</td>
<td>.014</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, grade ≥3</td>
<td>3 (12.5)</td>
<td>4 (16.7)</td>
<td>.34</td>
</tr>
<tr>
<td>Laser surgery for ROP</td>
<td>7 (29)</td>
<td>11 (46)</td>
<td>.26</td>
</tr>
<tr>
<td>Postnatal days to reach full feeding</td>
<td>17 (14.3–25.8)</td>
<td>20 (13–27)</td>
<td>.86</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>81.5 (56.5–99)</td>
<td>89 (69.3–109.8)</td>
<td>.44</td>
</tr>
<tr>
<td>Death</td>
<td>6 (25)</td>
<td>5 (12.5)</td>
<td>.46</td>
</tr>
</tbody>
</table>

Values are median (IQR) or number (%). ROP, retinopathy of prematurity.

* Fisher’s exact test or Mann-Whitney U test was used for analysis.

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