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초극소 재태 주령 미숙아에서 구강 내 초유 투여에 대한 이중 맹검 무작위 대조 임상시험

Randomized Double-blind Placebo-controlled Trial on Oropharyngeal Colostrum Administration in Extremely Premature Infants

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Abstract

Randomized Double-blind Placebo-controlled Trial on Oropharyngeal Colostrum Administration in Extremely Premature Infants

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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, 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 = 0.04) and 2 weeks (233.8 vs. 48.3 ng/g creatinine, P = 0.006), and lactoferrin at 1 week (3.5 vs. 0.9 μg/g creatinine, P = 0.01) were significantly higher in colostrum group. Urine interleukin-1β level was significantly lower in colostrum group at 2 weeks (55.3 vs. 91.8 μg/g creatinine, P = 0.01). Salivary transforming growth factor-β1 (39.2 vs. 69.7 μg/mL, P = 0.03) and interleukin-8 (1.2 vs. 4.9 ng/mL, P = 0.04) 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 = 0.003).

Conclusions: This small 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.

Keywords: colostrum, extremely premature infant, human milk

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Introduction

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.[1] 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.[2-5] Several studies indicate that immune-protective factors are more highly concentrated in the colostrum of mothers who deliver preterm infants than those who give birth at term.[6-8] Similarly, studies suggest that closure of the tight junctions in the mammary epithelium might be delayed following preterm compared to term birth.[9, 10] However, many preterm infants cannot tolerate enteral feedings due to 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.[12] 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.[11, 13] Although theoretical and preclinical support for this practice exists, there is insufficient evidence that oropharyngeal administration of colostrum is beneficial to date.[13-16] 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 neonatal intensive care unit (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 website 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 to all investigators, nurses, doctors, and parents, with the exception of one 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, e.g., bilious gastric remain, fixed dilated bowel loop on x-ray and severe hemodynamic instability. Both groups of neonates were fed breast milk or preterm formula, whichever was prepared first. The probiotic, Duolac baby® (Cell Biotech, Co., Ltd, Seoul, Korea), was added according to the local practice protocol when the amount of each feeding was more than 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 electrical pumping of breast milk every 2 to 3 hours. Mothers were given pre-labeled sterile milk collection bags and instructed to collect their colostrum using a sanitary hand-expression method and then to immediately send the colostrum to the NICU 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 pre-labeled plastic cups and stored at 4℃ in a specified milk refrigerator.

Beginning at 48 to 96 hours after birth, each neonate received 0.2

mL of its own mother's colostrum or sterile water every 3 hours for 72 consecutive hours, regardless of whether the infant was being fed enterally. At each session, two pre-filled 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 towards the posterior oropharynx for at least 10 seconds (Fig 1). The same process was repeated on the opposite site, as described in a previous study.[14] Heart rate (HR), respiratory rate (RR), blood pressure (BP), and SpO_2 were recorded immediately before and after every intervention session. Colostrum or sterile water was not administered during surgery under general anesthesia. A session was discontinued if any of the following issues developed: requirement of an increase in fraction of inspiratory oxygen (FiO_2) >0.1 to maintain a SpO_2 >85%, bradycardia (HR <100 /min) or tachycardia (HR >200 /min), and tachypnea (RR >80 /min).

Figure 1. A still image demonstrating oropharyngeal colostrum administration.

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, e.g., necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), ventilator-associated pneumonia (VAP), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), clinical or proven sepsis, time to reach full feeding (100 mL/kg/d), hospitalization duration, and mortality. We defined VAP as clinical signs of pneumonia combined with pneumonic infiltration on two or more 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 one or more 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 for more than 3 days. The use of antibiotics was decided by dedicated attending physicians, Clinical signs of infection included all three of the following categories and at least one sign in each of the three 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 one 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 was 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, at 8 and 15 days of life. Urine was obtained 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℃ until biochemical analysis.

The concentrations of sIgA, lactoferrin, transforming growth factor (TGF)-β1, and interleukin (IL)-10 from the urine and saliva specimens were measured using enzyme-linked immunosorbent assay (ELISA) kits (sIgA: USCN Life Science, Wuhan, China; lactoferrin:

EMD Millipore, Billerica, MA, USA; TGF-β1 and IL-10: R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocols. Epidermal growth factor (EGF), tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-1β, IL-2, IL-4, IL-6, and IL-8 were measured using luminex fluorescent bead human cytokine immunoassays (MILLIPLEX MAP, Millipore Corp., Billerica, MA, USA).

Sample Size Calculation and Statistical Analysis

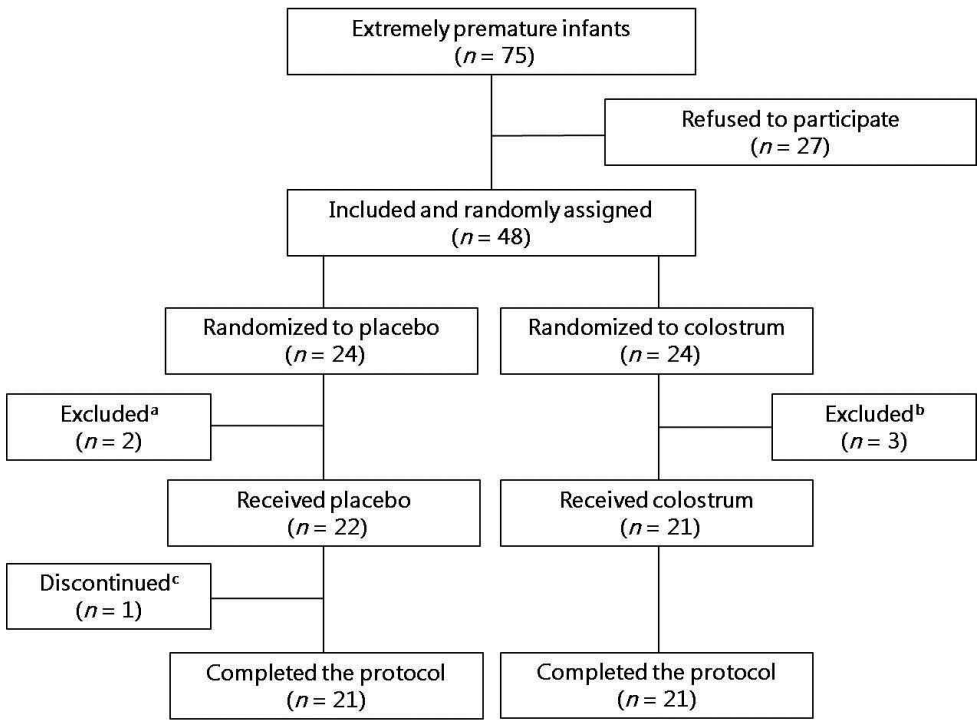
Based on results from a previous study,[14, 18] we assumed a mean difference in urinary sIgA of 29.75 μg/mL between the two groups, and the standard deviations were 41.55 μg/mL for the colostrum group and 9.75 μg/mL for the placebo group. Given an asymptotic relative efficacy on the 80% power and a 5% 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 using SPSS version 21.0 (SPSS, Chicago, IL, USA). Mann-Whitney U-tests or Fisher's exact tests and regression analyses were used for group comparisons.

Results

Of 75 extremely premature infants born less than 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 babies were excluded from the placebo group because of death prior to study initiation, and one baby was withdrawn from the study due to parental wishes. Three babies were excluded from the colostrum group; 2 due to the absence of colostrum until 96 hours after birth, and 1 due to death prior to study initiation. Forty-two of 48 babies completed the protocol. The median number of received doses was 24 (interquartile range [IQR]: 23 – 24) in both groups. Fifteen and sixteen babies received all 24 doses for the placebo and colostrum group, respectively. The median GA of the population was 26^{+5} weeks (range: 23^{+1} – 27^{+6} weeks), and the median birth weight was 815 g (range: 400 – 1,450 g).

Figure 2. Study profile.



[a]Excluded from the placebo group due to death prior to intervention (n = 2). [b]Excluded from the colostrum group given the absence of maternal colostrum (n = 2) or death prior to intervention (n = 1). [c]One infant discontinued the study based on the parents' withdrawal of consent.

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) prior to the study, and 18 (37.5%) infants did not start enteral feeding during the first week of life.

Table 1. Patient Demographics and Baseline Characteristics

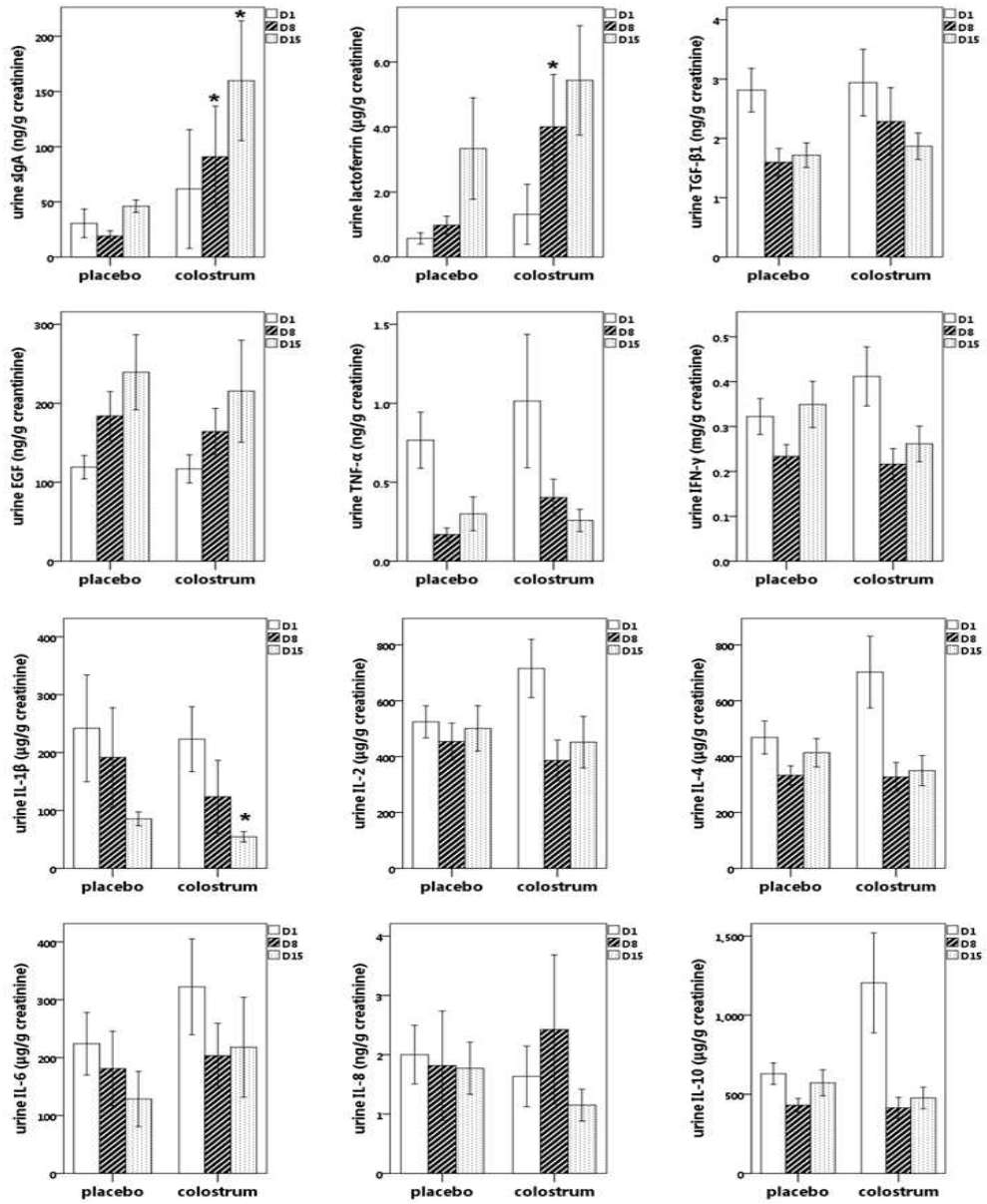
	Placebo group (N = 24)	Colostrum group (N = 24)
Gestational age, wk	26^{+5} (24^{+3} - 27^{+1})	26^{+5} (24^{+2} - 27^{+4})
Birth weight, g	815 (610 - 1,003)	830 (701 - 993)
Boy : Girl	10 : 14 (42 : 58)	12 : 12 (50 : 50)
Apgar score at 1 min	3 (2 - 5)	3 (2 - 5)
Apgar score at 5 min	7 (5 - 7)	6 (5 - 7)
Multiple gestation	16 (67)	22 (92)
Vaginal delivery	11 (46)	11 (46)
Antenatal steroid use	20 (83)	21 (88)
Histologic chorioamnionitis[a]	14 (58)	8 (33)
Surfactant use	20 (83)	17 (71)
Feeding prior to the protocol	12 (50)	11 (46)
Feeding during the protocol	15 (63)	15 (63)
Breast milk : Preterm formula : Mixed : None	5 : 9 : 1 : 9	4 : 8 : 3 : 9
Feeding for 2 weeks after birth	20 (83)	20 (83)
Breast milk : Preterm formula : Mixed : None	5 : 11 : 4 : 4	6 : 11 : 3 : 4
Mechanical ventilation at randomization	18 (75)	14 (58)
≥1 transfusion during 2 weeks after birth	18 (75)	17 (71)
Prostaglandin inhibitor use	11 (46)	11 (46)
Postnatal steroid use	8 (33)	12 (50)
H2 blocker use	7 (29)	8 (33)
Probiotic use	18 (75)	19 (79)

Values are median (IQR) or number (%).

[a]Presence of acute inflammatory changes on fetal membranes (subchorion, chorion, amnion or umbilicus).

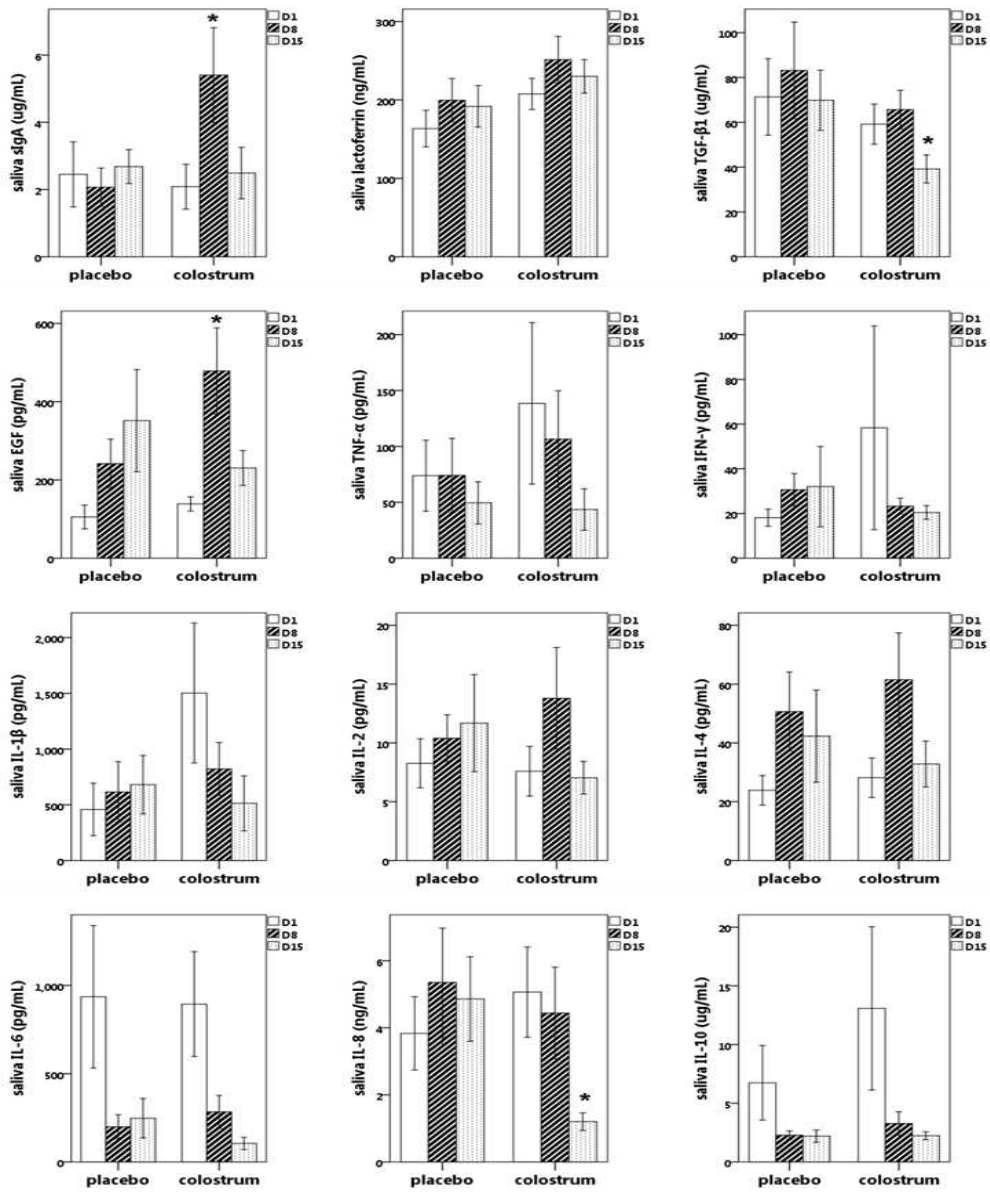
Figure 3 demonstrates urine levels of immune substances based on creatinine concentrations. The urinary sIgA level at 1 week was significantly increased in the colostrum group (71.4 vs. 26.5 ng/g creatinine, P = 0.04), and remained elevated at 2 weeks (233.8 vs. 48.3 ng/g creatinine, P = 0.006). Urinary lactoferrin level was also significantly increased at 1 week in the colostrum group (3.5 vs. 0.9 μg/g creatinine, P = 0.01). Among the interleukins, urinary IL-1β level was significantly reduced at 2 weeks in the colostrum group (55.3 vs. 91.8 μg/g creatinine, P = 0.01). Regarding the immune substances in saliva (Fig 4), the concentrations of sIgA (5.4 vs. 2.1 μg/mL, P = 0.02) and EGF (464.3 vs. 258.4 pg/mL, P = 0.04) 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 = 0.03) and IL-8 (1.2 vs. 4.9 ng/mL, P = 0.04) were significantly reduced in the colostrum group at 2 weeks compared with the placebo group.

Figure 3. Urinary levels of immune substances based on creatinine concentrations on days 1, 8 and 15.



Each error bar represents one standard error. Mann-Whitney U-tests were used for group comparisons, $*P < 0.05$ versus placebo group.

Figure 4. Salivary levels of immune substances on days 1, 8 and 15.



Each error bar represents one standard error. Mann-Whitney U-tests were used for group comparisons, $^{*}P < 0.05$ versus placebo group.

No differences in NEC, BPD, VAP, grade 3 and higher IVH, ROP that needs laser surgery, time to reach full enteral feeding, hospitalization duration, and mortality were noted (Table 2). Although there was no difference in culture-proven sepsis (46% vs. 58%, P = 0.56), the colostrum group had less clinical sepsis (50% vs. 92%, P = 0.003) and shorter total antibiotic duration (6 [IQR: 3.8 – 8.5] vs. 9.5 [IQR: 7 – 19] days, P = 0.014). The distribution of clinical signs of infection at the diagnosis of clinical sepsis was similar between two groups (Table 3). 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% CI: 3.8 – 1,186.9, P = 0.004). 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.

Table 2. Clinical Outcomes at the Time of Discharge

	Placebo group (N = 24)	Colostrum group (N = 24)	P[a]
Necrotizing enterocolitis, Bell's stage ≥2	6 (25)	4 (17)	0.72
Bronchopulmonary dysplasia[b]	14 (58)	15 (63)	0.58
Ventilator associated pneumonia	8 (33)	3 (12.5)	0.17
Proven sepsis	14 (58)	11 (46)	0.56
Clinical sepsis	22 (92)	12 (50)	0.003
Total antibiotic days	9.5 (7 - 19)	6 (3.8 - 8.5)	0.014
Intraventricular hemorrhage, grade ≥III	3 (12.5)	4 (16.7)	0.34
Laser surgery due to retinopathy of prematurity	7 (29)	11 (46)	0.26
Postnatal days to reach full feeding	17 (14 - 26)	20 (13 - 27)	0.86
Hospital stay days	82 (57 - 99)	89 (69 - 110)	0.44
Death	6 (25)	3 (12.5)	0.46

Values are median (IQR) or number (%).

[a]Fisher's exact test or Mann-Whitney U-test was used for analysis.

[b]Defined as requiring supplemental oxygen at 36 weeks.

Table 3. Clinical Signs on Clinical Sepsis

	Placebo group (N = 22)	Colostrum group (N = 12)
1. General signs of clinical sepsis		
fever	2 (9)	1 (8.3)
apnea or tachypnea	20 (91)	9 (75)
respiratory distress	17 (77)	8 (67)
positive fluid balance	5 (23)	3 (25)
2. Laboratory results		
leukopenia or leukocytosis	12 (54.5)	5 (42)
increased C-reactive protein	19 (86)	11 (92)
3. Hemodynamic alterations		
hypotension	6 (27)	4 (33)
tachycardia	18 (82)	9 (75)
altered skin perfusion	3 (14)	4 (33)
decreased urine output	5 (23)	3 (25)
increased base deficit	15 (68)	9 (75)

Values are number (%).

Discussion

To the best of our knowledge, this is the first double-blind, randomized, placebo-controlled trial to provide immunological 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 one 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 immune-protective 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 babies during the early postnatal period.[11-14, 16] Rodriguez et al[12] described the expected mechanisms by 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 following 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 the so-called 'gut closure,' and our findings support this hypothesis.[23, 24] On the other hand, as well as 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 very 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 (TNF-α)[25] or markedly reduced (IL-4, IL-6, IL-8, IL-10, and IFN-γ),[26-29] IL-1βis 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 regards, our data suggest the hypothesis that oropharyngeal colostrum administration down-regulates production and/or excretion of IL-1βwhich 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 demonstrated a significant reduction in the incidence of clinical sepsis but not of 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 infections 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 down-regulate 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 babies in our study was too small to make any conclusion about decreased risk of NEC or VAP.

Our trial had several other limitations. Although there was a wide range (400 – 1,450 g) in the birth weight of included babies, we used 0.1 mL fixed dose of colostrum for each side based on the previous study.[12] It could be too much amount for 400 g premature infants, but for babies weighing more than 1,000 g. There was a high incidence of clinical and proven sepsis. And the incidence of NEC was also relatively high, in spite of probiotic use. Furthermore, breast feeding 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, use of postnatal steroids, H2 blocker and probiotics, between the two 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 babies. Additionally, our findings suggest a 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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국문초록

연구 목적: 본 연구는 초극소 미숙아에게 구강 내 초유 투여가 면역학적으로 어떠한 효과를 나타내는지 그 유효성을 평가하고자 하였다.

연구 방법: 서울대학교 어린이병원 신생아중환자실에 입원한 출생 재태 28주 미만의 초극소 재태 주령 미숙아 48명에게 전향적, 무작위 배정, 이중 눈가림, 대조 통제, 평행 설계 임상시험을 시행하였다. 생후 48-96 시간에 시험군과 대조군은 각각 초유와 위약(멸균 증류수) 0.2 mL를 3 시간마다 총 24회, 72시간 동안 구강 내로 투여 받았다. Secretory IgA, 락토페린을 비롯한 면역 관련 단백과 cytokine 분석을 위해 생후 24시간 이내, 8일, 15일째 타액 및 소변을 각각 2 mL 이상 멸균백 또는 멸균관에 채취하였다. 각 피험자의 퇴원 시점 또는 사망 시점에 임상 자료를 수집하였다.

연구 결과: 소변 크레아티닌으로 보정한 소변 내 secretory IgA 농도는 1주째(71.4 vs. 26.5 ng/g, P = 0.04), 2주째(233.8 vs. 48.3 ng/g creatinine, P = 0.006) 모두 초유를 투여한 시험군에서 유의하게 높았다. 소변 락토페린도 1주째 시험군에서 유의하게 높았다(3.5 vs. 0.9 μg/g, P = 0.01). 2주 소변 IL-1β 농도는 시험군에서 유의하게 낮았다(55.3 vs. 91.8 μg/g, P = 0.01). 타액의 TGF-β1(39.2 vs. 69.7 μg/mL, P = 0.03)와 IL-8(1.2 vs. 4.9 ng/mL, P = 0.04)은 2주째 시험군에서 유의하게 낮았다. 초유를 투여한 시험군에서 임상적 패혈증의 발병률이 유의하게 낮았다(50% vs. 92%, P = 0.003).

결론: 본 연구는 출생 후 첫 수일 내에 초극소 재태 주령 미숙아에게 구강 내로 투여한 소량의 초유가 타액 및 소변의 항염증인자를 증가

시키고, 염증유발인자의 분비를 감소시키며, 이로 인해 패혈증을 감소시킨 것을 확인하였다. 이를 입증하기 위해서는 더 큰 규모의 연구가 필요하겠지만, 구강 내 초유 투여는 초극소 미숙아의 면역 증강을 위한 중요한 방법으로 제시될 수 있을 것이다.

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주요어: 초유, 초극소 재태 주령 미숙아, 모유

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