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Original Article

Randomized Controlled Trial of Oral Immunotherapy with Colostrum or Breast Milk and Clinical Outcomes among Preterm Babies

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ABSTRACT

Background: It is well known that mother's milk is the best nutrient for the baby. Some formal studies have investigated its effectiveness and supported it as a safe feasible practice. The effects on other variables are vague since the evidence is not strong to observe significant differences in the outcomes, such as necrotizing enterocolitis (NEC), sepsis, length of hospital stay, and mortality.

The present study was carried out to assess the effect of oral therapy with colostrum or breast milk on the clinical outcomes using a questionnaire on clinical outcomes.

Methods: A total of 48 babies were randomly assigned to receive 0.2 ml of their own mother's colostrum, breast milk, or sterile water via oropharyngeal route every 4 h, and it was continued till the baby independently could suck via bottle or breast. The babies were followed since admission until discharge by the unit.

Results: According to the obtained results, there was no statistical difference among the preterm babies who received oral immunotherapy with colostrum, breast milk, and sterile water regarding the clinical outcomes, such as NEC, culture-proven late-onset sepsis, intraventricular hemorrhage, retinopathy of prematurity, chronic lung disease, jaundice, and mortality. The oral therapy with colostrum was observed to have a significant influence on age at discharge (P=0.02).

Conclusion: Oral therapy with colostrum is an alternative method of providing mothers' milk for babies who are kept nil per oral. Oral therapy with colostrum or breast milk leads to earlier weeks of discharge.

Keywords: Mortality, Necrotising enterocolitis, Oral therapy with colostrum, Sepsis

Introduction

Preterm infants are a vulnerable population in the neonatal intensive care unit (NICU) due to associated morbidities some of which are chronic lung disease, sepsis, feed intolerance, necrotizing enterocolitis (NEC), and intraventricular bleeding. To provide optimal care, several invasive maneuvers are required which may contribute to these morbidities (1).

During all the provided intensive care period, the availability of mothers' own breast milk is of immense importance as it is uniquely tailored to the needs of individual preterm (2). Breast milk remains the standard to which all infant nutrition is compared (3). Colostrum is the milk produced by female mammary glands in the initial days after giving birth (4).

In preterm birth, colostrum is produced longer, up to the end of the first week of life. It is rich in bioactive proteins secretory immunoglobulin A (sIgA), growth factors, lactoferrin, anti-inflammatory cytokines, and pro-inflammatory cytokines with bacteriostatic, bactericidal, anti-viral, anti-inflammatory and immunomodulatory effects (5). These factors are also observed to

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be more concentrated in preterm colostrum, compared to those reported for term colostrum, with an inverse correlation with gestational age (6) and provision of preterm neonates with higher immunity (7). Therefore, the availability of mothers' own milk is suggested to reduce the incidence of nosocomial (8-10) or late-onset sepsis (11, 12).

Moreover, the practice of Kangaroo mother care allows the maternal immune system to get exposed to microorganisms in the preterm infant's environment and produce sIgA specific to them. This is readily available through mother's breast milk and specific immunity to the neonate (13).

When mothers milk is oropharyngeally administered, the immune factors and cytokines (14-18) bind with the lymphoid tissues lining with the respiratory and gastrointestinal tract and protecting from pathogens (19-20).

The initial Nil per oral days and prophylactic use of antibiotics lead to intestinal atrophy and increase the risk of feeding intolerance, NEC, and abnormal intestinal colonization (21, 22). Therefore, there is an urgent need for providing mothers' colostrum for preterm babies admitted to the NICU. This can be achieved through oral immunotherapy (OIT). There are several studies reported on OIT and clinical outcomes; however, they were unable to prove clinical significance.

The present study aimed to assess the effectiveness of oral immunotherapy with colostrum or breast milk in various clinical outcomes, such as NEC, sepsis, length of hospital stay, and mortality.

Methods

Design

The current study was a single-centered, prospective, randomized, controlled, and double-blinded study.

Randomization

The estimated sample size for the study was 48 subjects. Therefore, there were six blocks with every eight preterm babies in each block. Research randomizer was used to generate 48 sets of random sequence. Sequentially Numbered, Opaque, Sealed Envelopes were used to retain concealed allocation. Blinding is performed by covering the syringe with an adhesive tape.

In the control group, mothers' milk was provided only if feeding was initiated. The syringes were prepared by the lactation consultant not involved in the bedside care of the neonate. Neither the researcher nor the bedside nurse or mothers were aware of the allocation of the preterm babies to the experimental or control group.

The syringes were prepared by the lactation consultant and handed over to the assigned bedside nurse. The study was conducted in the NICU of Al-Adan Hospital in Kuwait. The inclusion criteria were preterm babies under 33 weeks of gestation (32+6 weeks) or birth weight of < 1500 g. The exclusion criteria included preterm babies with congenital anomalies, preterm babies with congenital infection, babies born in other hospitals, babies of single mothers with unknown partners, confirmed immunodeficiency disorder, inborn error of metabolism, parental refusal to participate, and preterm babies with overt bleeding.

Procedure

The subjects were selected using purposive sampling based on the sampling criteria. The subjects were randomly assigned after obtaining written consent from the parents. The concealed envelopes were sequentially opened during recruitment. The name and assigned number of participants would be written on the envelope after opening. The data were collected by the researcher from medical records and coded by the lactation consultant. The study was conducted within 16th August 2018 to 7th January 2019

Delivery of intervention

Colostrum or breast milk that is fresh or refrigerated within 24 h was collected by the assigned lactation consultant and prepared using 1-ml syringes clearly labeled with patient identification data plus the date and time of expression. The syringes were covered with adhesive silk tapes. These syringes were handed over to the responsible nurse. The tip of the syringe was placed toward the posterior end of the buccal cavity, and 0.1 ml of the milk was slowly squirted into the area. This was to be slowly performed drop by drop in 30 days.

The milk should not pool in the buccal cavity. If it pools, give a few seconds to let it get absorbed, and the rest may be manually rubbed using a swab along the gums and inner surface of the cheek for 10 sec with two strokes in each area. Repeat the procedure on the opposite side. If the colostrum is refrigerated, the syringe might be kept in the baby's incubator for 5 min before administering (23-25).

The OIT was initiated soon after birth as colostrum was available and continued even every 4 h as it was available. The OIT might be provided for the babies who are kept nil per oral and continued even when enteral feeding has been

ordered to get a minimum of 20 doses and can be continued until the baby reaches full oral feeding. The assigned nurse documented the time of oral therapy in the proforma attached to the file.

The control group will receive 0.1 ml of sterile water on each cheek that would be prepared and applied in an identical manner and frequency similarly performed among the preterm neonates in their intervention group. This would start as mothers' milk was available to avoid the disclosure of the intervention to the control group. However, as soon as the mother's milk was available it would be enterally initiated if the baby was stable to be fed.

Ethical considerations

Administrative permission was obtained from the Head of Neonatal Department of the NICU in Adan Hospital in Kuwait, Ministry of Health in Kuwait, Institutional Ethical Committee of Kasturba Hospital in Manipal, India, and Institutional Research Committee of MCON of Manipal. Written informed consent was obtained from the parents. The trial was registered with a Clinical Trial Registry code of INCT03633500.

Outcome measures

The outcomes were measured using a questionnaire on clinical outcomes. The questionnaire consists of 13 items categorized into three headings of mortality, morbidity, and others. The items in the morbidity include NEC, medical and surgical NEC, culture-proven late-onset sepsis and number of episodes, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), chronic lung disease, and neonatal jaundice. Mortality includes the cause of death and age of death. Others include the length of stay in days, age at discharge, inotropic support, and nitric oxide. The aforementioned information was collected from the medical records by the researcher.

Results

The CONSORT flowchart of the subjects recruited for the study is depicted in Figure 1. A

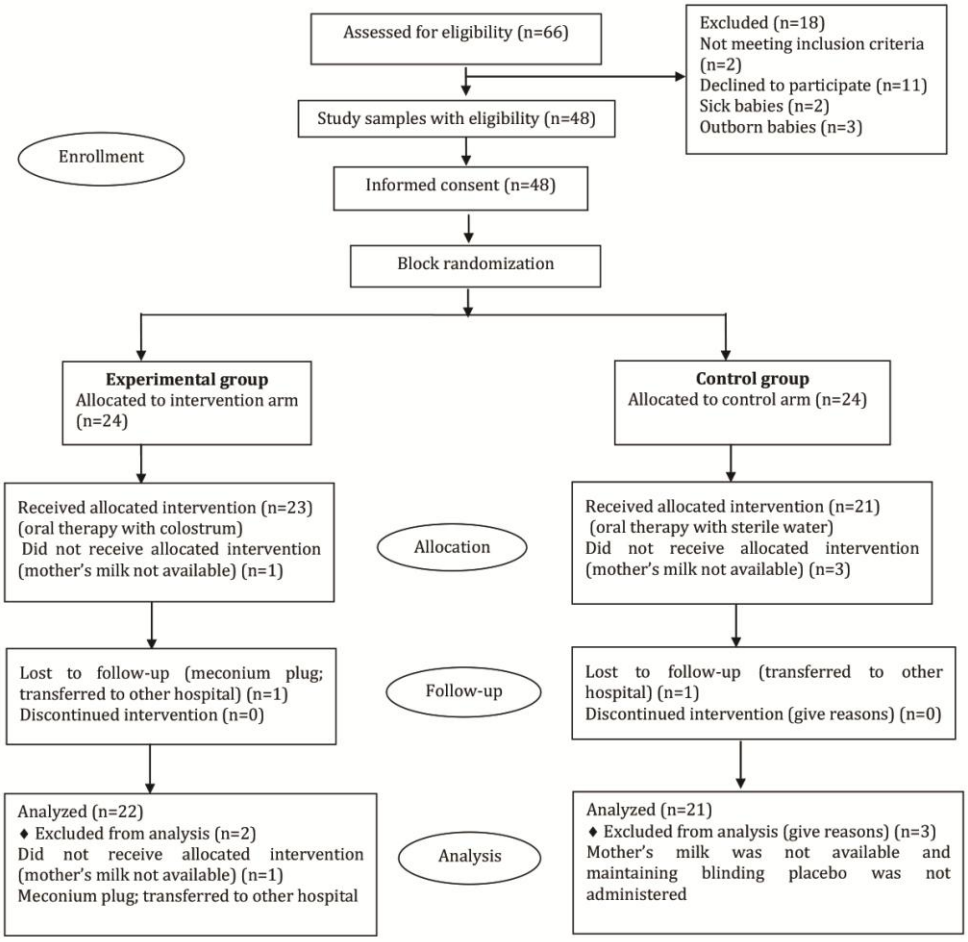

Figure 1. CONSORT flowchart of Randomized Controlled Trial

total of 48 babies were enrolled in the study. In the experimental group, one baby (4.16%) transferred to another hospital due to a meconium plug, and one baby (4.16%) expired and did not receive any intervention since the mother's milk was not available for initiating the intervention. Therefore, two babies (8.3%) were excluded from the analysis. Moreover, two babies (8.3%) in the experimental group died; however, they received the intervention and were included in the analysis. As a result, total babies included for the analysis in the experimental group were 22 subjects.

In the control group, about 24 babies were allocated using sequence generation out of whom 3 babies (12.5%) did not receive the intervention since the mother's milk was not available. One baby was transferred to another hospital because of NEC as one of the measured outcomes. Therefore, three babies were excluded from the analysis, and a total of 21 babies were included for the analysis in the control group.

Sample characteristics

The baseline characteristics of the preterm infants in the experimental and control groups (tables 1 and 2) and socio-demographic characteristics of preterm infants' mothers are depicted in Figure 2. The p-value was greater than 0.05 indicating that the experimental and control groups did not differ significantly with regard to the baseline variables.

Clinical outcomes

The clinical outcomes are summarized in Figure 3. The Chi-square was computed to assess the effectiveness of oral therapy with colostrum in NEC, culture-proven late-onset sepsis and number of times, IVH, ROP, chronic lung disease, jaundice, and mortality (P>0.05). One baby (4.5%) in the experimental group had NEC stage II A, and two babies (9.52%) in the control group had medical NEC and surgical NEC, respectively. About four babies (18.18%) in the experimental group and one baby (4.76%) in the control group had culture-proven late-onset sepsis. Among them, two babies (50%) in the experimental group had *Staphylococcus epidermidis* infection.

One baby (25%) had Staphylococcus stimulus, and one baby (25%) had *Bacillus* infection; however, one baby in the control group had *Staphylococcus epidermidis* infection. One baby in the experimental and control groups had a second

Table 1. Baseline characteristics of preterm infants in experimental and control groups with homogeneity comparison

	Experimental (n=24)		Control (n=24)		Test value	P-value	df
	f	%	f	%			
Gender							
Male	13	54.17	13	54.17	0.000	1	1
Female	11	45.83	11	45.83			
Gestational age at birth (week)	29.1±2.88		29.8±2.31		-0.923 t	0.445	46
Birth weight	1242.50±485.64		1351.5±438.19		-0.816 t	0.683	46
Chorioamnionitis							
Yes	1	4.16	0	0	1.408#	.235	1
No	23	95.83	24	100			
Surfactant							
Yes	21	87.50	24	100.00	4.395#	0.234	1
No	3	12.50	0	0			
Prostaglandin inhibitor use							
Yes	6	25	9	37.5	0.873	0.350	1
No	18	75	15	62.5			
Postnatal steroid use							
Yes	4	18.18	2	9.5	0.683#	0.408	1
No	18	81.8	19	90.47			
Excluded	2		3		0.908	0.635	2
H2 blocker use							
Yes	2	9	1	4.76	0.317#	0.574	1
No	20	91	20	95.2			
Excluded	2		3		0.541	0.76	2
Inotropes							
Yes	6	25	6	25	0.000	1	1
No	18	75	18	75			
Nitric oxide							
Yes	0	0	0	0	0.225#	0.636	1
No	22	100	21	100			

Excluded	2	3

Test of significance #: Chi-square test/ Fischer's Exact test, Independent t-test

Table 2. Resuscitation and ventilation details of preterm infants in experimental and control groups (n=48)

Variable	Experimental (n=24)		Control (n=24)	
	f	%	f	%
Apgar score at 1st min	5.13±2.173*		5.17±1.971*	
Apgar score at 5th min	7.71±0.999*		7.83±0.917*	
Surfactant				
Yes	21	87.50	24	100.00
No	3	12.50	0	0
Mode of ventilation at randomization				
Invasive	18	75.00	17	70.83
Noninvasive	6	25.00	7	29.17
Duration of invasive ventilation (hour)	21.5#	0-216	18.5#	0-47.5
Synchronized inspiratory positive airway pressure (hour)	13#	0-90	36#	1.5-135.75
High flow nasal cannula (hour)	0.0#	0-96	0#	0-102
Oxygen (hour)	1.5#	0-90	0#	0-42

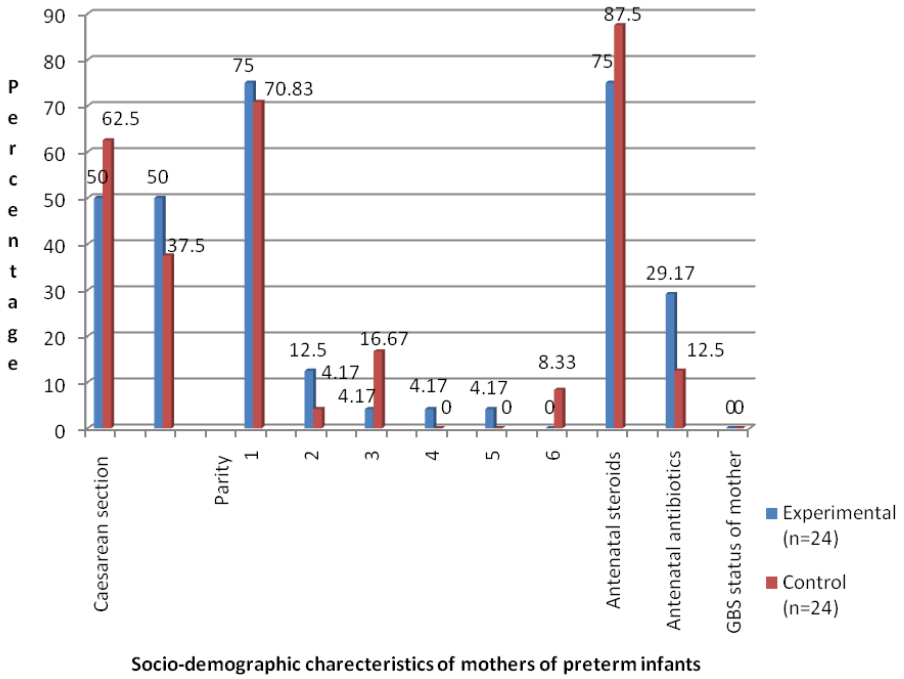

Figure 2. Bar diagram showing socio-demographic characteristics of preterm infants' mothers

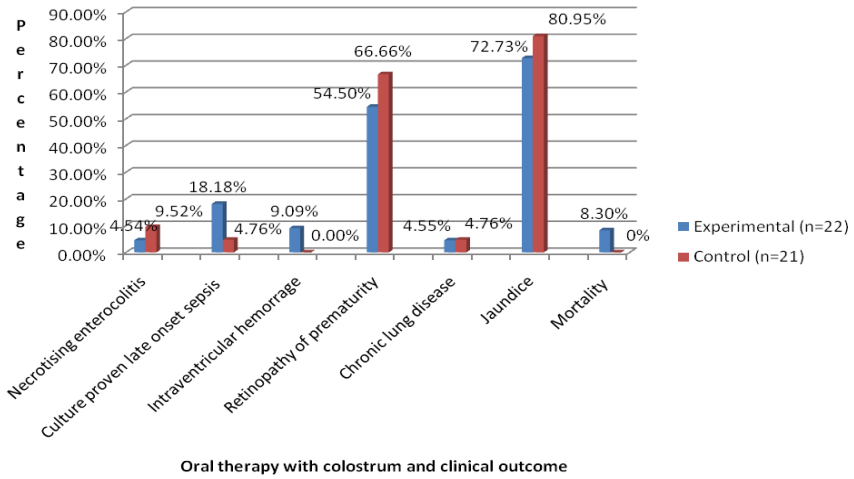

Figure 3. Bar diagram showing oral therapy with colostrum and clinical outcomes among preterm babies

episode of culture-proven late-onset sepsis, and the organism was Klebsiella Pneumonia.

Two babies (9.09%) in the experimental group had IVH, and 50% of them had grade III IVH, and the others had grade IV IVH. The majority of the babies in the experimental and control groups had hyperbilirubinemia and received phototherapy (72.73% and 80.95%). The majority of the babies in the experimental (54.50%) and control (66.66%) groups had ROP. In addition, 58.3%, 16.7%, and 16.7% of them in the experimental group had stage 0, stage 1, and stage 2 ROP, respectively. Moreover, 8.3% in the experimental group had stage 3 ROP. However, 64.3%, 14.3%, and 14.3% in the control group had stage 0, stage 1, and stage 2 ROP, respectively. Furthermore, 7.1% in the control group had stage 3 ROP.

The ROP screening was not performed in about 45.5% of the babies in the experimental group and 28.57% of the babies in the control group. The mean age at discharge among the experimental group was 36.23 weeks, and it was 36.1 weeks the control group with standard deviations of 3.68 and 1.68, respectively. The independent t-test showed that oral therapy with colostrum was observed to have a significant influence on age at discharge (P=0.02). Therefore, it was concluded that oral therapy with colostrum or breast milk led to earlier weeks of discharge. The median lengths of hospital stay were 43 and 41 days in the experimental and control groups with the interquartile ranges of 25-63 and 27-57.25, respectively. The Mann-Whitney U test showed that oral therapy had no statistically significant influence on the length of hospital stay (P=0.955).

Discussion

Oral therapy is an alternative method of providing mothers' own colostrum or breast milk for babies who are kept nil per oral. The median ages of OIT initiation were 27 and 22 h in the experimental and control groups with the interquartile ranges of 22-57.25 and 12.50-33, respectively. The total numbers of received OIT doses were 69.50 and 109 by the experimental and control groups with the interquartile ranges of 23-117.75 and 42-135, respectively. The experimental group received 74.59% of the allocated intervention, whereas the control group received 81.8% of the allocated intervention.

The intervention was missed in both groups due to the non-availability of mothers' milk. Breast milk was available among 90.91% of the mothers of preterm babies in the experimental group and 87.72% of mothers in the control group. The intervention was well tolerated by all the preterm babies. In addition, no adverse events occurred. The practice of oral therapy with colostrum promoted the early initiation of lactation and expression of milk by hand or electric breast pump.

Conclusion

The purpose of the present study was to investigate the effectiveness of oral therapy with colostrum in clinical outcomes. Oral therapy with colostrum had no statistically significant influence on the clinical outcomes, such as NEC, culture-proven late-onset sepsis, IVH, ROP, chronic lung disease, jaundice, and mortality, among preterm infants. However, it was observed that that oral therapy with colostrum or breast milk led to earlier weeks of discharge. Despite the small sample size, this study provides guidance for future research determining the dose and frequency of intervention and long-term

outcomes.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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