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ORIGINAL ARTICLE

Role of Lactoferrin Supplementation in Prevention of Late Onset Sepsis in Preterm Neonates

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ABSTRACT

Background: Late-onset sepsis affects a large proportion of pre-term neonates in neonatal intensive care units worldwide, with high morbidity and mortality. Due to the frequency, severity and difficulties in early diagnosis and prompt therapy, prevention is crucial for decreasing the burden of infection-related complications in NICUs. The aim of this study was to evaluate the role of lactoferrin supplementation in prevention of late onset sepsis in preterm neonates.

Methods: A randomized controlled double-blind interventional pilot study was conducted in Neonatal Intensive Care Unit of Zagazig University and ElQenayate Central Hospital. The Research Ethics Committee of Zagazig Faculty of Medicine approved the study and an informed consent was obtained from the parents of preterm infants before enrollment in the study. Sixty Preterm neonates were included and randomly assigned into two groups; Lactoferrin group and Control group. All neonates were followed for four weeks to follow and confirm the occurrence of late onset sepsis.

Results: Comparing to control group, the frequency of late onset sepsis was significantly lower in Lactoferrin group. There was statistically significant lower frequency of feeding intolerance. The lactoferrin group had significantly lower duration of mechanical ventilation, central line insertion, antibiotics use and oxygen supplementation with less NICU stay duration. Coagulase-negative staphylococci and Klebsiella were the most common organisms found among the septic neonates. Hemoglobin level was significantly higher in Lactoferrin group started from the first week also weight gain was significantly more started from the third week.

Conclusion: Preterm neonates supplemented with oral Lactoferrin had significantly lower incidence of late onset sepsis. Lactoferrin supplementation significantly improve feeding tolerance so allowing to reach full enteral intake in short period lead to decrease duration of hospitalization and improve weight gaining. lactoferrin decreased duration of O2 requirement, antibiotics treatment and hospital stay among preterm neonates.

Key words: Lactoferrin (LF), Late-onset sepsis (LOS) , Preterm neonates.

INTRODUCTION

Neonatal sepsis is a worldwide public health problem, with higher incidence in the developing countries [1]. Despite advances in diagnosis and treatment, infections in the neonatal period remain a major cause of death in neonates especially preterm neonates. Globally, 3.1 millions of neonates die per year, 12 % of them due to sepsis or meningitis [2]. Neonates are at risk to acquire infections, especially preterm and low-birth-weight newborns. In addition to the high morbidity and mortality associated with neonatal sepsis, these patients are at high risk for impairment [3]. Therefore, several interventions, including intravenous immunoglobulin, glutamine, anti-staphylococcal monoclonal antibodies and granulocyte/granulocyte–macrophage colony-stimulating factors have been evaluated for reduction in rates of neonatal sepsis, but have not shown efficacy [4]. Given the failure of these approaches, lactoferrin (LF) prophylaxis, if effective, could be an important strategy to prevent infections in this period [4-5]. The first trial testing LF for the prevention of late onset sepsis was performed by Manzoni and coworkers in Italy. They found that the incidence of sepsis and death from sepsis were significantly lower in the LF-treated groups compared with the placebo [6].

Lactoferrin is the main whey protein in mammalian milk. It is an iron-binding glycoprotein that is important in innate immune host defense and has many biological properties. In human milk, its concentration peaks in the colostrum (7 mg mL) and then decreases to (1 mgmL), the rate of reduction being slower in the breast milk of premature neonates**.** This trend in concentration is suggestive of the role of this protein, in the pre-term infant, in preventing infectious diseases related to prematurity, with a natural function that could be more crucial in the smallest infants [7].

Direct antimicrobial effect on bacteria, fungi, viruses, and parasites, which occurs via anticell wall actions and leads to disintegration of the pathogen's action has been demonstrated against all membranes. Bovine LF is synergistic with many antimicrobials and antifungals, including fluconazole [8]. In addition, LF has ability to promote growth and differentiation of the immature gut; this ability seems to be related to LF concentration: it is maximum at the highest concentration, as in the milk of mothers of premature neonates [9]. Finally, LF has bifidogenic activity, enhancing the growth of the normal commensal microflora in the gut [10]**.**

SUBJECTS AND METHODS

A randomized controlled double-blind interventional pilot study was conducted in Neonatal Intensive Care Unit of Zagazig University Children's Hospital and ElQenayate Central Hospital. The Research Ethics Committee of Zagazig Faculty of Medicine approved the study and an informed consent was obtained from the parents of preterm infants before enrollment in the study. The study was done according to the Code of Ethics of the World Medical Association (declaration of Helsinki) for studies involving humans. Sixty Preterm neonates were included and randomly assigned into one of two groups, Lactoferrin group and control group, each group included thirty neonates. Inclusion criteria were: Preterm neonates delivered at gestational age ranging from 28 to less than thirty seven weeks and admitted within the first seventy two hours of life. Exclusion criteria were : Neonates older than thirty seven weeks gestational age, Early onset sepsis (before the third day of life), Underlying gastrointestinal problem that prevent oral intake , Predisposing conditions that increase the risk of sepsis such as chromosomal abnormalities, congenital disorders; structural brain anomalies, spina bifida, inborn errors of metabolism and history of surgery or expected need for surgical interference , family background of cow milk allergy, and whose parents refuse to participate in the study. **All preterm neonates included were subjected to the following:**

1. Thorough history taking including:

- Gestational age was assessed by menstrual history, early ultrasound scan or the new Ballard score [11]**.**
- Sex
- Postnatal age
- Mode of delivery
- Pregnancy complications
- Need for mechanical ventilation or CPAP
- Central venous line insertion
- Date of onset of enteral feeding
- Date of full enteral feeding and signs of feeding intolerance: in the form of abdominal distension, vomiting and gastric residual volume > 50% [12].
- Duration of hospital stay
- Duration of antibiotics therapy

2. Clinical examination including:

- Growth parameters: weight, length and head circumference
- Vital signs: heart rate, respiratory rate, temperature and blood pressure
- Cardiovascular system examination: heart rate, blood pressure, skin perfusion, pulsations, heart sounds and murmur
- Chest examination: respiratory rate, signs of respiratory distress and abnormal adventitious sounds
- Gastrointestinal examination for signs of feeding intolerance and organomegaly
- Central nervous system: activity, neonatal reflexes, abnormal tones and seizures

3. Laboratory investigations:

- **Complete blood count (CBC):** was done at enrollment and every week thereafter till 4th week by Sysmex x5-800 (Sysmex Corporation, Japan). .
- **C-reactive protein (CRP):** CRP was done by Cobas 8000 (roche) at enrollment and every week till 4th week. CRP more than 10 mg\dl was considered elevated [13] **.**

4. Follow up:

Follow up of all neonates was done daily including:

- Age at which baby reach full enteral intake
- Feeding intolerance
- Blood product transfusions
- Development of clinical sepsis according to **Resch and coworkers** [14]

Empirical antibiotics in the form of ampicillin with gentamycin were started at the first suspicious of LOS. Antibiotics therapy was modified according to culture results.

- Development of necrotizing enterocolitis (NEC) using Bells staging **[15]**
- Development of bronchopulmonary dysplasia (BPD) [16]
- Laboratory follow up every week till fourth

week. Neonates with suspected LOS (14 neonates in LF group and 24 in Control group) later to randomization were investigated by CBC and CRP at first suspicion of sepsis and one week later. Blood culture as well as chest x-ray, urine culture and lumbar puncture as suggested by the neonatologist were performed at first suspicion of sepsis. Late onset sepsis was proven in (7 neonates in LF group and 19 in Control group) by a positive blood culture in the presence of clinical symptoms and signs of infection.

5. Intervention :

Group I : 30 preterm infants received oral lactoferrin at a dose of 100 mg/day and

Group II : 30 preterm infants received distilled water continued till the end of the study (28 days).

1.***Statistical analysis:*** The collected data were analyzed by computer using Statistical Package of Social Services version 24 (SPSS), Data were represented in tables **.**Suitable statistical tests of significance were used after checked for normality. The results were considered statistically significant when the significant probability was less than 0.05 ($P < 0.05$)

RESULTS

Results are presented in tables {1-11}.Both Lactoferrin and Control groups were comparable as regards gestational age, mode of delivery, sex, body weight at enrollment (table 1) as well as maternal risk factors including prolonged rupture of membranes, hypertension, UTI and DM table (2). The frequency of late onset sepsis was significantly lower in lactoferrin group (table 4). There was statistically significant lower frequency of feeding intolerance, lower duration of mechanical ventilation, central line insertion and oxygen supplementation with less NICU stay duration among lactoferrin supplemented group (table 4-5). Coagulase-negative staphylococci and Klebsiella were the most common organisms found among the septic neonates (table11). Hemoglobin level is significant higher in lactoferrin group started from the first week (table 7) also platelets count starting two weeks after initiation of lactoferrin and thereafter (table 9). weight gain was significantly more started from the third week (table 6).

Table (1): Gestational age , sex Birth weight, mode of delivery and resuscitation of the studied groups.

Item		The studied groups: lactoferrin group (n=30) Mean ± SD Median (Range)		The studied groups: Control group (n=30) Mean ± SD Median (Range)		MWt	P-value
Gestational age (Weeks)		33.57±2.28 33 (28-36)		33.8 ± 2.14 34 (28 – 36)		430.5	0.767 (NS)
Birth weight (gram)		1831.3± 520.9 1800 (1100 – 3000)		1903.3± 555.1 1945 (900 – 2930)		415.50	0.609
		n	%	n	%	χ^2	
Sex	Female	16	53.3 %	14	46.7 %	Fisher exact	1.000 (NS)
	Male	14	46.7 %	16	53.3 %		
Mode of delivery	NVD	9	30%	6	20%	Fisher exact	0.522
	CS	21	70%	24	80%		
Resuscitation	Oxygen	11	36.7%	9	30.0%	0.300	0.785
	ETT	0	0.0%	1	3.3%	1.01	1.000

Mann Whitney U test. . $\chi 2$: Chi square test

$P > 0.05$ is not significant. EET: endotracheal tube

$P < 0.05$ is significant. NVD :normal vaginal delivery

CS: cesarean section

Table (2): Maternal medical history among the studied groups

Maternal medical history	Total n=60	The studied groups				Chi-square test	P-value
		Lactoferrin group(n=30)		Control group (n=30)			
		n	%	n	%		
PROM	22	9	30.0%	13	43.3%	1.14	0.422
Hypertension	21	9	30.0 %	12	40.0%	0.659	0.589
UTI	9	5	16.7%	4	13.3%	0.131	1.000
DM	8	2	6.7 %	6	20%	2.30	0.254

PROM; premature rupture of membrane UTI; Urinary tract infection
DM: Diabetes mellitus P > 0.05 is not significant.

Table (3): CBC at admission among the studied groups

Variables	Lactoferrin group(n=30)	Control group (n=30)	t-test	P- value
	Mean ± SD Median (Range)	Mean ± SD Median (Range)		
Hemoglobin (gm/dl)	16.51 ± 1.95 19.8(14 -21)	16.92 ± 1.91 17(13- 21)	-0.815	0.419 (NS)
			MWt	**P- value**
TLC (x 10^9/L)	13.09 ± 6.36 12(5 -31)	13.71 ± 4.6 13(6 -27)	399.50	0.455
Platelet (x 109/L)	275 ± 120.1 256.5(49 -507)	224.07 ± 73.6 220(106 -405)	326.00	0.098

Mann- Whitney test CBC: complete blood cell count
P > 0.05 is non-significant

Table (4): Clinical course among the studied groups

Variable	The studied groups				χ^2	P-value
	Lactoferrin group(n=30)		Control group (n=30)			
	n	%	N	%		
CPAP –MV	17	56.7	25	83.3	5.07	0.024*
Vomiting	11	36.7	14	46.7	0.617	0.601
Central Venus line	14	46.7	22	73.3	4.44	0.035*
Suspect LOS	15	50.0	25	83.3	7.50	0.013*
Duration on CPAP –MV (days)					**MWt**	
Mean ± SD	5.71 ± 4.19		9.24 ± 3.75		88.500	0.001*
Median (Range)	4(2– 15)		8(5– 16)			

Mann Whitney U test, χ^2 =Chi-square test,
*P < 0.05 is significant, P > 0.05 is non-significant
CPAP: continuous positive airway pressure
MV: mechanical ventilation

Table (5): Secondary outcomes among the studied groups

Variable in (Days)	Lactoferrin group (n=30)	Control group (n=30)	MWt	P- value
	Mean ± SD Median (Range)	Mean ± SD Median (Range)		
Time to full enteral intake	12.53 ± 5.52 12.5(4 -25)	17.62 ± 7.94 17(7- 35)	253.500	0.024* (S)
Antibiotic use duration	11.97 ± 6.89 12.5(3 -29)	15.57 ± 7.3 15(4 -30)	314.00	0.044* (S)

Variable in (Days)	Lactoferrin group (n=30) Mean ± SD Median (Range)		Control group (n=30) Mean ± SD Median (Range)		MWt	P- value
Hospital stay	14.4 ± 6.3 12(5 -29)		20.07 ± 9.76 18.5(6 -38)		298.50	0.025* (S)
	n	**%**	**n**	**%**	χ^2	**P-value**
BPD	0	0.0	4	15.4	4.97	0.041*
NEC	0	0.0	2	6.7	2.06	0.492
Feeding intolerance	13	43.3	**22**	73.3	5.01	0.035*
Mortality	2	6.7	**4**	13.3	0.741	0.671

Mann- Whitney test *P < 0.05 is significant
χ2 =Chi-square test,
P > 0.05 is non-significant (NS).
BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis

Table (6): Weight gain among of the studied groups

Weight (gram)	Lactoferrin group (n=30) Mean ± SD Median (Range)	Control group (n=30) Mean ± SD Median (Range)	P- value
weight at 1st week	1735.6 ± 500.7 1750(1050-2700)	1833.3 ± 552.9 1760(850-2900)	0.491
weight at 2nd week	1759.3 ± 471.9 1730(1050-2850)	1843.9 ± 509.1 1780(1000-2840)	0.539
weight at 3rd week	2154±483.92 2000(1500-3400)	1811.53 ±450 1800(1200-2980)	**0.014***
weight at 4th week	2387.14 ± 568.05 2150(1690-3500)	2076.53 ± 378.4 2000(1500-2900)	**0.034***

Mann- Whitney test, P > 0.05 is not significant

Table (7): Comparison of hemoglobin follow up among the studied groups

Hemoglobin(gm/dl)	Lactoferrin Group(n=30) Mean ± SD Median (Range)	Control group(n=30) Mean ± SD Median (Range)	P- value of t-test
at admission	16.51 ± 1.95 19.8(14 -21)	16.92 ± 1.91 17(13- 21)	0.328
1st week	14.28 ± 2.2 14.5(10-18)	11.78 ± 2.19 12(7.6-16)	0.000*
2nd week	13.3 ± 2.2 13.2(8-17)	10.78 ± 2.12 11(7-15.5)	0.000*
3rd week	13.5±1.38 14(10-15)	11.9 ±2.10 11.7(8-15.8)	0.005
4th week	13.8 ± 0.67 13.9(11.9-15)	11.7 ± 1.55 12(8-15)	0.000*
P-value of Freidman	0.000* (HS)	0.000* (HS)	

P > 0.05 is not significant
Freidman test for comparison between all through follow up.

Table (8): Comparison of TLC follow up among the studied groups

TLC (x 10^9/L)	Lactoferrin group(n=30)	Control group(n=30)	P- value of MWt
	Mean ± SD Median (Range)	Mean ± SD Median (Range)	
at admission	13.09 ± 6.36	13.71 ± 4.6	0.455
	12(5 -31)	13(6 -27)	
1st week	13.56 ± 7.97	13.9 ± 7.2	0.695
	12(4-38)	13(5-33)	
2nd week	14.42 ± 6.63	15.37 ± 6.63	0.607
	12.6(5-30)	13(5.6-33)	
3rd week	11.24±5.09	13.2 ±5.4	0.091
	9.50(5-30)	11(7-28)	
4th week	9.06 ± 2.61	10.11 ± 2.18	0.086
	8.5(5-15)	9.7(7-15)	
P-value of Freidman	0.000* (HS)	0.000* (HS)	

Mann- Whitney test, P > 0.05 is not significant, NS: Not significant.
Freidman test for comparison between all through follow up.
TLC: total leukocytic count

Table (9): Comparison PLT follow up among the studied groups

PLT(x 10^9/L)	Lactoferrin group(n=30)	Control group(n=30)	P- value of MWt
	Mean ± SD Median (Range)	Mean ± SD Median (Range)	
at admission	275 ± 120.1	224.07 ± 73.6	0.098
	256.5(49 -507)	220(106 -405)	
1st week	246.8 ± 138.05	178.4 ± 134.9	0.052
	234(10-506)	157(10-485)	
2nd week	307.4 ± 158.7	184.9 ± 138.04	0.004*
	360(4-562)	198(2-452)	
3rd week	339.3±130.9	248.6 ±131.7	0.016*
	384(36-511)	240(24-490)	
4th week	385.9 ± 88.76	334.9 ± 106.06	0.066
	426.5(189-495)	340(150-530)	
P-value of Freidman	0.000* (HS)	0.000* (HS)	

Mann- Whitney test, P > 0.05 is not significant
Freidman test for comparison between all through follow up PLT:platelets

Table (10): Comparison of CRP follow up among the studied groups

CRP	Lactoferrin Group		Control group		P- value
	n	**%**	**n**	**%**	
CRP at 1st week	**(n=30)**		**(n=30)**		
elevated	11	36.7	25	83.3	**0.000***
CRP at 2nd week	**(n=29)**		**(n=29)**		
Elevated	14	48.3	21	72.4	**0.060**
CRP at 3rd week	**(n=28)**		**(n=26)**		
Elevated	6	21.4	9	34.6	**0.281**
CRP at 4th week	**(n=28)**		**(n=26)**		
Elevated	0	0.0	0	0.0	**1.000**

χ^2 =Chi-square test ,P > 0.05 is not significant,
CRP more than10 mg\dl was considered elevated {24}.
CRP: C-reactive protein

Table (11): Comparison of Blood culture results among the suspected septic neonates

Blood culture		Lactoferrin Group n = 14		Control group n = 24		P- value
Positive growth		7		19		**0.015***
Isolated organisms	E.coli	1	7.1	4	16.7	
	CoNS	2	14.2	5	20.8	
	Klebsiella	4	28.5	8	33.3	
	Pneomococci	0	0.0	1	4.2	
	MRSA	0	0.0	1	4.2	

, P > 0.05 is not significant

CONS : coagulase negative staphylococci

DISCUSSION

Lactoferrin (Lf) is an iron-binding glycoprotein of the transferrin family, which is expressed in most biological fluids with particularly high levels in mammalian milk. Its multiple activities lie in its capacity to bind iron and to interact with the molecular and cellular components of host and pathogens. Lf can bind and sequester lipopolysaccharides, thus preventing pro-inflammatory pathway activation, sepsis and tissue damages. LF is also considered a cell-secreted mediator that bridge the innate and adaptive immune responses [17]. In agreement with ***Akin et al*** [18] study, feeding intolerance assessed by frequency of vomiting and feeding residuals, need for central venous line and the duration of mechanical ventilation were less in preterm infants who received Lactoferrin than Control group.

Frequency of late onset sepsis was significantly higher among infants in the Control group than in the Lactoferrin group and number of sepsis episodes was increased in Control group. Our results are in concordance with ***Manzoni and coworkers*** [6].When we evaluated Lactoferrin effect on growth we found significant increase in body weight in Lactoferrin group more than control one in third to fourth weeks after enrollment attributed to better feeding tolerance and achieving full enteral feeding earlier. No significant difference between both groups was observed as regards BPD since only few of our studied infants developed BPD. This was in agreement with the result of a Cochrane analysis in 2015 [19] As regards effect of lactoferrin on preventing NEC, we found no significant difference in its incidence between both studied groups. This was in agreement with ***Akin et al*** [17] found that number of infants who developed NEC was lower in Lactoferrin group, however, it didn't reach a statistically significant difference. We found significant decrease in the duration of antibiotics and hospital stay that may be related to decreased number of sepsis episodes in Lactoferrin group. Mortality occurred in Control group more than Lactoferrin group but didn't reach a statistically significant difference which may be due to small sample size. In our study, preterm infants in the group receiving LF showed significantly higher platelets count starting two weeks after initiation of lactoferrin and thereafter while hemoglobin level was significantly higher in Lactoferrin group one week after lactofenin initiation and thereafter. As we compared CBC and CRP among infants who developed sepsis in both Control and Lactoferrin groups of our study, no significant difference was reported between them at first suspicion of sepsis. We noticed significantly decreased level of CRP in preterm infants receiving lactoferrin after one week and thereafter more than septic infants in Control group. According to blood culture results in our study, positive blood culture (proven LOS) was found in 19 Control infants versus 7 Lactoferrin receiving ones however, this didn't reach a statistically significant difference. The main pathogens isolated in preterm infants who developed LOS in our study were Klebsilla and Coagulase negative Staphylococci (CONS) in both Control and Lactoferrin groups without demonstrating any significant difference between them. In general, LF binds to the lipoteichoic acid on the surface of Gram- positive organisms, disrupting the bacteria cell membrane and decreasing biofilm formation. Among Gram-negative bacteria LF causes disruption of bacterial biofilms of specific microorganisms [20], such as Escherichia coli and Klebsiella [21]. LF kills antibiotic resistant Klebsiella pneumoniae in mice [22]. According to Manzoni et al, efficacy of lactoferrin on gram-positive LOS may be limited [23].

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