Early versus Late Lactoferrin in Prevention of Neonatal Sepsis

Thesis

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List of Abbreviations

Abb.	Full term

AAP.....: *American Academy of Pediatrics*
ARDS.....: *Acquired respiratory distress syndrome*
BLF.....: *Bovine lactoferrin*
BPD.....: *Bronchopulmonary dysplasia*
CBC.....: *Complete blood count*
CDC .....: *Centers for Disease Control and Prevention*
CRP.....: *C reactive protein*
CSF.....: *Cerebrospinal fluid*
CXR.....: *Chest x ray*
DIC.....: *Disseminated intravascular coagulation*
DM .....: *Diabetes mellitus*
DNA .....: *Deoxyribonucleic acid*
ECHO .....: *Echocardiography*
E-Coli.....: *Escherichia coli*
ELBW .....: *Extremely low birth weight*
EOS.....: *Early onset sepsis*
EPO.....: *Erythropoietin*
ETT.....: *Endotracheal tube*
GBS.....: *Group B streptococci*
G-CSF.....: *Granulocyte colony-stimulating factor*
Hb .....: *Hemoglobin*
HCT .....: *Hematocrit*
HLF.....: *Human lactoferrin*
IAP.....: *Intrapartum antibiotics prophylaxis*
IFN.....: *Interferon*
IL.....: *Interleukin*

List of Abbreviations (Cont....)

Abb.	Full term
LBW	*Low birth weight*
LF	*Lactoferrin*
LGG	*Lactobacillus Rhamnosus GG*
LOS	*Late onset sepsis*
LPS	*Lipopolysaccharide*
LSCS	*Lower segment cesarean section*
NEC	*Necrotizing enterocolitis*
NICU	*Neonatal intensive care unit*
NPO	*Nil per Os*
NS	*Neonatal sepsis*
PAI-1	*Plasminogen activator inhibitor-1*
PAMG-1	*Placental alpha microglobulin-1*
pH	*Power of hydrogen*
PLT	*Platelets.*
PMN	*Poly morphnuclear cells*
PPV	*Positive pressure ventilation*
Pulm hge	*Pulmonary hemorrhage*
RDS	*Respiratory distress syndrome*
rhTFF3	*Recombinant human Trefoil Factor 3*
ROP	*Retinopathy of prematurity*
S. Ferritin	*Serum ferritin.*
sICAM-1	*Soluble intracellular adhesion molecules-1*
SD	*Standard deviation*
SGA	*Small for gestational age*
SPSS	*Statistical Program for social science*
SVD	*Spontaneous vaginal delivery*
t PA	*Tissue plasminogen activator*
TAT	*Thrombin – antithrombin III complex*

List of Abbreviations (Cont...)

Abb.	Full term
TLC	*Total leucocytic count*
TNF alpha	*Tumor necrosis factor alpha*
TPN	*Total parenteral nutrition*
U/S	*Ultrasound*
VLBW	*Very low birth weight*
WBC	*White blood cells*

Abstract

Background: sepsis related morbidity and mortality is a concern in neonatal intensive care units (NICUs) specially in preterm and low birth weight (LBW) infants who are more vulnerable due to immaturity of immune defenses and protective barriers. Lactoferrin is the main whey protein in mammalian milk, and is involved in innate immune host defenses. In vitro, Bovine lactoferrin (BLF) shows potent direct antimicrobial activity against all types of pathogens, which occurs via anti-cell wall actions and leads to disintegration of the micro-organism's membranes. BLF is also synergistic with many antimicrobials and antifungals, and promotes growth and differentiation of the immature gut.

Objective: to evaluate the effectiveness of oral bovine lactoferrin in prevention of neonatal sepsis and feeding intolerance in preterm neonates with comparison of early (1^{st} day) versus late (48-72 hours) lactoferrin administration; secondary aim was to study effect of lactoferrin supplementation on serum ferritin and follow up long term outcome (broncho-pulmonary dysplasia, retinopathy of prematurity and necrotizing enterocolitis).

Patient & methods: A prospective randomized, single blind, placebo controlled study was carried out on 180 preterm neonates admitted to the Neonatal Intensive Care Units of Ain Shams University Hospitals and Shobra General Hospital in the period from August 2014 to December 2015.Enrolled subjects were further randomly subdivided into three groups according to the dose regimen of lactoferrin supplementation. Early lactoferrin group (60) Preterm neonates received oral BLF 100 mg/day starting on day 1 and continued for 4–6 weeks or discharge whichever comes first. Late lactoferrin group (60) Preterm neonates received oral BLF 100 mg/day starting on day 3 (48hrs-72hrs) of life and continued as in early lactoferrin group. Control group (60) Preterm neonates received placebo in form of distilled water starting on day 1. History and clinical examination were carried out laying stress on signs of sepsis according to Tollner score; and laboratory investigations, CBC with differential cell count classified according to hematological scoring system (Rodwell score), CRP, blood culture and arterial blood gases when clinically indicated. Serum ferritin was done on day 14 of age. Radiological investigations were done when clinically indicated, data were analyzed using the statistical package for social sciences (SPSS).

Results: Early lactoferrin group included 25 males (41.7%) and 35 females (58.3%) with mean gestational age (32.37 ± 1.31weeks). Late

lactoferrin group included 23 males (38.3%) and 37 females (61.7%) with mean gestational age (32.58 ± 1.54 weeks). Control group included 33 males (55.0%) and 27 females (45.0%) with mean gestational age (32.45 ± 1.56 weeks). the incidence of late onset sepsis was significantly lower in early (10%) and late (26.7%) lactoferrin groups compared to control group (45%). Coagulase-negative staphylococci and Klebsiella were the most common organisms found among the septic neonates in the current study (38%, 26% respectively). There were highly significant decrease in age of full enteral intake among early lactoferrin group with mean value (10.04 ± 2.75) days compared to late lactoferrin group and control group with mean values (12.15 ± 2.75) days and (14.43 ± 4.47) days respectively.

Also there were highly significant reduction in total days of feeding stoppage among early and late lactoferrin groups with mean values (2.14 ± 1.75 days), (3.47 ± 1.82 days) respectively compared to control group with mean values (4.92 ± 3.65 days), and among early lactoferrin group compared to late lactoferrin group. Moreover the results of the present study revealed that there were statistically significant increase in occurrence of abdominal distension in control group 48.3% as compared with early 1.7% and late 3.3% lactoferrin groups.

There were no statistically significant differences between studied groups as regard gastric residual, vomiting and diarrhea. Moreover, NEC incidence and staging showed no statistically significant differences between studied groups, nevertheless we can see the difference in the percentage of occurrence of NEC higher in the control group (6.7%)) than that in early lactoferrin group (1.7%) and late lactoferrin group (3.3%). Also there were non-significant statistical differences between studied groups as regard incidence of broncho-pulmonary dysplasia, ROP and pulmonary hemorrhage. Also there were no statistically significant differences between studied groups as regard serum ferritin withdrawn in 2nd week of life.

Statistically significant decrease in mortality was detected among early lactoferrin group (3.3%) compared to control group (13.3%).
In the current study the duration of total parenteral nutrition was significantly shorter in early lactoferrin group with mean value (4.24 ± 2.66 days) compared to control group with mean value (8.83 ± 7.24 days).

Also, NICU stay duration was significantly decreased in early and late lactoferrin groups with mean values (12.63 ± 3.84 days), (14.63 ± 2.80 days) respectively compared to control group with mean value (17.70 ± 3.56 days).

Conclusion: Preterm neonates supplemented with oral bovine lactoferrin had significantly lower incidence of late onset sepsis compared to control group. Oral bovine lactoferrin supplementation significantly decreased feeding intolerance, parenteral nutrition and NICU stay duration among preterm neonates. Early lactoferrin administration was significantly more effective than late lactoferrin administration in prevention of late onset sepsis.

Keywords: Lactoferrin, Neonatal sepsis, Preterm.