Effect of Bovine Colostrum On CD 4–T cells, Prevention of Late Onset Sepsis and Necrotizing Enterocolitis in Preterm Neonates

Thesis

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List of Abbreviations

Abb.	Full term
AAP	*American Academy of Pediatrics*
ACOG	*American College of Obstetricians and Gynecologists*
APC	*Antigen presenting cells*
BLF	*Bovine lactoferrin*
BW	*Birth weight*
C3	*Complement 3*
C5a	*Complement 5a*
CD	*Cluster of differentiation*
CD62L	*L-selectin*
CLA	*Conjugated linolenicacid*
CONS	*Coagulase-negative staphylococci*
CRP	*C-reactive protein*
CSF	*Cerebrospinal fluid*
CSF	*Colony-stimulating factors*
CT	*Computed tomography*
DIC	*Disseminated intravascular coagulation*
EGF	*Epidermal growth factor*
EOS	*Early onset sepsis*
FoxP3	*Nuclear transcription factor Forkhead box P3*
GA	*Gestational age*
GALT	*Gut associated lymphoid tissue*
GBS	*Group B streptococcal*
GH	*Growth hormone*
HLA-DR	*Human leukocyte antigen – antigen D related*
I/T ratio	*Immature to total neutrophils ratio*
IFN-gamma	*Interferon-gamma*
Ig	*Immunoglobulins*
IGF	*Insulin like growth factor*

List of Abbreviations (Cont...)

Abb.	Full term
IL	*Interleukin*
IL-1β	*Interleukin 1 beta*
IVIG	*Intravenous immunoglobulins*
LOS	*Late onset sepsis*
MDR GNB	*Multidrug-resistant Gram-negative bacilli*
MHC-class-I	*Major histocompatibility complex class-1*
NEC	*Necrotizing enterocolitis*
NICUs	*Neonatal intensive care units*
NO	*Nitric oxide*
NPO	*Nulla per os*
PAF	*Platelet-activating factor*
PAMP	*Pathogen associated molecular pattern*
PCR	*Polymerase chain reaction*
PDGF	*Platelet derived growth factor*
PE	*Preeclampsia*
PLT	*Platelets*
PMNs	*Polymorphnuclear cells*
PROM	*Premature rapture of membranes*
PRR	*Pattern-recognition receptor*
PT	*Prothrombin time*
PTT	*Partial thromboplastin time*
RBCs	*Red blood cells*
RD	*Respiratory distress*
rhEPO	*Recombinant human erythropoietin*
rhG-CSF	*Recombinant human granulocyte colony-stimulating factor*
TCR	*T-cell receptor*
TGF	*Transorfming growth factor*

List of Abbreviations (Cont...)

Abb.	Full term

TGF-β.....*Tumor growth factor beta*
TLR.....*Toll-like receptor*
TNF-α.....*Tumor necrosis factor alfa*
Treg cells.....*T regulatory cells*
VEGEF.....*Vascular endothelial growth factor*
VLA-1.....*Very late antigen-1*
VLBW.....*Very low birth weight*
WBCs .....*White blood cells*
Wt.....*Weight*

INTRODUCTION

Late-onset sepsis (LOS) and Necrotizing enterocolitis (NEC) are a major cause of mortality and morbidity, including adverse long-term neurodevelopmental outcomes in preterm infants ***(Dong and Speer, 2014)***.

Immaturity of the immune system is more pronounced in preterm neonates. In fact, they have deficiencies in both innate and adaptive immunity and in the interaction between these two systems ***(Strunk et al., 2011).*** So they are at higher risk of acquiring infections, and this is a significant contributor to mortality in this group ***(Laws et al., 2007).***

The incidence of LOS varies inversely with gestational age and birth weight ***(Hornik et al., 2012)***.

LOS and NEC are primarily occurs in premature and very low birth weight (VLBW) babies, the incidence varying from 5 to 10% in various neonatal intensive care unit (NICUs) ***(Thompson and Bizzarro, 2008)***.

Intestinal mucosa as a barrier contains a large number of immune cells, especially T lymphocytes which are localized within gut-associated lymphoid tissue (GALT) or diffusely throughout the intestinal lamina propria and overlying single layered epithelium ***(Agace, 2008).*** T-regulatory cells are a subset of CD4 T cells that are capable of regulating and suppressing the immune system and are essential for intestinal

immune homoeostasis through regulation of innate and adaptive host responses ***(Maloy and Powrie, 2001).***

Many researchers believe that an exaggerated inflammatory response mounted by immature intestinal epithelial cells in response to abnormal intestinal colonization plays a vital role in the pathogenesis of NEC ***(Grave et al., 2007)***, and bacteria belonging to Enterobacteriaceae have often been linked to NEC ***(Hsueh et al., 2003)***.

Colonization with commensal bacteria soon after birth is essential for the development of normal intestinal function; however, this process is often altered in premature babies in NICUs, leading to colonization with pathogenic bacteria ***(Hsueh et al., 2003)***.

Colostrum is the first milk secreted at the time of parturition, differing from the milk secreted later, by containing more lactalbumin and lactoprotein, and also being rich in antibodies that confer passive immunity to the newborn, also called “foremilk”. It lasts for 2- 4 days after the lactation is started. Colostrum is very important component of the breast milk and it has role to play in immune system of every mammal. The use of human milk has been consistently shown to reduce the incidence of NEC and sepsis ***(Kafetzis et al., 2003)***.

Immunoglobulins in human milk reduce the adherence of pathogenic bacteria to the gut epithelium and thus decrease colonization by such bacteria ***(Van de Perre, 2003)***.

Other anti-infective factors and growth factors in human milk are also believed to play an important role. However, the use of exogenous oral immunoglobulins has not been shown to reduce NEC or sepsis ***(Foster and Cole, 2004)***.

A possible reason could be that anti-infective factors act in synergy and a single agent may not be effective. Commercially available bovine colostrum has high concentrations of anti-infective factors such as immunoglobulins, lactoferrin, organism-specific antibodies, lactoperoxidase, insulin-like growth factors and transforming growth factors. These components have substantial homology to their human counterparts ***(Balachandran et al., 2017)***.

Bovine colostrum has been tried in the treatment of Escherichia coli and Shigella ***(Ashraf et al., 2001)*** and Rotavirus diarrhea in children, Helicobacter pylori infection in children and E. coli intestinal infection in term and preterm neonates ***(Lodinová - Zádníková et al., 1987)***.

No major adverse effects were reported in any of the studies using bovine colostrum in infants and preterm babies ***(Rathe et al., 2014)***.

In an in vitro study, the authors showed that bovine colostrum significantly reduces the adherence of various Enterobacteriaceae species—known to be associated with NEC—to human intestinal epithelial cells ***(Aunsholt et al., 2014)***.

A randomized controlled trial has shown that the use of bovine lactoferrin reduced the incidence of neonatal sepsis ***(Manzoni et al., 2010).***

Till date, there are no studies in neonates on the use of bovine colostrum for the prevention of NEC.

In view of the above observations, we hypothesize that bovine colostrum by its content of immunoglobulin, lactoferrin and growth factors will decrease the incidence of late onset sepsis and necrotizing enterocolitis in artificially fed preterm neonate.