

Role of Colostrum in Gastrointestinal Infections

Pawan Rawal, Vineet Gupta and B.R. Thapa

Division of Pediatric Gastroenterology, Department of Gastroenterology, Post Graduate Institute Medical Education and Research (PGIMER), Chandigarh, India

ABSTRACT

Colostrum is breast milk produced after the birth of the newborn and lasts for 2-4 days. Colostrum is very important part of breast milk and lays down the immune system and confers growth factors and other protective factors for the young ones in mammals. This is the source of passive immunity transferred to the baby from the mother. The biological value of bovine colostrum in present day medical practice is documented in clinical trials and large databases containing case reports and anecdotal findings. The main actions include an antibacterial effect and modulation of immune response with the ability to neutralize lipopolysaccharides arising from gram negative bacterial pathogens. It has been found to be effective in infantile hemorrhagic diarrheas, other diarrheas and reduces the likelihood of disease progressing to hemolytic uremic syndrome. It has also been tested in H pylori infection and diarrhea in immunodeficiency. Side effects of clinical relevance are limited to possible intolerance due to lactose and sensitivity to milk proteins. [Indian J Pediatr 2008; 75 (9) : 917-921] E-mail-brthapa1@yahoo.co.in

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Before the birth, the fetus is absolutely sterile and is lying in the sterile atmosphere. At the time of delivery the newborn is exposed to micro-flora of birth canal and handling by the medical attendants or midwifery or otherwise hits the ground. The newborn from the sterile state is suddenly exposed to the environment full of micro-organisms and other agents. There has to be ready-made immunity to immunize. But at the same time nature provides the breast milk to which baby starts suckling soon after the birth. The first breast milk produced after giving birth is known as colostrum. The colostrum is very important component of breast milk and lays the foundation for immune system of every mammal. This contains protective antibodies to prevent infections in the newborn called passive immunity. This also provides vital nutrients for tissue development, growth and energy. The mother's lifetime achievements pass to the baby through colostrum.^{1,2}

Colostrum is a premilk substance produced immediately after birth. This lasts for 2-4 days after the lactation has started. This is the source of fats, proteins, sugars and micronutrients in the form of vitamins and minerals. This is very rich source of secretory IgA to give protection to gastrointestinal tract (GIT) from various infections in the new born. Certain maternal conditions

like eclampsia, diabetes and anemia can affect the composition of colostrum.¹ Historically colostrum has been used for various illnesses in India for thousands of years. Colostrum has been used for treatment of rheumatoid arthritis. Sabin, an anti-polio vaccine was prepared from bovine colostrum. Colostrum has been reported to be very safe and effective for its use in repair of tissue as well as for enhancing the immunity.³⁻⁵

Cow colostrum is richer in IgG (20%) as compared to IgG (2%) in human colostrum. The bovine colostrum also contains growth factors, so cow has been accepted as universal donor of colostrum to humans.² Colostrum is harvested within first few hours of calving from dairy animals. The herds of cows are kept under close supervision in good state of hygiene, without exposure to antibiotics, pesticides and anthelmintics. They are monitored according to FDA criteria. The colostrum collected within 24 hours contain maximum substances but less in amount, colostrum collected later will be more but contain less immunoglobulins.

IMPORTANT HEALTH FACTORS IN COLOSTRUM

There are ninety known components in the colostrum. There are two primary components of colostrum: immune factors and growth factors. Colostrum also contains vitamins, minerals and amino acids according to need of neonates.

Correspondence and Reprint requests : Dr. B.R. Thapa, Professor and Chief, Division of Pediatric Gastroenterology, Department of Gastroenterology, Post Graduate Institute Medical Education and Research (PGIMER), Sector 12, Chandigarh- 160012.

General immunity

Bovine colostrum (BC) has been studied for important therapeutic effect in various chronic infections like bacterial, viral, parasitic or fungal. When given as a nutritional supplement in certain chronic conditions like chronic fatigue syndrome, infectious diarrhea, sinusitis and fibromyalgia, it leads to immunological boosting. There are 4 immune enhancing factors in the bovine colostrum, like growth factor, immunoglobulin, putative permeability fraction and fraction containing enzymes protein, odd peptides *etc.*⁶

IMMUNE FACTORS

(a) Specific Antibodies. The immune factors obtained from the mother have shown to fight against viruses, bacteria, yeast and fungus. There are around 20 specific antibodies in the colostrum to fight microbes like *E.coli*, *Salmonella*, *Rotavirus*, *Candida*, *Streptococcus*, *Styphylococcus*, *Cryptosporidium*, *H. pylori etc.*^{3,4,7,8} There is adequate transfer of passive immunity against diarrhea.⁹

(b) Immunoglobulins: Immunoglobulins are superior in both treatment and prevention of viral infections, bacterial infections, allergies, yeast and fungus.⁷ There are five types of immunoglobulins IgA, IgD, IgE, IgG and IgM. Bovine colostrum contains 8%-25%, IgG whereas human colostrum contains 2% IgG. These are protein molecules which have important role in the body to fight against infections.

IgA: operates in tears, saliva and blood (secretory IgA in the gut)

IgD: anti-viral

IgE: anti-viral

IgM: anti-bacterial

IgG: abundant in lymph and blood, and neutralizes toxins.

(c) Prolin rich polypeptide (PRP): PRP has been shown to stimulate the thymus to regulate the immune system in the body. PRP stimulates the weakened immune system and also stabilizes hyperactive immune system due to autoimmune diseases and allergies in the body.

(d) Lactoferrin. This is an iron binding protein that plays important role against cancer cells and also has anti-viral, anti-bacterial and anti inflammatory properties. Lactoferrin can prevent reproduction of bacteria and releases iron for the red blood cells. Lactoferrin receptors have been identified on the immune cells and is involved in release of cytokines. Lactoferrin has been implicated in treatment of diseases like cancer, HIV, herpes, chronic fatigue, candidiasis and other infections.¹⁰

(e) Cytokines. These are the interleukines. They

regulate duration and intensity of immune responses. They boost T-cells activity and have antiviral and antitumor activity. Interleukine-10 has an antiinflammatory activity in arthritis and during injury.¹¹

(f) Lymphokines. These are the peptides involved in mediating the immune response.

(g) Oligopolysaccharides and glycoconjugate sugars. They attract and bind to pathogenic bacteria and prevent their entry in the mucosal lining. They block the entry of *Salmonella*, *Cryptosporidium* and *Clostridia* in leaky gut syndrome.^{5,9}

(h) Glycoproteins and trypsin inhibitors. They inhibit the breakdown of colostrum in the gut; hence it can have its effect in the GIT. Colostrum inhibits the *H.pylori* in stomach, so has antiulcer activity. They protect the immune and growth factors in GIT.⁸

(i) Lysozyme. This is an acid resistant hydrolyzing agent, that is capable of destroying bacteria and viruses on contact. This is being added to commercial baby food.

(j) Leucocytes. They stimulate interferon production and slow down the viral reproduction. Interferon also inhibits cellular wall penetration.¹²

(k) Lactoperoxidase-thiocyanate, peroxidase and xanthine oxidase enzymes. They oxidize bacteria by generating the release of hydrogen peroxide.

(l) Lactalbumins. Lactalbumins are active against many forms of cancers and viruses. Lactalbumins also raise the serotonin levels, decrease the cortisol levels and improve the mood under stress.^{4,5}

GROWTH FACTORS

The vital growth factors in the human colostrum are similar to that of bovine colostrum. They stimulate growth, help in regeneration and accelerate the repair of aged original muscle, skin, collagen, bone, cartilage and nerve tissue. Growth factors also stimulate the body to burn fat for fuel instead of the body's muscle tissue in times of fasting and lean built. Growth factors have also been used as an effective topical application for burns, injuries and skin rejuvenation.¹³

Insulin like growth factors

The insulin like growth factors (IGF) are of two types: IGF-I and IGF-II. Both promote the muscle and body growth. They are present in the BC and have similar effect as human growth hormone (HGH).^{13, 14} However, more clinical trials are required to show that IGFs in BC have similar effect as HGH.

Epidermal growth factor (EGF). It is also present in BC and stimulates the repair process at the site of

Role of Colostrum in Gastrointestinal Infections

inflammation. The EGF plays an important role in preventing bacterial translocation and stimulating gut immunity.¹⁵

Transforming growth factor (TGF)

Transforming growth factor is present in small quantity in colostrum. The TGF stimulates gastrointestinal growth and repair, inhibit acid secretion, stimulate mucosal restitution after injury and increases gastric mucin concentration. Both TGF alpha and TGF beta are helpful in the repair and integrity of epithelium of GIT.¹⁵

Platelet derived growth factor (PGDF)

The PGDF has mitogenic activity for fibroblasts and smooth muscle cells. They are very helpful for healing ulcer.

Bovine colostrum growth factor (BCGF)

This also has similar effect and enhances the immunity. The growth factors in the BC are responsible for the synthesis of protein. Excess of fat is utilized whereas muscle tissue is preserved. During the illness, post surgery and injury, the colostrum is very helpful for recovery and for rebuilding of tissues.^{2,16}

Cytokines and lymphokines

They trigger the acute response for chemotaxis and protein synthesis and play as immunomodulators.¹⁷

Lactoferrin

This is an iron binding glycoprotein which facilitates iron absorption and also acts as antimicrobial agent. It promotes the growth of fibroblasts and intestinal epithelial cells. It plays a role in gut immunity.

Transfer factor (TF)

Transfer factor present in BC is an immunoregulatory and immunosupportive agent with normalizing effect on the aberrant immune response. This affects the immune system by stimulating the inducer/ helper T-cells as well as the T suppressor cells in the body to keep the immune balance healthy.

Antioxidants

Nowadays, everybody is subjected to some form of stress or the other in life, and it is unavoidable. Moreover, there is stress to the body due to pollution and food material treated with chemicals. These lead to the production of free radicals which are responsible for the tissue injury. Colostrum has adequate amount of vitamin A, D, C and E which has antioxidant property hence, protective for our body.¹⁸

Anti-aging

Colostrum has properties to build immune system and help in the healing process. It has an antioxidant effect on

our body. Through these types of influences BC is able to maintain our health. Colostrum is being used by athletes for building body tissues and increasing longevity of life.

THERAPEUTIC USES OF BOVINE COLOSTRUM

Gastrointestinal tract (GIT)

Gastrointestinal tract (GIT) is barraged with lots of microbiological organisms, antigens, food ingredients and drugs. These do have an effect on the GIT by way of direct action or by stimulation of the immunological process. Colostrum has the immunological factors which protect against these organisms. Colostrum contains trypsin inhibitor and the unchanged colostrum goes down into the intestine and maintains the health of epithelial lining and immune system. This way BC is protective against many GI disorders.⁶ The hyper immune bovine colostrum raised against particular infection is very specific to treat and prevent the infection in host.¹⁹

Infectious diarrhea

Diarrhea can be due to bacterial, viral, protozoal and fungal infections. The BC, by virtue of having specific antibodies, can give protection against enteric infections.⁷ The therapeutic effect of BC has been shown in study published from Dhaka. The immunoglobulins were extracted from BC containing high titers of rotavirus antibodies. This was a double blind placebo-controlled trial. Eighty children with rotavirus diarrhea were randomly assigned to receive orally either 10 grams of HBC containing 3.6g of anti Rotavirus antibodies daily for 4 days or same amount of placebo preparation. The daily stool and ORS intake were recorded. The children receiving HBC had significantly less daily total stool output and stool frequency and required small amount of ORS as compared to children who received placebo ($p < 0.05$). The clearance of Rota virus was also earlier in HBC group (1.5 vs. 2.9 days $p < 0.001$). No side effects were encountered. The treatment with anti rotavirus immunoglobulins of bovine colostrums is effective in management of acute Rota virus diarrhea in children.²⁰ In another study where hyper immune colostrum was given for 10 days to the children of 3-15 months of age, 55 were in trial group, whereas 65 were in placebo group. Nine (14%) of 65 on placebo developed rotavirus diarrhea, whereas none in the trial group developed diarrhea. This indicates that hyper immune colostrums gives protection against rotavirus infection in infants.^{7, 8, 20, 21} The protection against cryptosporidium, shigella and toxin producing *E.coli* has also been shown when treated with colostrum. Colostrum also contains antibodies against salmonella, *E.coli*, Candida and *H pylori* infection.²²⁻²⁷

Bovine colostrum concentrate (BCC) has also been tried in hemorrhagic diarrhea in infants. In a phase II

placebo controlled randomized clinical study,²⁸ 30 children with acute hemorrhagic diarrhea due to infection with enterohemorrhagic *E coli* (EHEC) were treated with BCC. During treatment the median value for stool frequency decreased from three to one per day, whereas during treatment with placebo, there was no change. In the patients treated with BCC, the duration required for a reduction in stool frequency of at least 50% was shorter. Treatment with BCC also decreased the excretion of *E coli* expressing intimin and EHEC- hemolysin although the differences did not reach the statistical significance.

Sepsis

Two controlled trials carried out with BCC to examine whether the components in the preparation were able to bind LPS and inhibit invasive process in gastrointestinal tract, showed that the Bee produced a marked and in part statistically significant decrease in LPS in blood.^{29,30}

Comparison of data on patients with sepsis of non-enteric origin with those having enterosepsis may not be very informative since the site of infection and stage of disease have a marked influence on the course of disease and the effects of therapy.

H. pylori Infections

H. pylori requires lipid to bind with the gastric mucosa. Colostrum prevents the organisms from attaching to the lipid binding sites in GIT. *In vitro* studies have shown that BC has potential to stop adhesion activity of *H pylori* and *H mustelae*. Colostrum also inhibits the growth of *H. pylori* and so can prevent the occurrence of peptic ulcer.⁸ Studies have shown breast-feeding to protect from early acquisition of *H. pylori* in breast-fed infants.¹³ The concept of passive immunization is a logical alternative approach as it mimics the natural means of protecting the young ones from a number of infections.

Prophylactic value of bovine colostrum in necrotizing enterocolitis of neonates

A number of Enterobacteriaceae strains colonize the intestinal tract of preterm infants with and without NEC. Inadequacy of the mucous layer combined with reduced or delayed anaerobic colonization may allow Enterobacteriaceae, which under normal circumstances are confined to the lumen, to adhere to the intestinal epithelium, proliferate and instigate damage through the production of endotoxin. Subsequent translocation of bacteria across the gut wall is then believed to occur. While it is generally accepted that the bacteria adhere to the epithelium, direct evidence is lacking. However, work with a rabbit model of NEC strongly supports this contention. Although not all NEC cases are associated with Enterobacteriaceae, this family of bacteria is associated with a high proportion and animal studies suggest endotoxin is involved in the pathogenesis of NEC.

In addition to a deficiency in mucus production, preterm infants lack secretory IgA (sIgA) as well as gut associated IgG. Breast-feeding and administration of preparations of human IgA-IgG antibodies have both been shown to be important in preventing the development of NEC. One way that breast milk could protect against NEC is by providing sIgA and IgG in the gut lumen. These immunoglobulins are thought to aggregate bacteria so that they can no longer adhere to the epithelium and both sIgA and IgG have been shown to reduce the number of bacteria translocating across the gut wall.

Retreatment with bovine colostrum produced a significant decrease ($P < 0.001$) in attachment of bacteria to HT-29 cells. Bovine colostrum significantly increased the production of IL-8 in HT-29 cells and IL-8, IL-6 and TNF- α in THP-1 cells ($P < 0.001$). The potential of bovine colostrum to increase the production of inflammatory mediators could limit its usefulness.

BCC to treat chronic recurrent diarrhea in patients with AIDS and other forms of secondary immunodeficiencies

Therapy of this disease using oral BCC (10g/day for 10 days) was investigated in a multicentric pilot study in 37 immunodeficiency patients with chronic diarrhea.²⁶ Of these 29 were HIV+, 2 had common variable immunodeficiency, 1 had immunodeficiency of unknown etiology and 5 had graft versus host disease following allogenic bone marrow transplantation. A good response, in some cases with long lasting normalization of diarrhea was obtained in 22 of 33 treated patients and only 4 patients with AIDS were non-responders. The treatment was also successful in 4 of the 5 patients with GvHD and no serious side effects were recorded in any of the patients.

DOSAGE

3 g (colostrum equivalent of 700 mg) of colostrum can be given for both the treatment as well as prevention of disease. Duration of treatment is not optimized though it can be given for 7 to 10 days.

SAFETY ISSUES

No adverse effects were reported with BCC in three phase 1 clinical trials in healthy subjects especially if the production is by prescribed methods avoiding allergens and foreign materials.

Lactose intolerance can occur in infants and young children with acute diarrheal disease but the clinical significance of this is limited. The lactose in BCC causes a reinforcement of pain sensation in addition to causing

Role of Colostrum in Gastrointestinal Infections

typical gastrointestinal disorders.

So in conclusion, bovine colostrum is safe and protective for the body functions but data is limited for its clinical use and more clinical trials are required from our country.

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