

The role of bovine colostrum on recovery time and length of hospital stay of acute diarrhea in infants and children: a double-blind randomized controlled trial

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ABSTRACT

Background WHO standard treatment for acute diarrhea remains unsatisfying to the parents of acute diarrhea patients, particularly the need of medical treatment. Bovine colostrum contains immune and growth factors that is thought able to neutralize some agents causing acute diarrhea in infants and children.

Objective To evaluate the efficacy of bovine colostrum as adjuvant therapy on recovery time and length of hospital stay for acute diarrhea in infants and children.

Methods A double-blind randomized controlled trial was conducted on infants and children with acute diarrhea admitted to Sanglah Hospital. Treatment group received standard therapy with bovine colostrums and control group received standard therapy plus placebo. The primary outcomes were achievement of recovery time and length of hospital stay. Recovery time was determined by the number of days needed to achieve defecation frequency ≤ 3 times/day and needed to achieve normal stool consistency.

Results Seventy infants and children were enrolled. The treatment group significantly achieved recovery time earlier than the control group in regard to the time of achieving defecation frequency to ≤ 3 times/day [2.31 (0.76) vs 3.34 (1.45); mean difference of -1.03; $P=0.001$; CI 95% -1.58;-0.48] and normal stool consistency [2.40 (0.77) vs 3.43 (1.48); mean difference of -1.03; $P=0.001$; CI 95% -1.59;-0.46]. Length of hospital stay was shorter in the treatment group than the control group [2.89 (0.78) vs 3.94 (1.53); mean difference of -1.05; $P=0.001$; CI 95% (-1.3;-0.7)]. No significant difference was found in mean of body weight recovery in two groups [0.47 (0.16) vs 0.49 (0.20); mean difference of -0.03; $P=0.556$; CI 95%: -0.11;0.06]. Age, nutritional status, breastfeeding, and diarrhea before admission did not influence the study outcome.

Conclusion Bovine colostrums as an adjuvant in standard therapy for acute diarrhea in infants and children is effective in regard to achieve earlier recovery time and shorter length of hospital stay [Paediatr Indones 2006;46:127-133].

Keywords: Acute diarrhea, bovine colostrum, immune and growth factors, recovery time, length of hospital stay.

Acute diarrhea is remains a major problem of morbidity and mortality in the most developing countries. According to the *Sen-sus Kesehatan Rumah Tangga* (SKRT) in year of 2002, the cumulative incidence of acute diarrhea in Indonesia was 127.8% or 1.3 episode/children below 5 year old per year. In Bali, the incidence of acute diarrhea in the children below 5 year old was 62.1%.^{1,2}

The most frequent etiology of acute diarrhea is viral, bacterial, parasite, and fungal infections. Virus is the most frequent etiology, in which 30-60% caused by rotavirus, especially in infants and children ≤ 2 years. Many risk factors can influence duration and severity of diarrhea. Internal risk factors are age, nutritional status, and the type of nutrition, meanwhile the external risk factors are the etiology of diarrhea, breastfeeding, and the accompanying diseases.³⁻⁵

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According to WHO (1990), 90% cases of acute diarrhea in infants and children recover well with rehydration and early feeding, meanwhile the administration of antibiotics and antispasmodic are only for specific cases.^{6,7} However, it does not satisfy the patients' parents, because it does not significantly decrease the volume, frequency and the duration of diarrhea, yet they still expect drug administration. According to this consideration, there is an idea to develop a cheap, effective, and safe "drug" which can be combined with the standard management of acute diarrhea in order to accelerate the recovery time and shortening length of hospital stay. Bovine colostrums contain some antibody against viral, bacterial, parasite, and fungal that can kill most of the etiology of acute diarrhea in infants and children. Bovine colostrums also contain growth factors that are synergistically useful for the diarrhea recovery.⁸⁻¹⁰

This study aimed to evaluate the role of bovine colostrums to the recovery time and the length of hospital stay in infants and children who suffered from acute diarrhea.

Methods

This was a double blind randomized controlled trial, conducted at Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Denpasar, Bali, from December 2002 until May 2003. The study participants were acute diarrhea patients admitted to the Department of Child Health, Sanglah Hospital. The study was approved by the Ethics Committee of Medical Faculty, Sanglah Hospital, Denpasar.

The inclusion criteria were acute diarrhea patients with mild-intermediate diarrhea according to the WHO criteria, aged 1-24 months. Diarrhea patients with other problems or complications, such as severe malnutrition, patients who had received antibiotics, anti parasite, antiviral, antifungal, and or symptomatic drugs for acute diarrhea, acute diarrhea that lasted for ≥ 48 hours, or the patient refused to participate were excluded.

Acute diarrhea was defined as the defecation frequency > 3 times/day with/without blood and or mucous, lasts for ≤ 7 days.^{1,6} The recovery time of diarrhea was the number of days needed to defecation

frequency changed into ≤ 3 times/day with normal stool consistency.³ Treatment failure was considered if the diarrhea did not recover within 7 days of treatment or experiencing any complication within 7 days. Drop out was defined as termination to be involved in the study due to any reason, such as discharged without permission, or no recovery within 7 days. Diarrhea with complication included diarrhea accompanied by direct effect of acute diarrhea itself such as severe dehydration, hypernatremia or hyponatremia, metabolic acidosis, paralytic ileus, seizure, or renal failure.¹¹ Diarrhea with problem was defined as diarrhea episode accompanied by problems independent from the diarrhea, such as systemic diseases, congenital disorders at the gastrointestinal organ, and anemia.⁸ The length of hospital stay was calculated days between admission time and the day when patients left hospital due to recovery. Dehydration status was according to the WHO standard.⁷ Duration of diarrhea was time period when the consistency of the stool was watery and defecation frequency > 3 times/day until the stool was normal consistency and defecation frequency ≤ 3 times/day. Body weight recovery was the difference between body weight on admission time and body weight on discharge. Bovine colostrum was specially produced by *Combipharm Pharmaceutical*, contained 250 mg bovine colostrums per 5 ml solution. Placebo was also produced by *Combipharm Pharmaceutical* contained solution in similar bottle, color, and odor, but it did not contain bovine colostrum. Symptomatic drugs for diarrhea were anti spasmotic, anti secretory, anti motility, adsorbent, and binding agents.

The study participants were 70 patients which were randomly allocated using permuted block random assignment. The treatment group comprised 35 participants, as did the control group. Blinded was done by giving code A or B to either bovine colostrum and placebo done by *Combipharm Pharmaceutical*. Neither researchers, nurses nor patients knew about the code. The codes were opened at the end of the study.

Patients in the treatment group received standard therapy plus bovine colostrum 3x250 mg per day during hospitalization or within 7 days, while the control group got standard therapy plus placebo 3x5 ml per day during hospitalization or within 7 days. Each intervention was given by nurse.

The statistical analysis was performed using SPSS Software (SPSS for Windows, version 11.0. Chi square or Fisher exact test analysis was used for the variables of nutritional status, breastfeeding, and feces leukocyte count. Student's *t* test analysis was used to analyze variables of age, body weight at admission time, body weight when discharged from the hospital, duration of diarrhea before admission, in both groups. Independent *t* test was used to analyze the time needed to change of defecation frequency to ≤ 3 times/day, the stool consistency changed to normal, and the length of hospital stay. Finally, we did covariant analysis (Ancova) to determine the influence of other variables to the outcomes of the study. Statistical significant was defined if $P < 0.05$ and power was 80%.

Results

Three hundred sixty three infants and children with acute diarrhea were admitted in Department of Child Health Sanglah Hospital during the study period. As much as 293 patients were excluded due to severe

dehydration (16), accompanying diseases (48), severe malnutrition (4), received antibiotics (147), diarrhea ≥ 24 hours before admission (67) and refused to participate (21). As a result, 70 subjects were enrolled in the study (**Figure 1**).

The baseline characteristics of study subjects in treatment and control groups are shown in **Table 1**. The primary outcomes were recovery time and length of hospital stay showed in **Table 2**. The secondary outcome was shown in **Table 3**. The influence of other factors to primary outcomes and interactions among those factors were showed in **Table 4**.

In the treatment group, the time needed for defecation frequency changed to ≤ 3 times/day achieved earlier than the control group, and this difference was statistically significant. The time needed for reaching the normal stool consistency was shorter in the treatment group than that in the control group, and this difference was significant. The length of hospital stay for the acute diarrhea patients in treatment group was shorter than the control group, and this difference was significant statistically (**Table 2**). As the secondary outcome of this study, body weight recovery slight

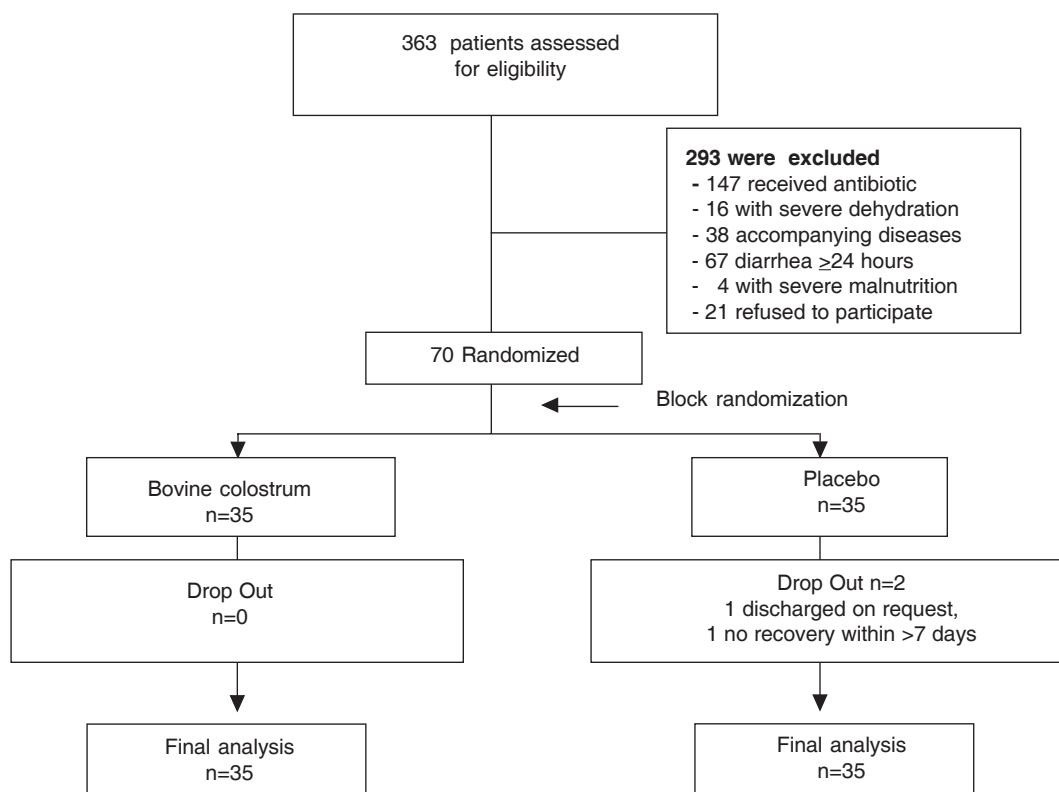


FIGURE 1. THE SCHEMATIC OF ENROLLMENT, RANDOMIZATION, FOLLOW-UP, AND ANALYSIS OF STUDY SUBJECTS.

bigger in the control group but this difference was not significant statistically (Table 3). Table 4 depicts the associations of several factors and the recovery time and length of hospital stay.

TABLE 1. THE BASELINE CHARACTERISTICS OF THE STUDY PATIENTS IN TREATMENT AND CONTROL GROUPS

Characteristics	Treatment group (n=35)	Control group (n=35)
Age (mo), mean (SD)	9.69 (6.17)	12.11 (5.97)
Gender		
Male, n (%)	19 (54)	18 (51)
Female, n (%)	16 (46)	17 (49)
BW at admission (kg), mean (SD)	7.90 (2.75)	8.60 (2.58)
Nutritional status		
Wellnourished, n (%)	30 (86)	27 (77)
Mild malnutrition, n (%)	5 (14)	8 (23)
Breastfeeding		
Breastfeeding, n (%)	10 (28)	10 (29)
Breastfeeding + formula, n (%)	23 (66)	19 (54)
Formula only, n (%)	2 (6)	6 (17)
Diarrhea before admitted (day), mean (SD)	1.09 (0.55)	1.06 (0.47)
Feces leukocyte count (/HPF)		
≤10/HPF, n (%)	30 (86)	28 (80)
>10/HPF, n (%)	5 (14)	7 (20)

SD=standard deviation; BW=body weight; n=sample size

Discussion

The use of whole bovine colostrum or hyperimmune bovine colostrum in addition to standard treatment for acute diarrhea has been reported in the previous studies in some countries and showed the consistent and significant results such as reduction of the acute diarrhea symptoms, shorten duration of viral excretion in the feces, acceleration in the recovery time, and shorten the length of hospital stay.^{8,9}

Our study shows that recovery time and length of hospital stay were shorter in the treatment group. Similar results were reported by Ylitalo *et al*⁸ in Finlandia which reported that the hyperimmune bovine colostrum could shorten the length of hospital stay for infants and

TABLE 4. THE RELATIONSHIP AMONG VARIABLES THAT INFLUENCE RECOVERY TIME AND LENGTH OF HOSPITAL STAY

	Defecation frequency to= 3x/day		Normal stool consistency		Length of hospital stay	
	F	p	F	p	F	p
Age	2.104	0.152	3.074	0.085	1.016	0.318
Diarrhea before admitted	1.390	0.243	0.383	0.538	1.033	0.314
Nutritional status	0.681	0.413	0.690	0.410	0.416	0.521
Breastfeeding	0.320	0.727	1.492	0.234	0.463	0.632
Bovine colostrum	4.244	0.044	6.690	0.012	4.468	0.039

F=Ancova statistics value; p=probability

TABLE 2. THE RECOVERY TIME AND THE LENGTH OF HOSPITAL STAY IN TREATMENT AND CONTROL GROUPS

	Treatment group (n=35)	Control group (n=35)	Mean difference (n=35)	P	CI 95%
Defecation frequency <3x/d (days), mean (SD)	2.31 (0.76)	3.34 (1.45)	-1.03	0.001	-1.58;-0.48
The normal stool consistency (days), mean (SD)	2.40 (0.77)	3.43 (1.48)	-1.03	0.001	-1.59;-0.46
The length of hospital stay (days), mean (SD)	2.89 (0.78)	3.94 (1.53)	-1.05	0.001	-1.63;-0.47

CI=confident interval; SD=standard deviation; n=sample size; P=probability

TABLE 3. BODY WEIGHT RECOVERY ON DISCHARGE IN TREATMENT AND CONTROL GROUPS

	Treatment group (n=35)	Control group (n=35)	Mean difference	P	CI 95%
Body weight(kg) mean (SD)	0.47 (0.16)	0.49 (0.20)	-0.03	0.556	-0.11; 0.06

CI=confidence interval ; SD=standard deviation; n=number of patients; P=probability.

children with acute diarrhea caused by rotavirus compared with the control group of 3.1 versus 3.6 days. The similar results was also reported by Mitra *et al*¹² in Bangladesh in which oral hyperimmune bovine colostrum was effective to accelerate the recovery time and the length of hospital stay for acute diarrhea caused by rotavirus in infants and children compared with control of 56 hours compared to 72 hours. Guarino *et al*,¹³ in Italy found the length of hospital stay was 76 hours in the group of acute diarrhea caused by rotavirus given antiviral human serum immunoglobulin compared to 131 hours in control group. In the Mieten *et al*'s study,¹⁴ bovine colostrum was given to 60 children with acute diarrhea by enteropathogenic *E. coli* (EPEC). This study results showed that 84.3% feces became *E. coli* negative after finishing the bovine colostrum treatment compared with 11.1% at the control group. Huppertz *et al*^{15,19} gave bovine colostrum to the children who suffered from acute diarrhea which was caused by diarrheagenic *E. coli*, shiga toxin producing *E. coli*, and *E. coli* expressing intimin and hemolysin with the milder frequency diarrhea and diseases severity as the results that was compared to the control group.

Those effects were resulted from the administration of bovine colostrum that contained antibody factors which act as antiviral (especially anti rotavirus), anti bacterial, and anti parasite, that could kill some kind of virus, bacteria, and parasite as the most frequent etiology of acute diarrhea in infants and children. Bovine colostrum also contains lactobacillus bifidus acidophilus as a probiotic that competitively pushed the pathogen bacteria in the alimentary tract. This bovine colostrum's effects caused etiologic agents for acute diarrhea was faster eliminated from the alimentary tract mucosa so that damages or functional disorders in the alimentary tract mucosa would not be continued. In acute diarrhea, damages or functional disorders in the alimentary tract mucosa lead to reduced local immunity of alimentary tract. In the local immunity deficiency condition as stated above, bovine colostrum administration was very useful for acute diarrhea recovery process. Besides that, proline-rich polypeptide, lymphokine, and cytokine in the bovine colostrum had immunoregulator effects that would make the patients' immune response be effective in order to increase patient's immunity.¹⁶⁻¹⁷

Acute diarrhea recovery process also depends on the recovery of alimentary tract damages. In acute diarrhea patients given bovine colostrum, recovery of

alimentary tract might be faster because colostrum contains growth factors such as insuline-like growth factor, transforming growth factor, and epithelial growth factor that worked in synergy by stimulating regeneration and differentiation of alimentary tract mucosa cells so that mucosa physiological functions could be restored to normal.²⁰

The study by Ylitalo *et al*⁸, in which infants and children suffered from acute diarrhea caused by rotavirus who were given bovine colostrum for 4 days, showed significant increase of body weight (403 g) compared to 343 g in control group. The different result in this study may be caused by different body weight observation duration, where in our study, observation was only done during hospital stay, meanwhile in the Ylitalo's study the observation was continued after hospitalization. Body weight recovery process may be happened faster in the intravenous than oral rehydration. In this study, we did not get specific review to that problem, so further study was needed.

The other advantages of the bovine colostrum for acute diarrhea patients are the possibility of decreasing nosocomial infection rate that associated with the virus, bacteria, parasite, and fungus transmission. This could be due to the effects of bovine colostrum in shortening the excretion duration of virus, bacteria, parasite, and fungus in the patients' feces so that the transmission chain could be broken down faster and the possibility of transmission to the surrounded population would be smaller.^{8,13} This was proved in the Sarker *et al*'s study⁹ which showed rotavirus excretion in the feces stopped faster in infants and children with acute diarrhea caused by rotavirus who were given bovine colostrums for 4 days compared to placebo, ie. 1.5 vs. 2.9 days. In our study, this issue could not be proved because the etiologic agents were not determined.

Some studies showed some adverse reactions of bovine colostrum such as nausea and vomiting, headache, insomnia, pruritus, and myalgia.^{17,18} In this study, there was no adverse reaction nor intolerance found. Bovine colostrums as well as mothers' milk colostrum was physiologic so it was safe to be given to infants and children.

To maintain the validity of the study, intention to treat analysis was also done by enclosing the drop out subjects in the last analysis by taking the worst assumption to the treatment result in those subjects.

Based on covariant analysis (Ancova), acute diarrhea recovery time and length of hospital stay were only significantly affected by bovine colostrum administration, meanwhile the influence factors such as age, diarrhea before admitted, nutritional status, and breastfeeding did not differ significantly because those variables were comparable at the two groups.

Finally, it is important to consider that in this study bovine colostrum was only an adjuvant therapy to the management of children with acute diarrhea, so that the main management of infants and children with acute diarrhea was in accordance to the WHO recommendation.

The limitation of this study was that the etiology of acute diarrhea, especially rotavirus as the most frequent etiology of acute diarrhea in the infants and children under two years, was not determined. We also did not differentiate between age subgroup in infancy and childhood.

In conclusion, addition of bovine colostrums to acute diarrhea standard treatment for infants and children maybe useful to accelerate the recovery time and shortening the length of hospital stay compared with the standard therapy alone.

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Editor's note

This was a potentially interesting study; however, certain issues, notably methodological aspects need to be considered. First of all the authors declared neither the sponsor of the study (to readers this should be Combiphar) nor any statement about conflict of interest. Secondly, although the preparation of placebo by the sponsor is acceptable, the practice of keeping blinding code by the sponsor can not be justified. Had other party not involved in the trial kept the blinding code, the validity of the study would have significantly increased. Thirdly, not even one out of more than 300 patients at initial assessment, had been excluded due to symptomatic drugs administration. It is very surprising since symptomatic drugs are commonly given by the doctor or by the patients' parents themselves. All aspects of research methods should be fulfilled in any study and this is mandatory for a clinical trial in which the results will give direct impact on the patients.