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Bovine Late Colostrum (Colostrum 6, 7 Days after Parturition) Supplement Reduces Symptoms of Upper Respiratory Tract Infection in Infants

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Abstract: This study was performed to evaluate the effect of bovine late colostrum, which is commercially available in Japan, in reducing symptoms of upper respiratory tract infection (URTI). The study was designed as a randomised, double-blind parallel group comparison involving 195 infants (number of subjects who completed the study) aged 3-9 years. Participants were divided into 2 groups: the late colostrum intake group (0.5g/day as bovine skim milk powder of late colostrum) and the placebo group (0.5g/day as bovine skim milk powder). The frequency of URTI and the duration of URTI were compared between the two groups during the 2 month study period (symptoms of URTI were reported by the guardian through a diary).

The mean frequency of URTI was lower in the late colostrum group (0.95 times) compared with the placebo group (1.28 times) ($p<0.05$). This difference was particularly marked in infants aged between 3 and 6 years (late colostrum group 0.88 times vs. placebo group 1.43 times, $p<0.05$). The mean duration of URTI accompanied by fever tended to be shorter in the late colostrum group (5.44 days) compared with the placebo group (7.00 days). In participants aged between 3 and 6 years, the duration of infection was significantly shorter in the late colostrum group (4.67 days) compared with the placebo group (8.14 days) ($p<0.05$).These results suggest that intake of bovine late colostrum is effective in the prevention URTI as well as reducing the duration of URTI in infants.

Key words: Bovine late colostrum, upper respiratory tract infection (URTI), infant

Introduction

The morbidity rate of infectious diseases has been declining due to improvements in hygiene and sanitation practices and advances in medicine. However, infectious diseases such as the common cold syndrome, influenza virus and upper respiratory tract infections (URTI) are still common in Japan and pose a significant health issue, especially in infants, who experience diseases that affect the ear, nose and throat numerous times a year.

95% of URTI are caused by viruses such as the rhinovirus and the coronavirus. Symptoms usually include sneezing, a runny and/or stuffy nose and sore throat that signify the infection of the upper respiratory tract, and may be accompanied by lower respiratory symptoms such as cough and phlegm. Other symptoms may include fatigue and chills as well as digestive symptoms such as nausea, vomiting and diarrhoea.

Studies in recent years have shown that the use of concentrated milk powder made from early colostrum 1-2 days after a cow has given birth to have protective effects against URTI[3]. In Japan, however, selling food products that contain milk produced within 5 days of parturition is not permitted due to the regulations set in the Food Sanitation Law by the Ministry of Health (Ministry of Health and Welfare No. 52). We have therefore conducted studies to verify the infectious disease prevention impact of bovine colostrum using the late bovine colostrum extracted 6-7 days after parturition.

Although milk is usually known for its nutritional properties, milk extracted from cows within a week of parturition is rich in immunoglobulin and antibacterial and antiviral factors such as lactoferrin, lysozyme, and lactoperoxidase[6-8]. It has been confirmed through previous studies that the late colostrum extracted on the 6th to 7th days after parturition is rich in these components when compared with milk extracted after the 8th day.

The purpose of this study was to examine the preventive effect of URTI and the recovery-promoting effect of bovine late colostrum by studying the effects of long-term ingestion of bovine late colostrum that can be sold legally within Japan.

Method

1) Research facility and research period

The scientific and logistical validity of the present study was examined by the Utsugikai Clinic Medical Corporation Ethics Committee and Kobayashi Pharmaceutical Co., Ltd. Ethics Committee. Utsugikai Clinic Medical Corporation conducted the studies from November 20th, 2006 to March 23rd, 2007 based on the results on these discussions and incorporating the principles of the Declaration of Helsinki (enforced in 1964, revised in 2000) and the *Logical Guidelines for Epidemiological Studies* (Ministry of Education, Culture, Sports, Science and Technology, notification of Ministry of Health, Labor and Welfare).

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Table 1: Selection and exclusion criteria for participants

Selection criteria
Older than 3 years and younger than 10 years at the start of trial. Healthy subjects with no prior history of hay fever, asthma, house dust allergy or other allergies with symptoms that include cough or sneezing.
Exclusion criteria
(1) Subjects who have a prior history of with severe lung and kidney disease and those with severe disease complications deemed inadequate for this study.
(2) Subjects who have previously experienced an allergic reaction to dairy or soy with a high chance of reoccurrence.
(3) Subjects who are taking antibacterial drugs (antibiotics, antiviral drugs) at the start of trial.
(4) Subjects or their guardians who are unable to keep a daily record or those deemed unable to follow instructions of the primary investigator.
(5) Subjects who are participating in other studies.
(6) Other subjects deemed unsuitable for the present study by the primary investigator.

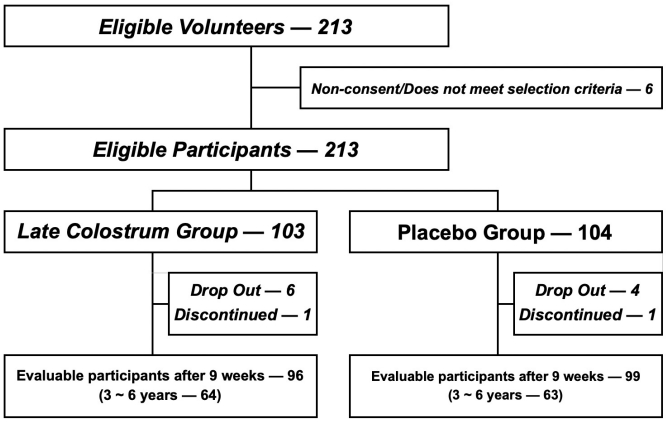

Figure 1: Research Protocol

2) Test food and intake method

The main food material used in this study is bovine late colostrum skim milk powder. This was created by extracting milk from cows 6-7 days after parturition and removing the fat until the fat content reached <5%. The milk is then pasteurised at 73 degrees for 15 seconds and dried by spray dry method.

A chewable tablet containing 166.7mg of bovine late colostrum with a diameter of 15mm (hereinafter, referred to as late colostrum food) was used as the test food in the intervention group. A chewable tablet of the same dimensions containing 166.7mg of regular skim cow milk (hereinafter referred to as placebo food) was used as a placebo in the control group. Adjustments were made to both foods to ensure that their physical appearance was undistinguishable.

3) Eligible participants

213 volunteers with an equal gender ratio and age distribution (3-4 years old, 5-6 years old, 7-9 years old) were recruited at the Utsugikai Clinic Medical Corporation. The study was explained in detail to all volunteers and their guardians in advance and in writing. After obtaining consent given out of the guardians' free will, the eligibility of each volunteer was examined using the selection and exclusion criteria shown in Table 1. 207 healthy males and females between the ages of 3-9 were confirmed as participants for this study (Figure 1).

4) Method of implementation

This study used a double-blind parallel group comparison study where the allocation of participants was conducted by EPS Co., Ltd on April 26, 2007. The table outlining participants' allocation was created by the allocation management using SAV Ver 8.2, where 4 case-blocks were randomly and evenly allocated into groups receiving late colostrum or the placebo food group.

The trial was carried out sequentially in participants who passed the eligibility test and had completed a consultation. Incorporation was terminated when the number of participants in each age and gender group reached 32-36.

The trial foods used in the study were confirmed to be physically indistinguishable by the allocation controller and distributed by the principal investigator in the order of incorporation. The intake amount of the test food was 3 tablets per day (500 mg bovine late colostrum skim powder milk or bovine skim milk powder), and the test subjects were asked to ingest these tablets continuously for 9 weeks. The time and frequency of ingestion was not specified.

During the trial period, guardians were asked to record various details regarding the participants' health condition, including cough, sore throat, fever by body temperature, poor physical condition, intake amount, presence/absence of hospital visits, medications, etc., by writing these details in a survey-type diary every day. Furthermore, all participants were asked to make 3 hospital visits; 1 week before the start of trial, 4 weeks after the start of trial and 8 weeks after the start of trial, where their health condition and body growth was checked by the principal investigator. It was also confirmed during these consultations whether participants had been vaccinated against the influenza virus.

5) Diagnostic criteria for URTI

The presence of URTI was determined by examining the health condition of participants as reported in the diary. A "cough lasting more than a day" or a "sore throat lasting more than 2 days" were considered as onset of URTI and the frequency of these events were recorded. In addition, the number of days the symptoms persisted was identified as the duration for each onset of URTI[5,8-12]. Any symptoms that showed within 3 days of the initial onset of URTI were regarded as of the same onset, and the the number

of symptomatic days were grouped together. Furthermore, having a fever for more than a day was defined as a serious URTI.

The amount of food intake, presence or absence of hospital visits and medicine use was recorded and examined.

Infection with the influenza virus was identified through consultation (examination of clinic history) and the judgment of the principal investigator based on the drugs used.

6) Statistical processing

In order to eliminate the influence of infectious disease infection before the start of the trial, the results of the first week after the start of intake (1 week before the start of the trial) was not included in the evaluation, and only the results from the subsequent 8 weeks were compared between groups. In addition, subjects who took 80% or less of the prescribed food intake were excluded from the analysis.

A statistical comparison was performed between the two groups, the late colostrum food intake group (late colostrum group) and the control food intake group (placebo group). In addition, a statistical comparison was also performed between the two groups for participants aged 3 to 6 years, which is an age group with known high epidemiological incidence of URTI.

Welch's t-test was performed for the number of onsets and days affected by symptoms of URTI and serious URTI, and Fisher's exact test was used for the distribution of the number of onset and non-onset participants.

Results

1) Participant characteristics

At the start of trial, there were 103 participants in the food intake group and 104 participants in the placebo group. In the former group, a total of 7 participants dropped out of the study due to personal reasons (4), lack of food intake (2) and adverse events (1). In the placebo group, there were a total of 5 participants who dropped out of

Table 2: Height and weight difference of participants between groups

	n	Height	Weight
Late colostrum group			
3～4 years (male)	16	97.7±6.4	15.1±2.2
3～4 years (female)	16	96.8±5.1	14.9±1.7
5～6 years (male)	17	110.0±6.2	20.1±5.5
5～6 years (female)	15	114.7±8.9	20.7±6.0
7～9 years (male)	14	125.4±7.3	25.5±6.1
7～9 years (female)	18	127.0±6.1	26.8±4.9
Placebo group			
3～4 years (male)	16	98.3±4.5	15.8±1.7
3～4 years (female)	15	101.4±5.3	16.2±1.7
5～6 years (male)	17	110.2±5.3	19.2±2.7
5～6 years (female)	15	114.1±7.0	19.9±3.4
7～9 years (male)	18	126.5±6.7	26.4±4.7
7～9 years (female)	18	127.1±6.4	26.5±4.2

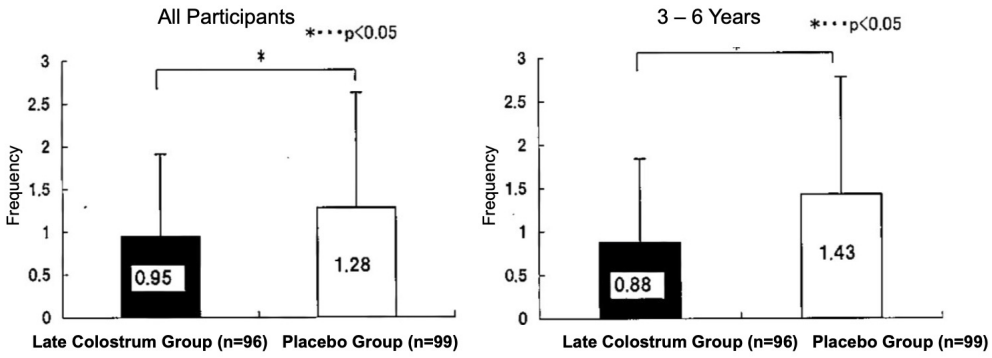

Figure 2: Average Frequency of URTI

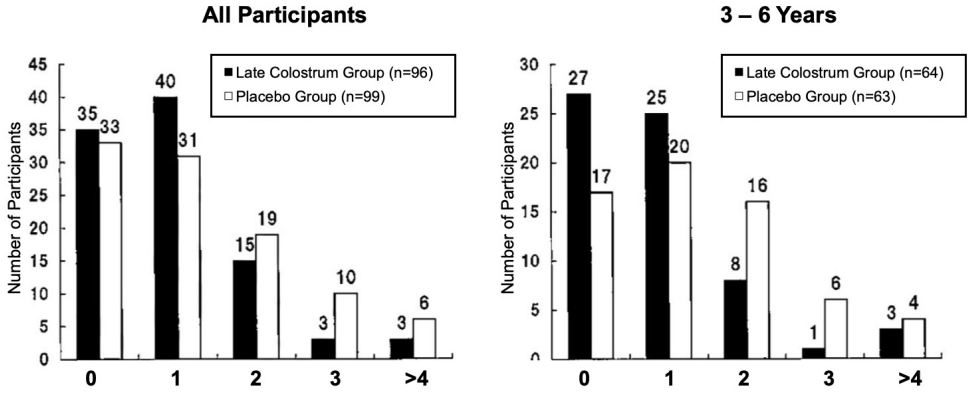

Figure 3: Onset of URTI (By Frequency)

the study due to personal reasons (4) and adverse events (unexplained rash)(1). Therefore, a total of 96 participants in the food intake group and 99 participants in the control group were included in the assessment. In addition, the number of participants within the 3-6 age range were 64 in the food intake group and 63 in the placebo group (Figure 1).

The characteristics of participants included in the assessment are outlined in Table 2. There was no statistically significant differences in the sample size, gender, age, height and weight between the two groups.

2) The frequency of onset of URTI

The average frequency of onset of URTI during the trial period is outlined in Figure 2. The average frequency of onset was 1.28 times in the placebo group compared to 0.95 times in the late colostrum group, and the difference between the 2 groups was found to be statistically significant (p=0.047). Furthermore, the average frequency of onset in participants aged 3-6 years was found to be 1.43 times in the placebo group compared with 0.88 times in the late colostrum group, and the differences in these groups were found to be even more statistically significant (0.015).

The number of participants is summarised according to frequency of onset and shown in Figure 3. Researchers observed a notable decline in the frequency of multiple URTI onset (twice or more) in participants in the food intake group.

Table 3 shows the contrast in number of participants who did or did not experience an onset of URTI between the 2 groups. Although the differences data from in these groups is not significant, there is evidence of decline in number of participants experiencing onset of URTI in the food intake group (p=0.096).

Table 3: Participants who did/did not experience onset of URTI

#p:<0.10

		Onset	No onset	
All participants	Late colostrum group	61	35	
	Placebo group	66	33	
3〜6 years	Late colostrum group	37	27	#
	Placebo group	46	17	

3) Number of symptomatic days of URTI

The average number of symptomatic days of URTI during the trial period is shown in Table 4. We found no statistically significant difference between the two groups in terms of the number of symptomatic days of URTI.

However, in severe URTI cases where participants suffered from a fever for more than 1 day during the symptomatic period, the average number of symptomatic days in the placebo group was 7.00 compared with 5.44 days in the late colostrum group, showing a notably lower figure albeit not being statistically significant (p=0.181). Furthermore, the average number of symptomatic days of URTI in participants in the 3-6 year age group was 8.14 days in the placebo group compared with 4.67 days in the late colostrum group, indicating a statistically significant difference (p=0.036).

4) Other considerations

A statistically significant difference could not be detected in the number of participants infected with the influenza virus, the number of days in poor health, frequency of hospital visits and the frequency of drug use between both groups.

Discussion

This study showed bovine late colostrum had similar effects when compared with bovine early colostrum in terms of preventative action against URTI and reducing the number of symptomatic days. These effects were especially pronounced in participants aged between 3-6 years.

Bovine late colostrum powder used in this study had 10% of IgG (early colostrum : IgG 20%). Additionally, studies have detected traces of IgG in the laryngeal mucosa over several hours after

Table 4: Average number of symptomatic days of URTI

*:p < 0.05

All cases	URTI Late colostrum group (92 cases)	URTI Placebo group (127 cases)	Severe URTI Late colostrum group (27 cases)	Severe URTI Placebo group (21 cases)
Symptomatic days (Average)	4.37	4.07	5.44	7.00

3〜6 years	URTI Late colostrum group (52 cases)	URTI Placebo group (90 cases)	Severe URTI Late colostrum group (12 cases)	Severe URTI Placebo group (14 cases)
Symptomatic days (Average)	4.02	4.30	4.67	8.14

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participants have ingested the test food. These factors have informed the idea that ingesting bovine late colostrum may prevent virus cells from attaching to the larynx and prevent the frequency of onset of URTI.

Furthermore, bovine early colostrum has been found to increase the concentration of s-Ig-A in saliva after 2 weeks of continuous ingestion[13]. The bovine late colostrum used in the present study has been found to be effective in increasing intestinal antigen-specific s-Ig-A in mice after 36 days of continuous oral administration. Due to these factors, one of the mechanisms that reduces duration of URTI may caused by enhancement of mucosal immunity by increasing the production of specific s-Ig0A against pathogens that infect the pharyngeal mucous membrane.

The present study also planned to study the impact on the influenza virus, however the onset of the virus was greatly delayed in the winter of 2006-2007 and arrived in March, thus could not be included in our statistical analysis. However, a portion of participants underwent the trial between February and March and had received the influenza vaccine, and comparison of the number of participants who experienced onset of influenza was found to be 0 in the late colostrum group and 3 in the placebo group. There is a possibility that bovine late colostrum played a role in preventing onset of influenza and this shall be pursued in further studies.

Bovine early colostrum has been found to have protective properties against URTI[5] and intestinal infections in adults[14,15], therefore similar effects are expected from the ingestion of bovine late colostrum. Furthermore, ingestion of bovine early colostrum and its properties is said to have various advantageous effects such as increase in IGF[13] and the body's recovery rate[13,16], useful for Alzheimer's treatment[17], relieve the symptoms of diarrhoea[15] and aid in the recovery of intestinal damage[18,19]. There is great expectation that bovine late colostrum could provide similar beneficial results. Future studies may unravel the tertiary function of bovine late colostrum and examine its effects, not just on URTI prevention and recovery, but on overall health. We believe that it will become an important food source in supporting the health and well-being of Japanese people.

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