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Caysido ECL, Ganggangan F. and Runez R. Effect of Bovine Colostrum on ANC Acute Lymphocytic Leukemia PatientsUndergoing Chemotherapy

ORIGINAL ARTICLE

EFFECT OF BOVINE COLOSTRUM ON THE ABSOLUTE NEUTROPHIL COUNTS OF ACUTE LYMPHOCYTIC LEUKEMIA PATIENTS UNDERGOING CHEMOTHERAPY: A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED STUDY

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

3RD Place, PIDSP Research Contest 2017.

ABSTRACT

Background: Changes in the blood cell counts, such as leukopenia and neutropenia, in patients with Acute Lymphoblastic Leukemia (ALL) are common events following chemotherapy. These commonly delay further administration of chemotherapeutic agents. Furthermore, the risk of infection rises correspondingly with the degree of neutropenia. Bovine colostrum is a rich source of immunoglobulins and other antimicrobial factors. These immunoglobulins are believed to improve the immune function and may be effective in the prevention of neutropenia following chemotherapy.

Objective: To determine the efficacy of bovine colostrum in preventing neutropenia among ALL patients undergoing chemotherapy.

Methods: This study included pediatric patients, aged 6 months to 18 years old diagnosed with ALL undergoing chemotherapy. Twenty-one subjects were randomly assigned to receive bovine colostrum or placebo that were taken twice a day for a week beginning from the first day of chemotherapy. Baseline complete blood count (CBC) and the absolute neutrophil count (ANC) were determined before and after 7 days of giving the colostrum or placebo. A t-test was applied to determine significant differences before and after the supplementation on each group.

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Results: Results showed that there was a significant increase in ANC of patients given bovine colostrum as compared to the placebo group with a p-value of 0.007. There were also significant increases in the white blood cells and platelet counts in those who were given bovine colostrum, with p-values of <0.001 and 0.001, respectively. No untoward effects were observed on both groups.

Conclusion: Bovine colostrum is effective in increasing the ANC of ALL patients undergoing chemotherapy and with no noted side effects.

KEYWORDS:
acute lymphoblastic leukemia (ALL), absolute neutrophil count, bovine colostrum

INTRODUCTION

Neutropenia is a common complication noted among ALL patients after chemotherapy. Chemotherapy-induced neutropenia typically occurs three-to-seven days after chemotherapy drugs are administered and continues for several days before recovering to normal levels.[1] Treatment for neutropenia depends on the cause. For chemotherapy-induced neutropenia, the usual strategy in recent years has been the injection with a man-made protein that is similar to the naturally occurring protein, granulocyte-colony stimulating factor (G-CSF). G-CSF is produced in the body by the immune system and stimulates the formation of neutrophils.[2] The injections are usually given shortly after the last treatment of a chemotherapy cycle and are continued until the desired ANC level, usually 1,000, is reached. However, its cost and availability limit the compliance of patients to the regimen hence a search for other remedies is warranted.

Bovine colostrum is a milk secreted during the first few days after calving and is a rich source of immunoglobulins and other antimicrobial factors.[3] These immunoglobulins are believed to improve the immune function and may be effective in treating immune system deficiencies and in the treatment of neutropenia. Bovine colostrum has shown some promise in different fields of medicine and has a lot of scope in the prevention and treatment of various illnesses including cancer in human beings.[4] There are limited data regarding the use of bovine colostrum in neutropenia and most are based on anecdotal reports. Dr. Dwyer in 2011 in the New England Journal of Medicine claims that "Immunoglobulin in colostrum has been used to successfully treat thrombocytopenia, anemia, neutropenia, and other conditions such as Myasthenia Gravis, Guillain Barre Syndrome, Multiple Sclerosis, Systemic Lupus, Rheumatoid Arthritis, Bullous Pemphigoid, Kawasaki Syndrome, Chronic Fatigue Syndrome and Crohn's disease".[3] On the other hand, a FactMed analysis in 2012 reported that 2 patients taking bovine colostrum developed neutropenia, however, this was not elaborated.[5] There have been no randomized trials to support these claims.

The objective of this study is to determine the efficacy of a one-week supplementation of bovine colostrum (Pro-Ig) in preventing neutropenia among patients with acute lymphocytic leukemia (ALL) undergoing maintenance chemotherapy.

MATERIALS AND METHODOLOGY

This randomized, double-blind, placebo-controlled trial involved pediatric ALL patients between the age of 6 months to 18 years undergoing chemotherapy using the standard protocol and was on the maintenance phase using mercaptopurine, methotrexate, vincristine, and prednisone. The study period was from February 2016 to September 2016.

The patients who met the following criteria were included in this study:

1. A baseline WBC of more than or equal to 2.8 x 10^9/L provided that the absolute neutrophil count is more than or equal to 1000.
2. A baseline hemoglobin of at least 100 g/L and a platelet count of at least 150 x 10^9/L
3. No other co-morbid illnesses like congenital heart disease, acute or chronic kidney disease and are not critically ill to be admitted to the intensive care unit or had an infection requiring antibiotic use.
4. No known allergy to dairy products.

5. Not presently taking other supplements/vitamins including bovine colostrum (Pro-Ig).
6. Either in-patient or outpatient.

Due to the limited number of ALL patients in this institution (2-4 cases of standard chemotherapy per month), the sample size was determined by total enumeration wherein, all patients satisfying the inclusion criteria were included in the study period of 8 months. All patients had informed consent. This study underwent technical review and approval by the hospital Ethics Review Committee.

The baseline values of the patients' complete blood count were obtained. Then the absolute neutrophil count (ANC) was computed by multiplying the WBC count with the neutrophils plus bands multiplied by 1000. (ANC = WBC X (neutrophils + bands) x 1000). Eligible participants were randomly assigned to either the treatment group or the placebo group by asking the parent or guardian to get a piece of paper from a box that contained the corresponding codes of the test products to be used. Each participant received either the bovine colostrum (Pro-Ig) or the placebo treatment and was blinded to the test product received. The bovine colostrum was manufactured by Essential International Ingredients Corporation, France distributed by Prebiotech Philippines. The placebo used contains starch and was similar in taste and appearance with the bovine colostrum. The test products were provided by Prebiotech Philippines. The identity of the test products was only obtained & revealed by the supplier after the statistical analyses have been made.

Upon enrollment, the resident-in-charge gave the corresponding test product that was picked by the patient or parent. In the package, an instruction, written in English and Filipino, on the proper administration of the test product was placed. The test products were to be dissolved in 2 tablespoons of water. The test products were taken orally, twice a day for 7 days (after breakfast & after dinner) under the supervision of the nurse on duty/and or parent/guardian for in-patients; and the guardian/parent for outpatients. The administration of the test products commenced on the first day of the standard maintenance chemotherapy treatment and daily thereafter, to complete the 14 doses before measuring the outcomes. As instructed, the participants collected the empty sachets and submitted them to the resident after the 7 days of treatment. Participants in this research were given 2 grams of colostrum per day. On the other hand, the placebo used contains pea starch. The test products were all tolerated.

After 7 days, complete blood count and platelet count were again measured using blood samples (0.5 ml if using aquisel microtainer tubes, or 2 ml if using EDTA tube) drawn from the patients' antecubital area. The blood tests were done at the same laboratory for all participants.

Statistical analysis:

Frequency distribution and percentage were used to describe the demographic data. Fisher's exact test was used to determine significant differences in the distribution proportion between treatment groups. Levene's test was used to compute and analyze the ANC and the CBC parameters to determine whether there are significant differences between the treatment groups before the intervention. Independent and dependent T-tests were conducted to compare the outcomes between two groups.

RESULTS

A total of 21 participants were enrolled in this study, 11 of which were randomized to the bovine colostrum group and 10 to the placebo group. All were able to complete the study. Eighty-six percent were below 10 years old and 66% were males.

Table 1. Demographic Profile and baseline CBC of bovine colostrum and placebo group (N=21)

PARAMETERS	Placebo Group(n=10)	Bovine Colostrum Group(n=11)	p-value*
a. Age			
1-9 y/o	8(38.1%)	10(47.6%)	
10 & Above	2(9.5%)	1(4.8%)	0.586
b. Sex			
Male	6(28.6%)	8(38.1%)	
Female	4(19.0%0	3(14.3%)	0.659
Hemoglobin	128.30	146.10	O.992
Hematocrit	0.38	0.44	0.472
WBC (x10^9/L)	6.00	5.68	0.307
Neutrophils (%)	0.70	0.61	0.974
Lymphocytes (%)	0.26	0.40	0.681
Monocytes (%)	0.03	0.02	0.405
Eosinophils (%)	0.02	0.04	0.066
Platelet Count (x 10^9/L)	382.50	316.1O	0.924
ANC	4215.49	3189.31	0.304

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 1 shows that there is no significant difference in the demographics of both groups as indicated by the p-value of 0.586 and 0.659 for age and gender, respectively.

Using Levene's test, no significant difference was noted in the baseline CBC, ANC, & platelet count values of both groups as shown by the p values of more than 0.05.

Table 2. Pre- and Post-Treatment blood count values of the Placebo Group (n=10)

Variables	Pre Treatment Values	Post Treatment Values	Change from baseline		P*
			Mean	%	
Hemoglobin(g/L))	128.30	125.20	-3.1	-2.4%	0.225
Hematocrit (%)	0.38	0.37	-0.01	-2.63	0.290
WBC (x10^9/L)	6.00	5.63	-0.37	-6.17	0.555
Neutrophils (%)	0.69	0.60	-0.09	-13.04	0.045 *
Lymphocytes (%)	0.26	0.31	0.05	19.23	0.098
Monocytes (%)	0.027	0.024	-0.003	-11.11	0.771
Eosinophils (%)	0.019	0.051	0.032	168.42	0.045 *
Platelet Count (x10^9/L)	382.50	407.6	25.1	6.56	0.269
ANC	4,215.50	3,406.96	-808.5	-19.18	0.167

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 2 shows that the hemoglobin, hematocrit, WBC, neutrophils, and ANC decreased after treatment in the placebo group, but only the neutrophils showed a significant decrease. Other CBC parameters, i.e. lymphocytes, monocytes and platelet count, showed no significant increase except for eosinophils.

Table 3. Pre- and Post-Treatment blood counts of the Bovine Colostrum Group (n=11)

Variables	Pre Treatment Values	Post Treatment Values	Change from baseline		P-value
			mean	%	
Hemoglobin (g/L)	132.82	120.27	-12.5	-9.45%	0.007*
Hematocrit (%)	0.397	0.36	0.037	-9.32%	0.003*
WBC (x10^9/L)	5.162	7.43	2.268	44.19%	<0.001 *
Neutrophils (%)	0.55	0.63	0.08	14.55	0.176
Lymphocytes (%)	0.36	0.32	-0.04	-11.11	0.355
Monocytes (%)	0.021	0.024	0.003	14.29	0.71
Eosinophils (%)	0.038	0.032	-0.006	-15.79	0.476
Platelet Count (x10^9/L)	287.36	378.O9	90.73	31.57	0.001*
ANC	2899.37	4561.19	1661	57.32	0.007*

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 4. Mean changes in the CBC, platelet count and ANC values of both study groups (N=21)

Variables	Placebo Group			Bovine Colostrum			P-value*
	Pre Treatment	Post Treatment	Mean change %	Pre Treatment	Post Treatment	Mean change %	
Hemoglobin (g/L)	128.30	125.20	-3.1	132.8	120.2	-12.5	0.051
Hematocrit (%)	0.38	0.37	-0.01	0.397	0.36	-0.03	0.020*
WBC (x10^9/L)	6.00	5.63	-0.37	5.162	7.43	2.268	0.002*
Neutrophils (%)	0.69	0.60	-0.09	0.55	0.63	0.08	0.021*
Lymphocytes (%)	0.26	0.31	0.05	0.36	0.32	-0.04	0.099
Monocytes (%)	0.027	0.024	-.003	0.02	0.02	.003	0.644
Eosinophils (%)	0.019	0.051	.032	.038	.032	-.006	0.027*
Platelet Count (x 10^9/L)	382	406	25.1	287	378	90.7	.041*
ANC	4,215.50	3,406.96	-808	2899.37	4561.91	1661.82	0.003*

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 3 shows that after treatment with bovine colostrum, the patients' hemoglobin and hematocrit decreased significantly; the lymphocytes also decreased but was not significant. The WBC, ANC, and platelet counts increased significantly after the administration of bovine colostrum. The increase in the neutrophils, monocytes of the patients were not significant.

Comparison of both groups after the treatment is shown in table 4. Both the hemoglobin and hematocrit decreased in both groups with the bovine colostrum group having the lower hemoglobin and hematocrit values but only the decrease in hematocrit was significant. The WBC and neutrophil values decreased in the placebo group (with a mean decrease of 0.37 and 0.09, respectively), while it increased in the bovine colostrum group, with a mean of 2.268 and 0.08, respectively. The mean increase in the platelet and ANC counts were significantly higher under the bovine colostrum group.

Both treatment groups did not experience any untoward event or side effect during the intervention until 7 days of follow up after the intervention.

DISCUSSION

Acute lymphoblastic leukemia is characterized by the overproduction and accumulation of cancerous, immature white blood cells known as lymphoblasts. It is most common during childhood, with a peak incidence at 2 to 5 years of age and slightly more common in males than in females as also seen in this study; the reason for this is still unknown.[6] Risk classification (such as standard-risk, high-risk, or very high-risk) is based on the age upon diagnosis and the initial white blood cell count.[7]

Standard chemotherapy or protocol for ALL consists of three phases: remission induction, intensification (consolidation), and maintenance therapy along with central nervous system (CNS) prophylaxis. All phases of chemotherapy can suppress the WBC, neutrophils, and platelets.

In this study, all subjects included were in the maintenance phase to standardize the

research. Maintenance therapy is intended to kill any residual cell that was not killed in the remission induction and intensification phases. Daily treatment includes the oral intake of mercaptopurine (40-50mg/m^2) for 6 days in a week; once weekly oral intake of methotrexate (15-20 mg/m^2); once monthly one-day course of intravenous vincristine (1.5mg/m^2 dose); and a 5 day oral prednisone (15-20 mg/m^2 PO) after vincristine given monthly. [7] This regimen is usually given for 36 months.

The bovine colostrum (Pro-Ig) used in this study is a granulated powder produced via thermisation treatment from France. It also contains food additives such as silicon dioxide and dextrose monohydrate. The only contraindication of this product is hypersensitivity to any component of the product. According to Dr. Keech, individuals who are lactose intolerant can easily tolerate up to 12 grams of colostrum per day without any negative side effects or symptoms. The proline-rich polypeptide in colostrum normalizes or modulates the levels of cytokines in the body, so the body does not recognize the lactose as a food allergen in cases of lactose intolerance.[8]

Noted in this study, bovine colostrum use during chemotherapy showed positive effects on the WBC, platelet, and ANC of ALL patients undergoing maintenance chemotherapy. There were no untoward events nor infections noted during the study until 7 days post-intervention. The beneficial effects noted here support the findings of previous studies by Tyrell, Lesmana et.al, Struff et.al, and Jamaroli et.al, that colostrum enhances the effect of immunoglobulins, and decreases signs and symptoms of upper respiratory tract infection, diarrhea, and sepsis. The increase in neutrophils as noted in this study is contrary to the finding of neutropenia on 2 patients given colostrum as reported in a FactMed analysis in 2012. The noted decrease in both hemoglobin and hematocrit may still be due to chemotherapy but the possible causes for significantly lower hematocrit observed in the bovine colostrum needs further investigation.

The decrease in the white blood cells including neutrophils, eosinophils, lymphocytes etc. is the common trend after chemotherapy however in this study, increase in the eosinophils was noted in both treatment groups. Increase in eosinophils is commonly seen among patients with hypersensitivity and parasitic infestations, however, there were no clinical manifestations of these conditions among treatment groups, hence this needs further elucidation.

The beneficial effects of bovine colostrum as seen in this study are promising and potentially beneficial for patients undergoing chemotherapy.

The scarcity of published data on the effects of bovine colostrum on blood parameters especially CBC, ANC and platelet counts made it challenging to conclude that such beneficial effects are directly due to bovine colostrum.

CONCLUSION

This study shows that bovine colostrum is effective in increasing the absolute neutrophil count among ALL patients undergoing maintenance chemotherapy thereby.

RECOMMENDATIONS

This study had small population size hence further studies with adequate sample size is recommended in order to validate the results of this study. Investigations on the effect of bovine colostrum on other forms of cancer is likewise a good endeavor to pursue.

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