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The Effect of Bovine Colostrum Supplementation in the Management of Respiratory Allergies in Children According to Allergen Sensitization: A Subgroup Analysis from the Results of a Randomized Double-blinded Placebo-Controlled Trial

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ABSTRACT

Introduction: Bovine colostrum supplementation has been shown to significantly reduce nasal allergy symptoms and improve lung function compared with placebo. The authors present a subgroup analysis to determine its effect on the management of respiratory allergies in monosensitized versus polysensitized children.

Methodology: The randomized controlled trial was conducted on children aged 7 to 18 years with respiratory allergies who were randomly assigned to receive bovine colostrum 1000 mg (n=19) or placebo (n=19) daily for three months. Total nasal symptoms score (TNSS), asthma control test (ACT), composite asthma severity index (CASI), and pulmonary function test were used to assess symptom improvement for six months. Subgroup analysis was done, and children were categorized into monosensitized and polysensitized groups.

Results: The subset of monosensitized patients in the bovine colostrum group showed significant improvement in nasal congestion (p=0.004). For both ACT and CASI scores, significant improvements from beginning to end were demonstrated in the scores of polysensitized children who were given bovine colostrum ($p = 0.011$ and $p = 0.018$, respectively). Improvement in lung function test was significantly observed in monosensitized patients given bovine colostrum supplement at the first month (FEV_1), second month (FEF_{25-75} and PEF), and third month (all parameters except FVC) of assessment. In the polysensitized subgroup, only FEV_1/FVC ratios at baseline and week two were found significantly improved in the bovine colostrum group (n = 9) than in the placebo group (n = 11).

Conclusion: Sensitization can affect an individual's response to bovine colostrum supplementation. Bovine colostrum supplementation significantly improved nasal congestion in monosensitized patients with respiratory allergies. The ACT and CASI scores significantly improved in polysensitized patients. Lung function response was more visible in monosensitized patients.

Keywords: bovine colostrum supplement, asthma, pulmonary function test

INTRODUCTION

The increased prevalence of allergic respiratory diseases is a major public health concern worldwide.[1] The global burden of allergic respiratory disease demands effective disease prevention strategies. Recent studies have shown that alternative therapy modalities are used in the treatment of allergic respiratory diseases.[2] One of these methods is the use of bovine colostrum.

Bovine colostrum contains many components that can affect immune function, such as pathogen- and allergen-specific immunoglobulins, antimicrobial proteins, oligosaccharides, and growth factors like TGF-β and interleukin 10 (IL-10).[3] Three of these components, bovine immunoglobulins (IgG), lactoferrin, and TGF-β, have been directly linked to the functional effects on immunity and have also been tested as bioactive ingredients in human studies.[3] It has been reported that constituents from bovine colostrum are 100- fold to 1,000-fold more potent than human mother's colostrum.[4]

Bovine IgG from non-immunized cows can bind to a wide range of pathogenic bacteria, viruses, and inhalation allergens. Importantly, recent experiments showed that bovine IgG could bind to human Fc γ receptors (FcγR), which suggests that they may be able to enhance antigen presentation to T cells, as well as phagocytosis and killing by phagocytes.[5] In relation to allergy, maternal transfer of IgG-allergen immune complexes in breast milk prevents subsequent sensitization in the offspring, which may contribute to the protective effect of raw milk on asthma.[6,7] These data suggest that oral ingestion of immunoglobulins modulates immune function in the airways, which is supported by recent findings that oral ingestion of serum-derived immunoglobulin prevents inflammatory tissue damage in acute lung inflammation in mice.[8,9]

Transforming growth factor-β is an anti- inflammatory cytokine that modulates immune function and is also involved in the regulation of epithelial differentiation and barrier function in the intestine.[3] Milk contains relatively high levels of TGF-β2 and TGF-β1.[3] The study done by Oddy and McMahon showed that TGF-β promotes mucosal immune development and reduces allergic disease as well as intestinal inflammation.[10] The concentration of TGF-β in breast milk is inversely correlated with the development of allergies, and the presence of TGF-β in murine milk is required for the induction of oral tolerance to allergens, which will protect against the development of allergies later in life.[11,12]

Lactoferrin, an iron-binding protein, inhibits tryptase, a mast cell mediator which degrades respiratory allergens and cross- linked IgE, thus decreasing inflammation in asthma and allergic reactions. Lactoferrin reduces the conversion of superoxide anion to reactive oxygen radicals such as H_2O_2 and/or ^{-}OH, which may augment antigen-induced airway inflammation in the nasal passages.[13] Lactoferrin may also decrease inflammation in asthma and allergic reactions by binding CpG dinucleotidescontaining oligodeoxynucleotides, which are potent inflammatory stimuli produced by certain bacteria.[14]

Another important component of bovine colostrum is proline-rich polypeptides (PRP), also known as colostrinin. It is one of the most powerful substances in colostrum that ensures its safety as a natural component to prevent allergic symptoms. It stimulates the production of either helper or suppressor T lymphocytes and anti-inflammatory cytokines, thereby reducing allergic symptoms.[15]

The common hallmark of atopic diseases is the production of serum-specific IgE (sIgE) against allergens.[16] Immunoglobulin E (IgE) found in colostrum is thought to be responsible for regulating the allergic response by limitingthe histamine release.[17] Assessment of sIgE antibodies with *in vivo* skin test confirms the allergic sensitization.[18] Monitoring the prevalence and patterns of IgE-mediated sensitization in populations over time is important because allergic sensitization is a significant risk factor for the development of atopic disease.[19] Polysensitization is a frequent phenomenon among adults and children. According to the study by Ciprandi et al., polysensitization is a relevant clinical characteristic as it affects about 70-80% of the global allergic population.[20] Baatenburg de Jong and colleagues concluded that polysensitization is common in children of school age, particularly boys.[21] In polysensitized children, the symptom scores and levels of total IgE are higher and the course of atopic disease is more severe.[22,23]

In the randomized-controlled trial by Wong-Chuah, bovine colostrum supplementation was effective in reducing symptoms of nasal allergy and improving lung function.[24] However, no previous prospective studies have investigated the relationship between bovine colostrum supplementation and allergic sensitization in patients with persistent allergic rhinitis and asthma.

OBJECTIVES

General Objective

To determine the effect of bovine colostrum supplementation in the management of respiratory allergies in children according to sensitization.

Specific Objectives

To determine if there is a difference in the response between polysensitized and monosensitized patients, given bovine colostrum supplement and placebo in terms of:

1. Total Nasal Symptom Score
2. Asthma Control Test score
3. Composite Asthma Severity Index score
4. Lung function test

METHODOLOGY

Study Design

This was a subgroup analysis of a prospective, randomized, double-blinded, placebo-controlled study conducted between November 2015 and June 2016 at the University of Santo Tomas Hospital. A total of 41 pediatric patients with allergic respiratory diseases were recruited from the outpatient department. Participants underwent skin prick tests for allergens and lung function tests. A detailedinterviewer-administered questionnaire was completed. All the questionnaires used were validated.

Study Participants

Eligible patients were aged 7 to 18 years old with mild to moderate persistent asthma and/or mild to moderate persistent allergic rhinitis, according to the criteria of the Global Initiative for Asthma (GINA) and Allergic Rhinitis and Its Impact on Asthma (ARIA), respectively.[25,26]

Exclusion criteria were patients on immunotherapy; diagnosis of any chronic illnesses, any anatomically relevant disease other than asthma and allergic rhinitis; patients undergoing immunosuppressive therapy; and have taken any herbal or similar supplement within 1 year from the time of consult, and patients with unlikely compliance with the study.

Assessment

A questionnaire had been provided for all patients and contained the patient's age, gender, family history of atopy, environmental and cigarette smoke exposure, use of oral, intranasal, and inhaled medications were obtained for all patients. They were allowed to continue their medications, such as short-acting β2 agonists (SABA), inhaled corticosteroids, a combination of inhaled corticosteroids with long-acting β2 agonists (LABA), antihistamines, and intranasal steroids. Baseline physical examination was done. The level of asthma severity was assessed using validated questionnaires such as the Asthma Control Test (ACT) and the Composite Asthma Severity Index (CASI). The Total Nasal Symptom Score (TNSS), was used for patients with allergic rhinitis.

The Asthma Control Test is a patient- completed questionnaire with five items assessing asthma symptoms (daytime and nocturnal), use of rescue medications, and the effect of asthma on daily functioning. Each item includes five response options corresponding to a 5-point Likert-type rating scale. In scoring the ACT survey, responses for each of the five items are summed to yield a score ranging from 5-25. Those with scores between 5-15 are classified as having poor control of asthma, 16- 20 as partial control of asthma, and 21-25 as having well control of asthma.

The Composite Asthma Severity Index can quantify disease severity by taking into account impairment, risk, and the amount of medication needed to maintain control.[27] CASI scores include five domains: day symptoms and salbutamol use, night symptoms and salbutamol use, controller treatment, lung function measures, and exacerbations. A maximum score of 20 indicates poor asthma control and severity.

The Total Nasal Symptom Score is the sum of 4 individual participant-assessed symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing, each evaluated using a scale of 0 = none, 1 = mild, 2 = moderate, or 3 = severe. The TNSS was obtained from the sum of all four individual symptom scores, with a total possible score ranging from 0 (no symptoms) to 12 (maximum symptom intensity).

Spirometry

Spirometry using MIR Spirolab III™ was performed in all patients. They were asked to breathe in maximally, hold the mouthpiece between their teeth, apply the lips for an airtight seal, and breathe out as hard and as fast as possible until the lungs were empty. The following spirometric parameters were obtained: forced vital capacity (FVC), forced expiratory volume at 1st second (FEV_1), and forced expiratory flow at 25% and 75% (FEF_{25-75}). The Spirolab III™ was used as the pulmonary function device. At least three maneuvers meeting the American Thoracic Society standards were required.

Based on the 2007 NAEPP guidelines, the following values were used to identify normal spirometry values: FEV_1 >80% predicted and FEV_1/FVC >85. Abnormal FEF_{25-75} was defined as <65% predicted.[28]

Allergy Skin Prick Test

Skin prick tests for aeroallergens were done in all subjects to categorize their sensitivity. Aeroallergens included common allergens such as house dust, *Dermatophagoidespteronyssinus*, *Dermatophagoides farinae*, cat pelt, dog epithelium, cattle hair, horse hair, cockroach, mosquito, mixed feathers, *Acacia*, and *Candida*. Histamine was used as the positive control and saline as the negative control. The skin prick test was positive if the wheal diameter was >3 mm after 15 minutes.

Sensitization

They were categorized as monosensitized if positive to only one class of allergens, polysensitized if positive to more

than one class of allergens, no sensitization if negative skin prick test result.[29,30]

Data Collection

Each subject enrolled was assigned an identification number. Patients were randomized on a 1:1 basis (computer- generated predefined block randomization list) to receive the bovine colostrum supplement or placebo. Both the investigator and the subject were blinded to the study treatment. The bovine colostrum group was given 1 gram sachet of bovine colostrum, which was instructed to be diluted in 10 ml of drinking water once a day for three months. The placebo group received identical sachets with the same weight, size, and color. These were also made of inert material without nutritional content. Concealed treatment allocation was made by an assigned data manager and was maintained in a sealed copy of the randomization sequence at the investigation site in case of need for emergency unblinding.

Each patient was instructed to take the study medication for three consecutive months without discontinuing any of their regular medications for asthma and allergic rhinitis. Study medications were dispensed upon inclusion in the study and during subsequent visits scheduled at 2 weeks and months 1, 2, and 3. Any unused study drug previously dispensed was asked to be returned on their next visit. Spirometry, questionnaires on asthma control and severity and allergic rhinitis, and clinical assessment were made at each follow-up visit at the 4th, 5th, and 6th months from the beginning of treatment.

Analysis

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Independent Sample T- test, Mann-Whitney U test, and Fisher's Exact/Chi-square test were used to determine the difference of mean, median, and frequency between groups, respectively. Repeated measures ANOVA and Friedman test were used to determine the effect of bovine colostrum on lung function from baseline to 6th month. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at 0.05 α-level of significance. STATA 12.0 was used for data analysis.

The primary endpoint was changed from baseline (efficacy) in the TNSS, the ACT score, the CASI score, and the different parameters in spirometry three months after starting the supplement (bovine colostrum and placebo) and three months post supplementation (month 6) in monosensitized versus polysensitized patients.

Safety and Ethical Considerations

The randomized controlled trial was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research involving human subjects, adopted by the general assembly of the World Medical Association. The primary investigator has complied with the training prerequisites and is certified with Good Clinical Practice (GCP). Approval of the University of Santo Tomas Hospital Institutional Review Board (IRB) was obtained prior to this subgroup analysis.

RESULTS

Thirty-eight pediatric patients were included in our study. All of them had allergic rhinitis and half had asthma. Of these 38 patients, 19 were from the bovine colostrum group and 19 were from the placebo group. There were 22 male (58%) and 16 female (42%) participants with a mean age of about ten years. Sensitization to *Dermatophagoides* was the most prevalent in both groups. Monosensitization was established in 16 children (42%), while 20 children (53%) were polysensitized. Of the two children (5%) with no sensitization, one was in the placebo group and the other in the bovine colostrum group. The two patients with no sensitization weren't included in the final analysis. Of the 16 monosensitized children, nine were in the bovine colostrum group, and seven were in the placebo group (47.4% vs. 36.9%). Polysensitized children were slightly greater in proportion in the placebo group compared to the bovine colostrum group (57.9% vs. 47.4%). These differences in distribution were not statistically significant (p = 0.865) (Table 1).

Total Nasal Symptom Score (TNSS)

The bovine colostrum-supplemented group reported significant improvements in all TNSS symptoms over time compared to the placebo group (Table 2).

In the subset of monosensitized patients, nasal congestion significantly improved in the bovine colostrum-supplemented children (p = 0.004). Nasal itching similarly improved in both experimental groups over time (p = 0.003) (Table 3).

In the subset of polysensitized children, there were significant improvements in rhinorrhea (p = 0.025) and sneezing (p = 0.015) intensities over time in the placebo group (Table 4). The sneezing intensity was likewise felt to be worse among the bovine colostrum children in the first month (p = 0.047). However, they reported less nasal itching compared to the placebo in the third and sixth months.

Asthma Control Test (ACT)

As for the level of asthma control, there were no significant differences in the patterns of symptom control among

Table 1. Baseline characteristics of children with respiratory allergies enrolled in the bovine colostrum supplementation trial (n = 38)

Patient Characteristics	Bovine Colostrum (n = 19)	Placebo (n = 19)	*p*
Age (years) mean ± SD	10.2 ± 2.9	9.9 ± 2.3	0.170*
	Frequency (%)		
Sex	12 (63.2)	10 (52.6)	0.511†
Male	7 (36.8)	9 (47.4)	
Female			
Family history of atopy			
Allergic rhinitis	10 (52.6)	16 (84.2)	**0.036†**
Bronchial asthma	9 (47.4)	12 (63.2)	0.328†
Atopic dermatitis	3 (15.8)	3 (15.8)	1.000§
Drug allergy	2 (10.5)	3 (15.8)	1.000§
Food allergy	1 (5.26)	2 (10.5)	1.000§
Exposure to smoking or air pollutants	9 (47.4)	11 (57.9)	0.516†
Exposure to pets			
Dog	3 (15.8)	7 (36.8)	0.141†
Cat	2 (10.5)	3 (15.8)	1.000§
Others	1 (5.3)	2 (10.5)	1.000§
Clinical diagnosis			
Allergic rhinitis	19 (100)	19 (100)	—
Bronchial asthma	8 (42.1)	11 (57.9)	0.330†
Atopic dermatitis	1 (5.26)	3 (15.8)	0.604§
Drug allergy	2 (10.5)	1 (5.26)	1.000§
Food allergy	3 (15.8)	2 (10.5)	1.000§
Skin prick test allergen			
Dermatophagoides farinae	18 (94.7)	17 (89.5)	1.000§
Dermatophagoides pteronyssinus	17 (89.5)	14 (73.7)	0.405§
Cockroach	6 (31.6)	6 (31.6)	1.000†
Mosquito	7 (36.8)	8 (42.1)	0.740†
Cat	4 (21.0)	5 (26.3)	1.000§
Dog	1 (5.3)	2 (10.5)	1.000§
Others	1 (5.3)	3 (15.8)	0.604§
Sensitization			0.865§
Monosensitized	9 (47.4)	7 (36.8)	
Polysensitized	9 (47.4)	11 (57.9)	
None	1 (5.3)	1 (5.3)	

*Statistical tests used: * – Independent sample T-test; † – Chi-square test; § – Fisher's exact test*

subgroups of monosensitized and polysensitized patients given bovine colostrum and placebo from baseline to month six (Table 5). However, improvement in symptoms was still noted throughout the whole study period in both subgroups of patients given bovine colostrum and placebo.

When subgroups of children with different sensiti-zations were analyzed, ACT scores at baseline, third month, and sixth month were comparable between trial arms (Table 6). Significant improvements from beginning to end were only demonstrated in the scores of polysensitized children who were given bovine colostrum ($p = 0.011$).

Composite Asthma Severity Index (CASI)

Analyzing subgroups of children with different sensiti-zation statuses, CASI scores were not different between trial groups at baseline, third month, and sixth month of assessment (Table 7). However, a significant improvement from baseline to endpoint was detected among polysensitized children given bovine colostrum ($p = 0.018$).

Lung Function Test

Among monosensitized patients, significantly better outcomes were demonstrated by the bovine colostrum group (n=9) at the first month (FEV_1), second month (FEF_{25-75} and PEF), and third month (all parameters except FVC) of assessment as compared to the placebo group (n = 7) (Table 8).

In the polysensitized subgroup, only FEV_1/FVC ratios at baseline and week two were found better in the bovine colostrum group (n=9) than in the placebo group (n = 11) (Table 9).

Safety and Adverse Reactions

Safety and tolerability were assessed by adverse events reported by subjects at each clinic visit. All patients in both treatment groups did not report any significant adverse effects such as diarrhea, vomiting, pruritus, and rash. Only two patients reported unpleasant taste, which did not necessitate treatment discontinuation.

DISCUSSION

This study showed that sensitization could affect an individual's response to bovine colostrum supplementation. The bovine colostrum-supplemented group reported significant improvements in all TNSS symptoms over time compared to the placebo group. However, only the subset of monosensitized patients in the bovine colostrum group showed significant improvement in one of the TNSS symptoms, which is nasal congestion (p = 0.004). In the subset of polysensitized children, there were significant

Table 2. Progression of TNSS responses between bovine colostrum and placebo groups before and after treatment in children with respiratory allergies (n = 38)

TNSS Response	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	*p***
	Median (Range)						
Rhinorrhea							
Bovine colostrum	2 (0–3)	1 (1–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	**0.002**
Placebo	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.793
*p**	0.061	0.338	0.918	0.520	0.196	0.080	
Nasal congestion							
Bovine colostrum	2 (0–3)	1 (0–2)	1 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	**0.001**
Placebo	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0 (0–2)	0.137
*p**	**0.017**	0.264	0.065	0.921	0.734	0.203	
Sneezing							
Bovine colostrum	2 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–1)	**0.007**
Placebo	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	0.713
*p**	**0.039**	0.217	0.566	0.117	0.326	**0.033**	
Nasal itching							
Bovine colostrum	2 (1–3)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–1)	1 (0–1)	**<0.001**
Placebo	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	0.607
*p**	0.081	0.534	0.728	0.183	0.133	**<0.001**	

*Statistical tests used: * – Mann-Whitney U test; ** – Friedman test*

Table 3. Comparison of TNSS responses between bovine colostrum and placebo groups at baseline and after treatment among monosensitized patients (n = 16)

TNSS Response	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	*p**
	Median (Range)						
Rhinorrhea							
Bovine colostrum	1 (0–2)	1	1 (1–2)	1 (0–2)	0 (0–2)	0 (0–1)	0.933
Placebo	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.464
P	0.812	0.484	0.746	1.000	0.162	0.071	
Nasal congestion							
Bovine colostrum	1 (1–3)	1 (1–2)	1 (0–2)	1 (0–1)	1 (0–1)	1 (0–1)	**0.004**
Placebo	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–1)	1 (0–2)	0 (0–1)	0.178
P	0.490	1.000	0.605	0.844	0.226	0.626	
Sneezing							
Bovine colostrum	2 (1–3)	1 (0–2)	1 (1–2)	1 (0–1)	1 (0–1)	1 (0–1)	0.513
Placebo	1 (0–2)	1 (0–2)	1 (1–3)	2 (0–2)	1 (1–2)	1 (1–2)	0.514
P	0.150	0.564	0.783	**0.024**	0.059	0.059	
Nasal itching							
Bovine colostrum	2 (1–3)	1 (0–2)	1 (0–1)	1 (1–1)	1 (0–1)	1 (0–1)	**0.003**
Placebo	1 (0–3)	2 (0–2)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	**0.003**
P	0.736	0.176	0.539	0.076	0.834	**<0.001**	

*Statistical tests used: Mann-Whitney U test; * – Friedman test*

Table 4. Comparison of TNSS responses between bovine colostrum and placebo groups at baseline and after treatment among polysensitized patients (n = 20)

TNSS Response	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	*p**
	Median (Range)						
Rhinorrhea							
Bovine colostrum	2 (1–3)	2 (1–2)	1 (0–2)	1 (0–2)	1 (0–1)	1 (0–1)	0.095
Placebo	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–1)	1 (0–2)	**0.025**
P	**0.011**	0.257	0.864	0.689	0.668	0.327	
Nasal congestion							
Bovine colostrum	2 (0–3)	1 (0–3)	1 (0–2)	1 (1–2)	1	1 (0–1)	0.744
Placebo	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	0.408
P	0.166	0.226	0.726	1.000	1.000	0.085	
Sneezing							
Bovine colostrum	2 (0–3)	1 (0–2)	2 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	0.055
Placebo	1 (0–3)	1 (0–2)	1 (0–1)	1 (0–2)	1 (0–2)	0 (0–2)	**0.015**
P	**0.047**	0.349	**0.047**	0.685	0.348	0.359	
Nasal itching							
Bovine colostrum	2 (1–3)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–1)	0 (0–1)	0.153
Placebo	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	0.337
P	0.082	0.802	0.657	0.652	**0.008**	**0.001**	

*Statistical tests used: Mann-Whitney U test; * – Friedman test*

Table 5. Level of asthma control between bovine colostrum and placebo groups before and after treatment by sensitization status

ACT Status	Monosensitized (n = 7)			*P*	Polysensitized (n = 12)			*P*
	Baseline	Month 3	Month 6		Baseline	Month 3	Month 6	
Bovine colostrum				0.558				0.061
Well-controlled	1 (25)	1 (25)	1 (25)		0	0	2 (50)	
Partially controlled	0	1 (25)	2 (50)		2 (50)	4 (100)	2 (50)	
Not controlled	3 (75)	2 (50)	1 (25)		2 (50)	0	0	
Placebo				0.369				0.135
Well-controlled	0	0	1 (33.3)		0	0	0	
Partially controlled	2 (66.7)	3 (100)	2 (66.7)		4 (50)	7 (87.5)	7 (87.5)	
Uncontrolled	1 (33.3)	0	0		4 (50)	1 (12.5)	1 (12.5)	
P	0.257	0.257	1.000		1.000	1.000	0.091	

Values are given as frequency (%). In each of the monosensitized and polysensitized subgroups, four were allocated to bovine colostrum supplementation.

Statistical tests used: Fisher's exact test

Table 6. Comparison of ACT scores between bovine colostrum and placebo groups at baseline and after treatment, by sensitization status

ACT Measurement Point	Monosensitized		*p***	Polysensitized		*p***
	Bovine Colostrum (n = 4)	Placebo (n = 3)		Bovine Colostrum (n = 4)	Placebo (n = 8)	
Baseline	17.7 ± 5.2	20 ± 1	0.506	18.3 ± 4.4	19.7 ± 3.1	0.418
Month 3	19.7 ± 4.8	20.7 ± 1.5	0.542	21.1 ± 3.4	22 ± 1.4	0.440
Month 6	21.5 ± 2.6	23 ± 1.7	0.437	22.9 ± 2.3	22.4 ± 1.7	0.634
p*	0.506	0.113		**0.011**	0.085	

*Values are given as mean ± SD. Statistical tests used: * – One-way ANOVA; ** – Independent sample T-test*

Table 7. Comparison of CASI scores between bovine colostrum and placebo groups before and after treatment, by sensitization status

CASI Measurement Point	Monosensitized		*p***	Polysensitized		*p***
	Bovine Colostrum (n = 4)	Placebo (n = 3)		Bovine Colostrum (n = 4)	Placebo (n = 8)	
Baseline	5.5 (3–7)	3 (3–8)	0.714	3.5 (2–13)	5 (3–11)	0.544
Month 3	3.5 (3–7)	3	0.186	3 (2–4)	3	1.000
Month 6	3	3	—	3 (1–3)	3	0.157
p*	0.210	0.076		**0.018**	0.197	

*Values are given as median (range). Statistical tests used: ** – Friedman test; ** – Mann-Whitney U test*

Table 8. Comparison of spirometric parameters between bovine colostrum and placebo groups before and after treatment among monosensitized patients (n = 16)

Spirometric Parameter	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	*p***
	Mean ± SD						
FVC							
Bovine colostrum	94.11 ± 6.68	98.44 ± 11.48	102.11 ± 13.39	100.56 ± 10.05	97 ± 11.24	93.89 ± 7.69	0.646
Placebo	91.29 ± 10.61	91.43 ± 9.78	95.29 ± 5.68	94.43 ± 8.66	93.29 ± 8.81	93.57 ± 6.9	0.968
*p**	0.524	0.218	0.230	0.221	0.485	0.933	
FEV_1 (%)							
Bovine colostrum	86.78 ± 9.97	94.44 ± 13.47	99.33 ± 13.77	98.44 ± 11.83	100.33 ± 11.03	95.22 ± 11.42	0.434
Placebo	91.14 ± 14.71	88 ± 15.24	85.57 ± 10.67	84.43 ± 15.39	81.14 ± 12.71	88 ± 15.83	0.715
*p**	0.491	0.385	**0.047**	0.058	**0.006**	0.306	
FEV_1:FVC ratio							
Bovine colostrum	91.11 ± 8.30	94.11 ± 4.54	94.44 ± 7.86	94.89 ± 4.23	99.67 ± 3.91	97.78 ± 7.87	0.275
Placebo	98 ± 9.26	95 ± 13.35	89.71 ± 10.64	87.86 ± 10.04	85.71 ± 10.67	89.71 ± 14.19	0.360
*p**	0.139	0.854	0.323	0.077	**0.003**	0.169	
FEF_{25-75} (%)							
Bovine colostrum	70.33 ± 19.80	82.44 ± 18.04	85.56 ± 23.66	90.33 ± 15.98	98.22 ± 10.96	92.44 ± 19.98	0.170
Placebo	79.29 ± 20.68	82.43 ± 30.25	63.57 ± 25.53	60.14 ± 23.17	57 ± 22.83	69.14 ± 25.38	0.253
*p**	0.394	0.999	0.097	**0.008**	**<0.001**	0.059	
PEF							
Bovine colostrum	69.11 ± 15.84	81.44 ± 21.14	95.67 ± 43.81	99.78 ± 32.13	101.78 ± 16.32	96 ± 15.43	0.112
Placebo	67.29 ± 19.46	74 ± 21.31	66.43 ± 20.74	60.71 ± 19.81	69.14 ± 22.98	75.57 ± 28.21	0.842
*p**	0.839	0.500	0.127	**0.014**	**0.005**	0.085	

*Statistical tests used: *—Independent sample T-test; **—Repeated measures ANOV*

Table 9. Comparison of spirometric parameters between bovine colostrum and placebo groups before and after treatment among polysensitized patients (n = 20)

Spirometric Parameter	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	*p***
	Mean ± SD						
FVC							
Bovine colostrum	87.89 ± 7.49	91.56 ± 17.51	88 ± 11.94	93.56 ± 10.04	93 ± 10.99	92.78 ± 7.22	0.810
Placebo	92.18 ± 10.51	101.82 ± 17.16	98.09 ± 15.76	97.18 ± 13.83	94.55 ± 13.04	94.64 ± 11.48	0.657
*p**	0.318	0.204	0.131	0.520	0.781	0.679	
FEV_1 (%)							
Bovine colostrum	87.33 ± 10.33	87.44 ± 15.65	82.11 ± 15.90	90.22 ± 11.66	92 ± 13.58	92.56 ± 10.92	0.573
Placebo	84.09 ± 14.33	87.45 ± 22.29	86.91 ± 21.51	86.73 ± 21.39	83.73 ± 19.83	88.36 ± 14.04	0.991
*p**	0.577	0.999	0.586	0.666	0.302	0.474	
FEV_1:FVC ratio							
Bovine colostrum	98.67 ± 7.09	95 ± 7.63	90.89 ± 8.05	94.67 ± 8.83	95.78 ± 9.93	96.67 ± 8.75	0.525
Placebo	90.18 ± 9.97	84.64 ± 12.19	87.36 ± 13.65	86.64 ± 13.50	86.54 ± 12.87	91.54 ± 8.88	0.773
*p**	**0.046**	**0.040**	0.504	0.143	0.095	0.213	
FEF_{25-75} (%)							
Bovine colostrum	75.89 ± 22.59	73.22 ± 22.71	65.22 ± 26.39	78.22 ± 24.08	84.33 ± 18.57	85.22 ± 24.96	0.479
Placebo	67.36 ± 24.06	67.73 ± 32.99	79.82 ± 47.21	68.18 ± 32.82	65.55 ± 28.48	71.82 ± 24.28	0.923
*p**	0.429	0.677	0.420	0.455	0.106	0.241	
PEF							
Bovine colostrum	67.56 ± 23.01	62.22 ± 29.13	68.89 ± 24.15	77.89 ± 20.67	88.44 ± 30.27	90 ± 25.87	0.129
Placebo	64.09 ± 22.94	77.27 ± 45.07	71.91 ± 31.73	69.45 ± 28.92	71.27 ± 21.77	74.36 ± 14.71	0.910
*p**	0.671	0.400	0.817	0.473	0.157	0.106	

*Statistical tests used: *—Independent sample T-test; **—Repeated measures ANOV*

improvements in rhinorrhea (p = 0.025) and sneezing (p = 0.015) intensities over time in the placebo group. For both ACT and CASI scores, significant improvements from beginning to end were demonstrated in the scores of polysensitized children who were given bovine colostrum (p = 0.011 and p = 0.018, respectively). Improvement in lung function test was significantly observed in monosensitized patients given bovine colostrum supplement at the first month (FEV_1), second month (FEF_{25-75} and PEF), and third month (all parameters except FVC) of assessment. In the polysensitized subgroup, only FEV_1/FVC ratios at baseline and week two were found significantly improved in the bovine colostrum group (n = 9) than in the placebo group (n = 11).

Monosensitization differs both immunologically and clinically from polysensitization.[23] From the study of Bousquet et al., polysensitization has been reported to be associated with a lower health-related quality of life in intermittent asthma patients.[31] In a local study of Biñas, polysensitization has been associated with persistent allergic respiratory diseases.[32]

The results from this study showed differences in the response of patients given bovine colostrum according to their sensitization. Polysensitization is highly prevalent in allergic patients.[33] In a US study of 1338 patients with objectively diagnosed mild-to-moderate asthma, 81% reacted to three or more allergens.[34] This was in concordance with other studies that have pointed out that up to 90% of patients are polysensitized.[22,35] In this study, there was only a slightly greater proportion of polysensitized patients (53%) compared to monosensitized patients (42%). This very little difference between monosensitized and polysensitized groups can be attributed to a younger population in this study. The study of Prigione et al. supported an immunological hypothesis that polysensitization develops due to functional defects of T regulatory cells. On the other hand, children with persistent monosensitization produced a higher quantity of IL-10 and IFN-ɣ than children developing polysensitization.[36]

Using the Total Nasal Symptom Score, the bovine colostrum-supplemented group reported significant improvements in all TNSS symptoms over time. This was also observed in the study of Keech, wherein itching of nasal passages, congestion, sneezing, and swelling of eyes were significantly relieved after intake of bovine colostrum over a thirty-day period.[2] According to Barrager et al., further aid in combating allergy and asthma-related inflammation may also come from the sulfur compound, methylsulfonylmethane or MSM, of which colostrum is a rich, natural source.[37] The study consisted of 55 seasonal allergic rhinitis (SAR) sufferers receiving 2,600 mg of MSM daily. Significant improvement in the upper and lower respiratory symptoms was reported after 30 days of supplementation. Thus, MSM may be efficacious in the reduction of symptoms associated with SAR.[38] However, in our study, when patients were categorized according to sensitization, only the monosensitized patients given bovine colostrum showed significant improvement in nasal congestion (p = 0.004). It is possible that due to their lower atopic index, they have responded earlier to bovine colostrum supplementation compared to polysensitized patients. In the study of Keech, continuous supplementation is suggested if further exposure to allergens exists.[2] In the study by Peternel et al., polysensitized patients had more severe symptoms than monosensitized ones.[38] According to Ciprandi et al., monosensitization seems to be characterized by a less severe clinical feature. This could be another reason why the monosensitized group showed significant improvement in one of the nasal symptoms compared to the polysensitized group.[39]

In this study, polysensitized patients in the bovine colostrum group had more significant improvements in ACT (p = 0.011) and CASI scores (p = 0.018) compared to monosensitized patients. According to some studies, most children with severe asthma are mostly polysensitized.[40,41] These polysensitized children with severe asthma can be categorized as having difficult-to-treat asthma or therapy-resistant asthma.[42]

Spirometry to measure lung functions is more objective than ACT and CASI scores. In this study, results showed that monosensitized children under the bovine colostrum group (n = 9) showed significantly better outcomes in the first month (FEV_1), second month (FEF_{25-75} and PEF), and third month (all parameters except FVC) of assessment as compared to the placebo group (n = 7). There is limited study correlating sensitization and the effect of bovine colostrum in respiratory allergies using spirometry.

CONCLUSION

This study showed that sensitization can affect an individual's response to bovine colostrum supplementation. Based on the assessment tools used, bovine colostrum supplementation significantly improved the symptoms of both monosensitized and polysensitized patients. In monosensitized patients with respiratory allergies, nasal congestion significantly improved. Significant improvement in the ACT and CASI scores was likewise observed in polysensitized patients. Finally, lung function response to bovine colostrum supplementation was more visible in the monosensitized patients.

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