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Effect of probiotic yogurt on antibiotic-associated diarrhea among pediatric patients; randomized controlled trial

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Abstract:

BACKGROUND: Diarrhea is a common unfavorable consequence of antibiotics. Probiotic yogurt is equally effective as probiotic capsules, so it may provide a simple and cost-effective means of preventing antibiotic-associated diarrhea (AAD). The study aimed to evaluate the effect of probiotic yogurt on AAD among pediatric patients.

MATERIALS AND METHODS: The randomized controlled trial design was adopted in this investigation, with a post-test-only control group. Data were obtained from 244 pediatric patients on antibiotics who were admitted to the hospital and included in the trial via full enumeration sampling. Selected subjects were randomly assigned to experimental (n = 122) or control (n = 122) groups. The experimental group received probiotic yogurt for five days, whereas the control group received standard care. The incidence and severity of diarrhea on the fifth day of the intervention were used to determine the study's results. The trial was registered with the Clinical Trials Registry - India (CTRI). Consolidated Standards of Reporting Trials (CONSORT) were followed. Descriptive and inferential statistics were used for data analysis. Statistical software was used for descriptive and inferential analysis.

RESULTS: AAD occurred in 13.90% and 36.88% of individuals in the experimental and control groups, respectively (*odds ratio: p: 0.27:0.001).* Further, yogurt intervention was found to be effective in terms of increasing the consistency of the stool (p. 001*), decreasing the duration and onset of diarrhea ($P \leq .001$*),* reducing the frequency and amount of loose stool ($P \leq .001$*), reducing the urgency of defecation ($P \leq .001$*), the presence of abdominal discomfort ($P \leq .001$*),* and dehydration ($P \leq .001$*).*

CONCLUSION: In hospitals, antibiotics are commonly prescribed, and the most common side effect of medications is diarrhea. Probiotic yogurt guards against this side effect of antibiotics. Nurse practitioners need to understand the value of probiotic yogurt as a preventive measure that could save children's lives.

Keywords:

Antibiotic-associated diarrhea, children, incidence, probiotic yogurt

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Introduction

The passage of more than three loose stools daily is referred to as diarrhea (or more frequent passing is typical for the individual). For several days, diarrhea can persist, depleting the body with the loss of minerals and water. Dehydration to a severe extent and fluid loss were the most frequent causes of diarrheal fatalities.[1]

Thousands of bacteria, yeast, and microbes inhabit our intestines, known as "normal flora." When the environment is balanced, these microbes promote good health, and gut

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bacteria aid digestion. Antibiotics disrupt this balance, causing antibiotic-associated diarrhea (AAD). Probiotics aim to restore healthy bacteria, but their effectiveness is uncertain. Limiting antibiotic use is crucial to preserve normal flora. Use antibiotics only when necessary to maintain a healthy microbial balance.[2]

Diarrhea affects one in five children who take antibiotics. Children under two years old are more likely to experience it, and any antibiotic can cause it.[3]

The majority of AAD cases are moderate and self-limited. Given the ubiquitous use of antibiotics, it is expected that this illness, which affects 5–39% of individuals receiving antibiotic treatment, is so prevalent.[4] Alterations in the gut microbiota leading to reduced absorption of short-chain fatty acids and the development of osmotic diarrhea seem to represent a notable mechanism in the context of AAD.[5]

Antibiotics with wide-ranging effectiveness, such as beta-lactams, clindamycin, and vancomycin can cause gastrointestinal (GI) distress by disrupting normal bowel flora, promoting unfavorable bacterial growth (e.g., Staphylococcus, Candida), and altering intestinal mucosa and motility. This often leads to AAD, affecting 11 to 30 percent of children on antibiotics, impacting patient adherence.[3]

Misuse of antibiotics, a significant public health issue, can lead to increased morbidity and mortality. Proper antibiotic usage, including completing treatment and avoiding overuse, has proven effective in reducing health risks.[6]

Probiotics, derived from the Greek word "for life," are live, non-pathogenic organisms with beneficial effects on their hosts. Coined by Vergin, probiotics aim to improve gut flora, defined by Fuller as non-pathogenic bacteria positively influencing the host's health and physiology.[5]

Probiotics refer to live microorganisms that offer advantages to the host when administered in suitable quantities. They work by forming a barrier against infections, enhancing mucus secretion, maintaining intestinal integrity, producing antimicrobial compounds, and boosting the immune system.[7]

Probiotics are living microorganisms that offer potential health benefits, including bacteria and yeasts. They are present in the human digestive system and various foods and supplements. These beneficial microorganisms, particularly in the gut, are gaining popularity due to emerging evidence linking gut flora to overall health. Probiotics, like Lactobacillus and Bifidobacterium, help to maintain a balanced gut microbiome. It is important to note that probiotics and prebiotics, which aid digestion but are not absorbed by the body, are distinct diet components.[8] Yogurt is an effective method for reducing the incidence of AAD in children.[9]

Material and Methods

Study design and setting

This was a two-group, randomized controlled trial (post-test-only control group design) conducted on 244 pediatric patients who were taking antibiotics and aged from 5 to 12 years admitted to the civil hospital in Mohali, Punjab, and Healthcare Multispecialty Hospital, Gharuan, Mohali, Punjab.

Study participants and sampling

The study's statistical population contained children admitted and on antibiotics. Inclusion criteria included male and female, aged 5-12 years, children who were on antibiotics and available at the time of data collection, and exclusion criteria included children who were not accessible at the time of data collection, children with lactose intolerance and chronic diarrhea and chronic GI disease. First, the study enrolled the children based on inclusion criteria through complete enumeration sampling. Afterward, with the help of software, subjects were randomized into experimental and control groups. The sample size was calculated based on precision rate (0.8), α (0.05), confidence level, i.e., at 95% ($Z = 1.96$), and standard deviation of 6.8 (roughly estimated based on the pilot study). Calculated effect size was 0.4. A minimum sample of 196 (98 in each group) was needed. By considering the attrition and loss of subjects during follow-up, a final sample size was fixed to 250 (125 for each group).

Data collection tools and technique

The sociodemographic profile of the participant and family profile was obtained with 11 questions information (e.g., age, gender, habitat, dietary habits, and parent's occupation and education), which was completed by questions from the children's self and family. The incidence of diarrhea was assessed by identifying the number of new cases of AAD reported within five days. A self-structured diarrheal severity assessment tool and the Bristol stool scale evaluated the severity of diarrhea. It was a 16-item scale to determine the diarrheal severity (e.g., duration, frequency, consistency, urgency of diarrhea, and signs of dehydration). It was completed by reviewing the children's records and questions from the family and nurse in charge of the children. Probiotic yogurt intervention was given to the children in the experimental group to evaluate its effectiveness in preventing AAD among pediatric patients taking antibiotics. Cronbach's alpha was used to determine the reliability of the tools, which was $P = 0.79$

for the Bristol stool scale and $P = 0.88$ for the diarrheal severity assessment scale.

Probiotic yogurt intervention

It includes the administration of 200 g of commercially available (epigamic) probiotic yogurt to the subjects on an empty stomach for five days. The control group received ward routine care. A post-test was conducted on the fifth day of the intervention among the experimental and control group subjects. The study was conducted using the Consolidated Standards of Reporting Trials (CONSORT) statement [Figure 1].

Data analysis

Data was analyzed using IBM SPSS-26 software. Data were checked for outliers, wild codes, irregularities, and missing values. The final analysis was performed on 244 subjects as 06 subjects (03 in the experimental and 03 in the control group) were lost during the follow-up period. (The response rate was 97.60). The equality of variances was determined using Levene's test. The Chi-square test and Fisher's exact test were used to analyze the categorical data, and an independent *t*-test was used to evaluate the effectiveness of the intervention. In all tests, a 95% confidence interval and a significance level of $\alpha = 0.05$ were considered. A *P* value of less than 0.05 was taken as an indicator of a difference in statistical significance [Figure 1].

Ethical consideration

The research was approved by the Institutional Ethics Committee (IEC) of the SPHE College of Nursing and dated April 2022 with registration no. IEC/SPHE/0011/2022. The Clinical Trials Registry - India (CTRI) approved the study protocol of clinical trials with the code CTRI/2023/05/052984. Informed consent was obtained from the legal guardian of the subjects whereas verbal assent was obtained from subjects aged above 7 years.[10] Anonymity and confidentiality of data were ensured.

Results

Description of sample characteristics

The sociodemographic characteristics of subjects in the experimental and control groups were found to be homogenous in terms of age ($P = .160$), gender ($P = .298$), number of antibiotics ($P = .118$), route of antibiotic ($P = .226$), and duration of antibiotic ($P = .844$) [Table 1].

Effectiveness of probiotic yogurt intervention

Part A: Incidence of AAD

The incidence of AAD was observed to be 13.93% among the children in the experimental group and 36.38% in the control group. The result indicates a substantial reduction in the incidence of AAD among those who used probiotic yogurt (*odds ratio: p: 0.27:0.001)*.

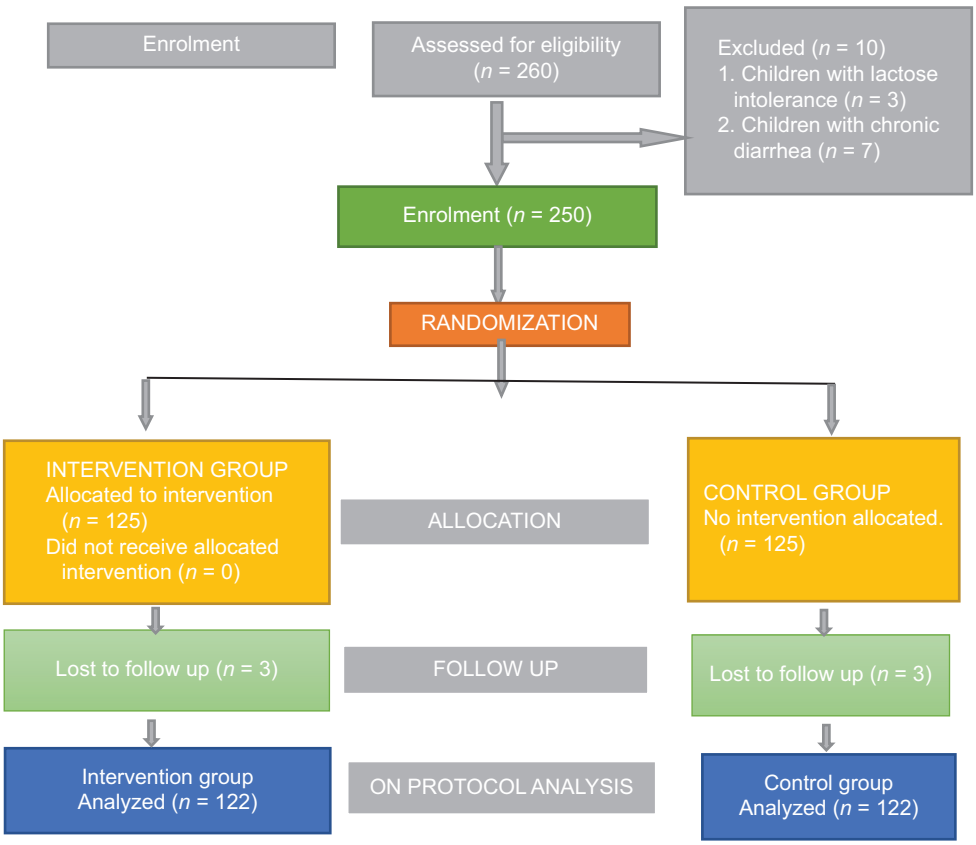

Figure 1: Consolidated Standards of Reporting Trials (CONSORT)

Table 1: Sociodemographic characteristics of the subjects (*n*=244)

Variable	Group		Ch, *t*	Sig value
	Experimental	Control		
Age	8.89±2.26 (Mean±SD)	9.29±2.19 Mean±SD)	1.62	0.160^{NS}
Gender				
Male	74 (48.40)	79 (51.60)	1.70	0.298^{NS}
Female	48 (52.70)	43 (47.30)		
Number of Antibiotics				
1.00	96 (52.50)	87 (47.50)	7.12	0.118^{NS}
2.00	26 (42.60)	35 (57.40)		
Route of Antibiotic Ingestion				
Intra venous	96 (51.60)	90 (48.40)	3.25	0.226^{NS}
Oral	26 (44.80)	32 (55.20)		
Duration of antibiotic (days)				
5	17 (51.50)	16 (48.50)	2.12	0.844^{NS} (Chi-square)
6	34 (50.00)	34 (50.00)		
7	39 (47.00)	44 (53.00)		
10	06 (42.90)	08 (57.10)		
11	26 (56.50)	20 (43.50)		

NS: Non-significant; **Significant

The odds of 0.27 suggest that the risk of continued diarrhea among patients in the control group (without intervention) is more than 3.63 times higher than those in the experimental group (received therapy) [Table 2].

Part B: Describing risks

The absolute risk for the experimental and control groups was 0.13 and 0.36, respectively. The calculated absolute risk reduction was 0.22, which means that 23% of subjects in the control group presumably would have recovered from diarrhea if they had received yogurt intervention, other than the 64% who recovered from diarrhea without yogurt intervention. Further, the relative risk was 0.37, which indicates that the incidence of diarrhea was reduced by 63% among those who received yogurt intervention. The number needed to treat (NNT) is 1/0.229 = 4.36. That means nearly five patients need to receive yogurt intervention to prevent one patient from continuing to have diarrhea [Table 3].

Part C: Effects on severity of diarrhea

A significant increase in the consistency of the stool ($P \leq .001$**), a decrease in the duration and onset of diarrhea ($P \leq .001$**), a decrease in the frequency and amount of loose stool ($P \leq .001$**), a decrease in the urgency of defecation ($P \leq .001$**), the presence of abdominal discomfort ($P \leq .001$**), and dehydration ($P \leq .001$**) were observed [Table 4].

Part D: Effect on hydration

Children in the experimental group exhibited less dehydration ($P \leq .001$**), improved physical appearance ($P \leq .001$**), better eye appearance ($P \leq .001$**), normal skin turgor ($P \leq .001$**), normal urine output ($P \leq .001$**), and good oral cavity appearance ($P \leq .001$**) [Table 5].

Table 2: Incidence of antibiotic-associated diarrhea (*n*=244)

Variable	Experimental group f (%)	Control group f (%)	Odds ratio	*P*
Antibiotic-associated diarrhea				
Yes	17 (13.93)	45 (36.88)	0.27	0.001
No	105 (86.06)	77 (63.11)		

Discussion

The present study aimed to assess the effectiveness of probiotic yogurt intervention in preventing AAD among children on antibiotics. The intervention reduced the incidence of AAD among pediatric patients, though the time between intervention and post-testing was short.

Utilizing yogurt as an intervention proved to be an efficient approach to decreasing the occurrence of AAD. A yogurt combination of LGG, La-5, and Bb-12 is an effective method for reducing the incidence of AAD in children.[9] The incidence of AAD in the experimental group was 13.93%, and in the control group was 36.38%. A study stated that 19.3% of patients in the probiotic group (106 out of 549) developed AAD, while in the placebo group, 17.9% (103 out of 577) experienced this condition.[11] Another study[12] reported that the subjects who received probiotic intervention had less incidence (12.5%) of AAD as compared to the control group (31.3%). Similarly, in another study, probiotic group was observed with a lower incidence of AAD (14%, 330 out of 2294), whereas the control group had a higher incidence, i.e., 19% (426 out of 2235).[13] Probiotics are a potential option for the prevention and treatment of AAD.[14]

Table 3: Absolute risks, Relative risk (RR), and Odds ratio of the subjects in the experimental and control group (*n*=62)

Risk parameter	Formula	Calculation	Value
Absolute risk in the experimental group (AR_E)	No. of subjects with the undesirable outcome/ total no. of the issues in the experimental group	17/122=0.139	0.139
Absolute risk in the control group (Ar_c)	No. of subjects with the undesirable outcome/ total no. of the issues in the control group	45/122=0.368	0.368
Absolute risk reduction (ARR)	Arc-AR_E	0.368-0.139=0.229	0.229
Relative risk (RR)	AR_E/Arc	0.139/0.368=0.377	0.377
Relative risk reduction (RR)	ARR/Arc	0.229/0.368=0.622	0.622
Odds ratio			
Experimental	Undesirable/Desirable outcome	17/105=0.161	0.275
Control	Undesirable/Desirable outcome	45/77=0.584	
Number Needed to Treat	1/ARR	1/0.229=4.36	4.36

Table 4: Assessment of severity of diarrhea (*n*=62)

Name of Variable	Group		Chi-square value
	Experimental	Control	
Consistency of stool			
Normal	07 (100.00)	00 (0.00)	<.001*
Normal	08 (100.00)	00 (0.00)	
Lacking fiber	02 (28.60)	05 (71.40)	
Mild diarrhea	00 (0.00)	20 (100.00)	
Severe diarrhea	00 (0.00)	20 (100.00)	
Duration of diarrhea (days)			
3	07 (100.00)	00 (0.00)	<.001*
4	01 (100.00)	00 (0.00)	
5	02 (4.80)	40 (95.20)	
6	07 (58.30)	05 (41.70)	
Frequency of loose stool (per day)			
1	00 (0.00)	04 (100.00)	<.001*
3	09 (100.00)	00 (0.00)	
4	06 (100.00)	00 (0.00)	
5	02 (16.70)	10 (83.30)	
7	00 (0.00)	15 (100.00)	
8	00 (0.00)	11 (100.00)	
9	00 (0.00)	05 (100.00)	
Characteristic of stool			
Watery	02 (05.40)	35 (94.60)	<.001*
Clustered	15 (60.00)	10 (40.00)	Fisher exact value
Presence of mucus/fat in stool			
Yes	03 (11.10)	24 (88.90)	<.001*
No	17 (36.20)	30 (63.80)	Fisher exact value
Presence of abdominal discomfort			
Yes	06 (13.60)	38 (86.40)	<.001*
No	11 (61.10)	07 (38.90)	Fisher exact value
Urgency of defecation			
Yes	02 (06.10)	31 (93.90)	<.001*
No	15 (51.70)	14 (48.30)	Fisher exact value

NS: Non-significant; **Significant

The absolute risk for the experimental and control groups was 0.13 and 0.36, respectively. The calculated absolute risk reduction was 0.22. The relative risk was 0.37, and the odds ratio was 0.27.[15] Probiotics intervention has resulted in a 38% reduction in the occurrence of AAD, with a relative risk of 0.62. In the probiotic group, the diarrhea rate stood at 23.0%, contrasting with the placebo group's lower rate of 17.6%, resulting in an absolute risk reduction of -5.35%.[16] The relative risk for AAD was reported as 0.7, along with a 95% confidence interval.[17] The relative risk was 0.56, and this measurement came with a 95% confidence interval (Patro-Golab B, Shamir R, Szajewska H. 2015).[18]

Table 5: Effect of probiotics on hydration of the subjects (*n*=62)

Variables	Group		Fisher exact value
	Experimental	Control	
Sign of dehydration			
Yes	04 (08.90)	41 (91.10)	<.001*
No	13 (76.50)	04 (23.50)	
Physical appearance			
Normal	12 (63.20)	07 (36.80)	<.001*
Lethargic	05 (11.60)	38 (88.40)	
Eye appearance			
Normal	12 (44.40)	15 (55.60)	<.001*
Sunken	05 (14.30)	30 (85.70)	
Skin turgor			
Normal	12 (70.60)	05 (29.40)	<.001*
Poor	05 (11.10)	40 (88.90)	
Urine output			
Normal	13 (48.10)	14 (51.90)	0.002*
Less than normal	04 (11.40)	31 (88.60)	
Oral cavity			
Normal	14 (41.20)	20 (58.80)	0.007*
Dry mouth	03 (10.70)	25 (89.30)	

NS: Non-significant; **Significant

The NNT was 4.36. That means nearly five patients need to receive yogurt intervention to prevent one patient from continuing diarrhea. The calculated NNT for low-dose probiotic intervention was 9 and high-dose probiotic was 6.[19]

Probiotic yogurt reduced the risk of AAD to 23% with a relative risk of 0.37. A similar study described that when probiotics were administered alongside antibiotics, the risk of AAD decreased by 37%, corresponding to a relative risk of 0.63.[20]

In the present study, only 13.60% of the subjects in the experimental group had reported abdominal discomfort as compared to 86.40% in the control group. The mean duration of antibiotic treatment was 7.71 + 2.7. A higher incidence of adverse events was reported, specifically abdominal pain was documented in 85.71% of the subjects, in contrast to the probiotic group, where it was reported in only 14.28% of cases.[9]

Patients with probiotic intervention were reported to have better improvements in various aspects, including the duration of diarrhea (measured in days), the intensity of abdominal pain, and stool consistency measured ($P \leq 0.01$).[21] The incidence of AAD episodes was notably reduced when probiotics were employed compared to situations where probiotics were not administered, with rates of 20% and 36%, respectively. This difference was statistically significant ($P = 0.022$).[22]

Probiotic yogurt intervention can be an effective strategy not only to decrease the duration of diarrhea but also to increase stool consistency.[23] Yogurt enriched with probiotics offers protection against alterations in the microbiome that can result in antibiotic-induced diarrhea and serves as a preventive measure against AAD.[24] The utilization of probiotics resulted in a significantly lower number of instances of AAD compared to situations where probiotics were not employed.[17] The administration of probiotic yogurt during antibiotic treatment has successfully prevented the occurrence of AAD.[25] Probiotic or regular yogurt consumption decreased the frequency, severity, and commencement of antibiotic-related diarrhea in children. Supplementing with probiotics has the potential to prevent aantibiotic-associated diarrhea. Certain probiotic strains can influence the intestinal mucosa by countering pathogens through the production of antimicrobial substances.[26]

Limitations and Recommendations

The limitations of this research were that the study was conducted in a limited setting that may restrict generalizability, even though a strong research design was used to ensure high internal and external validity. Reliance on self-reported data from participants can cause memory distortion and other biases that might have affected the quality of data even though data was collected diligently using standard protocol and as per the CONSORT guidelines. Furthermore, factors beyond the scope of the study, such as participants' diet, lifestyle, or other medications, could influence the results. Controlling for these variables may be challenging and could introduce confounding effects even though a control group was also taken to make accurate interpretations and limit extraneous variables. Only a post-test design was used. Hence, the initial homogeneity of the subjects in the experimental and control groups was not determined, which might have affected the results, even though randomization was used to ensure group equivalency.

It is recommended to develop strategies to monitor participants' compliance with the yogurt intervention, such as regular check-ins, dietary records, or objective biomarkers. Non-compliance can affect the intervention's efficacy and should be considered in the analysis and interpretation of results. Implement blinding techniques, such as double-blinding (participants and researchers are unaware of the assigned intervention),[10] to minimize bias and ensure the validity of the results.

Conclusion

Antibiotics are frequently prescribed in hospitals, and diarrhea is the most prevalent adverse effect of antibiotics. This negative effect of antibiotics is prevented

by probiotic yogurt. Nurse practitioners will recognize the importance of probiotic yogurt intervention, and the effectiveness of probiotic yogurt intervention may help them to use this intervention as an effective modality for the prevention of AAD and better outcomes of antibiotics.

Research involving humans

The research standards and the ethical committee responsible followed all the guidelines and procedures.

Consent for publication

All the authors agreed and consented to publication. Informed written consent was obtained from the children.

Availability of data and materials

The article incorporates all pertinent data related to the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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