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The Prophylactic Use of Probiotics in the Prevention of Acute Radiation-Induced Diarrhea in the Cervical Cancer Patient

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Abstract

Introduction: *Cervical cancer remains a major public health concern, particularly in developing countries, where access to early detection and treatment is limited. Radiotherapy, often combined with chemotherapy, is a cornerstone in the management of locally advanced cervical cancer. This study investigates the effectiveness of probiotics in reducing the incidence and severity of (Radiation Induced Diarrhea) RID among cervical cancer patients undergoing pelvic radiotherapy.*

Methods: *This quasi-experimental study was conducted at the National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka, from April 2022 to March 2023. A total of 70 patients with advanced-stage (IIB–IVA) cervical cancer undergoing concurrent chemoradiotherapy (CCRT) with external beam radiotherapy (EBRT) using a linear accelerator were selected through purposive sampling and divided into two groups: Arm A (probiotics group) and Arm B (placebo group), with 35 patients in each. Data were analyzed using SPSS version 25.*

Result: *The results of this study involving 70 cervical cancer patients showed that both arms (probiotics and placebo) were comparable in terms of baseline characteristics, including age, demographics, risk factors, histological type, grade, and staging ($p>0.05$). However, significant differences were observed in radiation-induced diarrhea (RID), with a higher incidence in the placebo group (82.9% vs 51.4%, $p=0.001$), earlier onset (9.82±0.61 vs 13.25±1.73 days, $p=0.016$), and higher grades of diarrhea. Loperamide use, dose, and initiation time also differed significantly, with higher use and earlier start in the placebo group. Stool consistency, abdominal pain, and fever over three weeks of follow-up did not show any significant difference between the groups ($p>0.05$).*

Conclusion: *This study suggests that prophylactic probiotics effectively reduce the incidence and severity of radiation-induced diarrhea and lower the need for loperamide in cervical cancer patients receiving pelvic radiotherapy. Fewer treatment interruptions in the probiotics group further indicate their protective role during therapy.*

Keywords: *Probiotics, Radiation-Induced Diarrhea, Cervical Cancer, Bleeding*

I. INTRODUCTION

Worldwide, it is estimated that 19.3 million new cases of cancer and almost 10.0 million cancer deaths occurred in 2020 [1]. Among these, cervical cancer is the 4th most common cancer in women after breast, colon, and lung cancer, and the 7th most common cancer in both sexes [2]. Worldwide, it is the 4th leading cause of cancer

death in women and the 9th leading cause of cancer death overall [3]. Although the incidence and mortality varied widely geographically. Over 85% of new cases are diagnosed in resource-limited countries, and in most of these countries, it is the most common cancer in females after breast cancer [1]. Like other low and middle-income countries (LMICs), cervical cancer is the 2nd most common cancer among females in Bangladesh and the 5th most common cancer in both sexes, and 7th leading cause of cancer death in both sexes in Bangladesh. According to the National for Cervical Cancer Prevention and Control Bangladesh (2017-22) every year 11,956 new case of cervical cancer is detected and 6,582 women die of this disease and according to the NICRH published cancer registry report 2018-2020 it is estimated that a total 83,795 new cases patients attended the outpatient department of NICRH, among them cervical cancer was 3,911 (10.9% of total patients) and the 2nd highest cancer in female and 3rd top malignancy in overall. Most cervical cancer is radiosensitive, and according to the NCCN guideline, external beam radiotherapy with concurrent chemotherapy and then brachytherapy is the standard option of treatment for locally advanced cervical cancer [4]. It was estimated that over 70% developed acute symptoms, whereas less than 5-30 % of the patients experienced chronic effects after pelvic radiotherapy [5,6]. Diarrhea is the most common acute side effect of pelvic radiation, and it may occur in up to 80% of patients [7]. Alomg with diarrhea, other acute symptoms such as rectal pain, rectal mucoid discharge, rectal bleeding, nausea, and malabsorption usually may occur during the 2nd to 3rd weeks of radiotherapy [8]. 5-10 % of the patients who have acute gastrointestinal tract complications during radiotherapy may suffer late serious complications, which include bowel obstruction, fistulation, perforation, and intractable bleeding, and the severity of acute bowel toxicity may predetermine the degree of chronic bowel change [9]. It is demonstrated that radiation-induced diarrhea (RID) may cause interruption and discontinuation of the treatment and worsen patients' quality of life [10]. The possible pathophysiology of radiation induced diarrhea are due to the change in the intestinal flora, composition of intestinal microflora, intestinal motility that altered metabolism of various intestinal enzyme lead to malabsorption of lactose and bile acid result in impaired secretion, change in vascular permeability of mucosal cell, altered the immune function of digestive tract that maintain the integrity of gut barrier [11]. According to the world Health Organization(WHO) "Probiotics are the live microorganism which when administered in an adequate amount confer a health benefit on the host" The possible mechanism of probiotics are correction of dysbiosis, down modulation of the severity of intestinal inflammation, down modulation of apoptosis, up regulation of the innate immune function and it helps in lactose digestion because lactose may reduce or lose due to damage of the intestinal villi [12] and these are the key factors in the prevention of radiation induced epithelial damage. The most commonly used probiotics are Lactobacillus and Bifidobacterium strains for preventing or reducing radiation-induced diarrhea, and some studies show positive results in the prophylactic use of probiotics in the prevention of radiation-induced diarrhea in pelvic radiotherapy in case of cervical cancer patients. This study aims to compare the effectiveness and convenience of probiotics for the prevention of acute radiation-induced diarrhea in patients receiving pelvic concurrent chemo radiotherapy in carcinoma of the cervix.

II. METHODS

This quasi-experimental study was conducted at the National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka, from April 2022 to March 2023. A total of 70 patients with advanced-stage (IIB–IVA) cervical cancer undergoing concurrent chemoradiotherapy (CCRT) with external beam radiotherapy (EBRT) using a linear accelerator were selected through purposive sampling and divided into two groups: Arm A (probiotics group) and Arm B (placebo group), with 35 patients in each. The inclusion criteria for the study were: women over 18 years of age with histologically confirmed cervical cancer of squamous, adenosquamous, or adenocarcinoma variants; an ECOG performance status of 0–2; and cancer staged between IIB and IVA according to FIGO clinical staging. Exclusion criteria included a history of prior pelvic radiotherapy, double malignancy, severe comorbidities, recent participation in another clinical trial within one month, pre-existing diarrhea, gastrointestinal diseases (such as IBS, IBD, or malabsorption syndrome), history of ileostomy or intestinal resection, daily use of antidiarrheal drugs before radiotherapy, immunosuppressive diseases or use of immunosuppressive drugs, presence of distant metastasis, development of unacceptable toxicity during treatment, or unwillingness to participate in the study. Arm A received probiotic capsules (Lactobacillus acidophilus 2 billion, L. bulgaricus 1 billion, Bifidobacterium bifidum 1 billion, and 100 mg fructo-oligosaccharide) thrice daily from the start to completion of CCRT, while Arm B received Vitamin B-complex capsules twice daily for the same duration. All patients were monitored daily during treatment and weekly for three weeks post-CCRT. Loperamide was administered in both arms when diarrhea occurred more than three times daily (initial dose 4 mg orally, then 2 mg after each unformed stool, max 16 mg/day). Data were analyzed using SPSS version 25, employing descriptive statistics (mean, SD, frequency, percentage) and inferential tests including Chi-square, Fisher Exact, and Student's t-test.

III. RESULTS

Table 1: Age distribution of the study subjects (n=70)

Age in years	Arm A (n=35)		Arm B (n=35)		p-value
	No	%	No	%	
31–40	6	17.6	3	8.6	0.729
41–50	17	50.0	21	60.0	
51–60	9	25.6	7	20.0	
>60	3	8.8	4	11.4	
Mean ± SD	49.85±9.09		50.17±7.73		

Data were analyzed using the Student t' t-test

Table 1 presents the age distribution of the study subjects. The mean±SD was 49.85±9.09 years in arm A and 50.17±7.73 in arm B. The p-value of 0.729 suggested that there was no significant difference in the age distribution between the two arms.

Table 2: Demographic characteristics of the study subjects (n=70)

Characteristics	Arm A (n=35)		Arm B (n=35)		p-value
	No	%	No	%	
Religion					
Muslim	32	91.4	35	100	0.077
Hinduism	3	8.6	0	00	
Marital status					
Married	35	100	35	100	-
Widow	0	00	0	00	
Occupation					
Housewife	28	80.0	31	88.6	0.478
Business	2	5.7	1	2.9	
Garment factory worker	5	14.3	3	8.6	
Socioeconomic status					
Lower class (<12260)	20	57.1	22	62.8	0.472
Middle class (12260–31640)	12	34.3	11	31.4	
Upper class (>31640/-)	3	8.6	2	5.8	

Data were analyzed using the Chi-square test.

Table 2 shows the number and percentage of individuals in arm A and arm B who belong to certain demographic categories such as religion, marital status, occupation, and socioeconomic status. Most of the patients were lower class in both arms, i.e., 57.1% in arm A and 62.8% in arm B. According to the p-value, statistically, there was no significant difference between the two arms.

Table 3: Risk factors of the study subjects (n=70)

Risk factor	Arm A (n=35)		Arm B (n=35)		p-value
	No	%	No	%	
Age of marriage					
≤18 years	29	82.9	32	91.4	0.427
>18 years	6	14.3	3	5.7	
Multi Parity	11	31.4	13	37.1	0.533
Malnutrition	20	57.1	22	62.9	-
Poor personal hygiene	7	20.0	5	14.3	-
H/O taking OCP	3	8.6	2	5.7	-
H/O tobacco	2	5.7	1	2.9	-

Data were analyzed using the Chi-square test.

Table 3 shows that in the majority of participants in both arms, the age of marriage was ≤18 years (82.9% vs 91.4%), and the prevalence of multi-parity was higher in arm B (37.1%) than in arm A (31.4%). In arm A, 57.1% were malnourished compared to 62.9% in arm B. 20% of cases in arm A showed poor personal hygiene compared to 14.3% in arm B. However, there was no statistically significant difference between the two arms in terms of risk factors.

Table 4: Histological type, grade, and staging of the study subjects (n=70)

Histological characteristics & stage	**Arm A (n=35)**		**Arm B (n=35)**		**p-value**
	No	%	No	%	
Histological type					0.521
Squamous cell carcinoma	34	97.1	33	94.3	
Adenocarcinoma	1	2.9	2	5.7	
Grade					0.447
Grade I	4	11.4	3	8.6	
Grade II	21	60.0	20	57.1	
Grade III	10	28.6	12	34.3	
Staging					0.414
IIB	12	34.3	15	42.9	
IIIA	4	11.4	6	17.1	
IIIB	15	42.9	11	31.4	
IIIC	3	8.6	2	5.7	
IV A	1	2.9	2	5.7	

Data were analyzed using Fisher's Exact test.

Table 4 presents the histological type, grade, and staging of 70 study subjects who were divided into two arms. The p-values for histological type, grade, and staging category were 0.521, 0.447, and 0.414, respectively, indicating there was no statistically significant difference between the two arms.

Table 5: Comparisons of the proportions of incidence of Radiation Induced Diarrhea (RID), onset of diarrhea, and grade of diarrhea between probiotics and placebo groups

Number and characteristics of RID	**Arm A (n=35)**		**Arm B (n=35)**		**p-value**
	No	%	No	%	
Radiation-induced diarrhea					
Yes	18	51.4	29	82.9	0.001
No	17	48.6	6	17.1	
Onset of diarrhea (Days)	13.25±1.73		9.82±0.61		0.016
Grading of diarrhea					
Grade I	12	37.1	1	8.6	
Grade II	6	17.14	16	45.7	0.001
Grade III	0	0.0	10	42.9	
Grade IV	0	0.0	1	2.9	

Data were analyzed using the Chi-square test.

Table 5 shows that the proportion of participants experiencing radiation-induced diarrhea was significantly higher in arm B (82.9%) compared to arm A (51.4%), with a statistically significant p-value of 0.001. The mean onset of diarrhea was significantly delayed in arm A at 13.25±1.73 days compared to arm B at 9.82±0.61 days, with a statistically significant p-value of 0.016. The grading of diarrhea showed a higher proportion of Grade I diarrhea in arm A (37.1%) and Grade II diarrhea in arm B (45.7%). The difference in grading of diarrhea between the two arms was statistically significant, as indicated by the p-value of 0.001.

Table 6: Comparisons of the proportions of the number of patients using loperamide, a dose of loperamide, and the starting time of loperamide between the two groups

Requirement of loperamide	**Arm A (n=35)**		**Arm B (n=35)**		**p-value**
	No	%	No	%	
Loperamide use					

Yes	18	51.4	29	82.9	0.001
No	17	48.6	6	17.1	
Loperamide (Dose)	10.30±0.28		18.18±0.35		0.001
Time of loperamide start (Days)	14.22±0.57		10.80±0.56		0.001

Data were analyzed using the Chi-square and t-test.

Table 6 shows the proportions of incidence of loperamide use, dose of loperamide, and time of loperamide start between the two groups. In arm B, 82.9% of the participants used loperamide, whereas in arm A, the proportion was 51.4%. This difference is statistically significant, as indicated by the low p-value of 0.001. Arm B had a significantly higher mean dose of loperamide (18.18±0.35 mg) compared to arm A (10.30±0.28 mg). The p-value of 0.001 suggested a statistically significant difference in the required dose of loperamide between the two arms. The starting mean time of loperamide for arm A was 14.22±0.57 days compared to 10.80±0.56 days in arm B. The p-value of 0.001 indicates a statistically significant difference in the time of loperamide initiation between the two arms.

Table 7: Assessment of consistency of stool in different follow-ups between the two arms (n=70)

Follow up	**Arm A (n=35)**		**Arm B (n=35)**		***p*-value**
	No	**%**	**No**	**%**	
1st week after treatment					
Normal bowel	32	91.4	33	94.3	
Loose bowel	3	8.6	2	5.7	0.664
Grade I	2	5.7	1	2.9	
Grade II	1	2.9	1	2.9	
2nd week after treatment					
Normal bowel	33	94.3	33	94.3	
Loose bowel	2	5.7	2	5.7	1.00
Grade I	1	2.9	1	2.9	
Grade II	1	2.9	1	2.9	
3rd week after treatment					
Normal bowel	35	100	33	94.3	
Loose bowel	0	00	2	5.7	0.398
Grade I	0	00	2	5.7	
Grade II	0	00	0	00	

Data were analyzed using Fisher's Exact test.

Table 7 shows the consistency of stool for 3 consecutive follow-ups after completion of treatment. The *p*-value indicating the difference between the two arms in terms of stool consistency during the follow-up was not statistically significant ($p>0.05$).

Table 8: Assessment of abdominal pain and fever up between two arms (n=70)

Follow up	**Arm A (n=35)**		**Arm B (n=35)**		***p*-value**
	No	**%**	**No**	**%**	
1st week after treatment Abdominal pain					
Mild pain (Grade I)	6	17.1	9	25.7	
None	29	82.9	26	74.3	0.382
Fever					
Yes (Grade I)	2	5.7	1	2.9	
No	33	94.3	34	97.1	0.553
2nd week after treatment Abdominal pain					
Mild pain (Grade I)	2	5.7	3	8.6	
None	33	94.3	32	91.4	0.641
Fever					

Yes (Grade I)	0	00	1	2.9	
No	35	100	34	97.1	
3rd week after treatment Abdominal pain					
Mild pain (Grade I)	1	2.9	1	2.9	
None	34	97.1	34	97.1	0.100
Fever					
Yes	0	00	0	00	
No	35	100	35	100	-

Data were analyzed using Fisher's exact test.

Table 8 shows the assessment of abdominal pain and fever for 3 consecutive follow-ups after completion of treatment. The *p*-value indicating the difference between the two arms in terms of abdominal pain and fever during the follow-up was not statistically significant ($p>0.05$).

IV. DISCUSSION

Among total patients (n=70) in this study, the mean age was 49.85±9.09 years in arm A and 50.17±7.73 in arm B, and the age distribution was almost similar without any statistical difference between the two arms (p=0.729). This finding was consistent with other studies (Linn et al., 2019). The age of marriage was analyzed, and it was observed that the age of marriage was ≤ 18 years in both arm A (82.9%) and arm B (91.4%), and statistically was not significant (p=0.427). This finding was consistent with other studies (Hossain et al., 2016). Socioeconomic status was determined according to the report of the Household Income and Expenditure Survey (HIES)-2016, Statistics and Information Division, Bangladesh Bureau of Statistics, Ministry of Planning, June 2019. Most of the patients in this study belonged to a lower socioeconomic status in both arm A and arm B (57.1% vs 62.8%), and there was no statistically significant difference between the two arms (p=0.472). In this study, arm B had a significantly higher proportion of subjects who experienced radiation-induced diarrhea compared to arm A (82.9% vs. 51.4%), which was statistically significant ($p=0.001$). This finding was consistent with previous studies and identified an association between radiation and the incidence of diarrhea in patients who underwent pelvic radiation therapy [13]. The mean onset of diarrhea was significantly earlier in arm B (9.82±0.61) days compared to arm A (13.25±1.73) days, with a statistically significant *p*-value of 0.016. According to the grading of diarrhea, a higher proportion of Grade I diarrhea was observed in arm A compared to arm B (37.1% vs 8.6%). In terms of Grade II diarrhea, the proportion was 54.3% in arm A and 45.7% in arm B. Regarding Grade III diarrhea, arm B developed a substantially higher proportion of diarrhea (42.9%) compared to arm A (0%). In arm B, a few patients developed grade IV diarrhea (2.9%) compared to arm A (0%). The difference in grading of diarrhea between the two arms was statistically significant, as indicated by the *p*-value of 0.001. This finding was consistent with other studies [13,14]. In arm B, 82.9% of the participants required loperamide as an antidiarrheal drug where whereas in arm A, the proportion was 51.4%. This difference was statistically significant, as indicated by the *p*-value of 0.001. The starting mean time of loperamide for arm A was 14.22±0.57 days compared to arm B, 10.80±0.56 days, where the *p*-value of 0.001 indicates a statistically significant difference. The required mean dose of loperamide for arm B was significantly higher, at 18.18±0.35 mg, compared to arm A of 10.30±0.28 mg. The *p*-value was statistically significant ($p=0.001$). The finding was consistent with another review [15,13]. In this study, the interruption of radiotherapy due to diarrhea in arm A was 5.7% compared to arm B, 14.3% with a *p* value of 0.033, indicating a statistically significant difference between the two arms, and this finding was consistent with other studies [14,15]. After completion of CCRT, patients were followed up weekly for three consecutive weeks to evaluate the incidence and grade of diarrhea, abdominal pain, and fever. Overall, the findings of this study highlighted the importance of probiotics in managing the radiation-induced diarrhea in patients with cervical cancer who underwent pelvic radiation therapy. Further research is warranted to investigate the potential adverse effects of probiotics in this setting. Additionally, the use of loperamide should be considered in patients experiencing severe or persistent diarrhea during radiation therapy, but careful monitoring is required to avoid constipation or other adverse effects associated with prolonged loperamide use.

V. Limitations of The Study

This study included only patients with cervical cancer who received pelvic radiation, and the assessment of radiation-induced diarrhea was based solely on self-reported symptoms by participants. It did not explore the long-term effects or potential risks associated with probiotic use. Additionally, the study was limited by a small sample size and was conducted at a single center, which may affect the generalizability of the findings.

VI. CONCLUSION

The results of this study suggest that the prophylactic use of probiotics is beneficial to reducing the incidence and severity of acute radiation-induced diarrhea in cervical cancer patients undergoing pelvic radiation therapy, and the requirement of loperamide as an anti-diarrheal drug is less in the probiotics group (Arm A) compared to the placebo group (Arm B). This study also shows the small proportion of subjects experienced interruption of radiotherapy in the placebo Group (Arm B) compared to the probiotics group (Arm A), indicating that probiotics are protective against diarrhea during radiation therapy.

VII. RECOMMENDATION

- Prophylactic use of probiotics may be considered for cervical cancer patients undergoing radiation therapy to prevent acute radiation-induced diarrhea.
- Further research is needed to investigate the optimal dose, duration, and type of probiotics to be used in this context, as well as potential interactions with other medications.
- Conducting additional research across multiple institutions with a substantial sample size could provide valuable insights into the long-term effect.

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