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Effects of Pentoxifylline and Tocopherol in Combating Toxicities Associated with Preoperative Concurrent Chemoradiation of Locally Advanced Rectal Cancer

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ABSTRACT: ***Background:*** Concurrent chemoradiation is an essential part in the treatment of locally advanced rectal cancer and causes significant toxicities. Severe toxicity may cause treatment interruption and decrease local control rate. Management of treatment related complications are being studied worldwide. ***Objectives:*** To determine the efficacy of Pentoxifylline and Tocopherol in combating toxicities in locally advanced rectal cancer during concurrent chemo-radiation. ***Methods:*** A quasi-experimental study was conducted from November 2020 to October 2021, involving 80 patients (40 in each arm). Arm A received Pentoxifylline (400 mg) and Tocopherol (400 mg) twice daily alongside CCRT, while Arm B received only CCRT. Toxicity data were collected from the start of CCRT until 12 weeks' post-treatment. Data was analyzed using independent sample t-tests for continuous variables and Chi-square tests for categorical variables. ***Results:*** Arm A demonstrated fewer cases of diarrhea, rectal bleeding, pelvic pain, and per rectal discharge at 4th and 6th weeks during CCRT and 6 and 12 weeks after treatment compared to Arm B. Hospitalization rates were significantly lower in Arm A (17.5%) compared to Arm B (37.5%) ($p < 0.05$). The mean length of hospital stay was shorter in Arm A (5.3 ± 1.7 days) compared to Arm B (10 ± 1.9 days) ($p < 0.05$). Treatment interruptions occurred in 20% of Arm A patients and 42.5% of Arm B patients ($p < 0.05$). No significant difference in treatment response was noted between the groups (67.5% in Arm A vs 62.5% in Arm B, $p > 0.05$). ***Conclusion:*** Prophylactic use of Pentoxifylline and Tocopherol at the beginning of CCRT in locally advanced rectal cancer may be beneficial in terms of minimizing toxicities, preventing treatment break and reducing hospital admission.

Keywords: Pentoxifylline and Tocopherol, Chemoradiation of Locally Advanced Rectal Cancer.

Article at a glance:

Study Purpose*: To evaluate the effectiveness of Pentoxifylline and Tocopherol in reducing toxicities during preoperative concurrent chemoradiation for locally advanced rectal cancer.*

Key findings: *Pentoxifylline and Tocopherol reduced toxicities like diarrhea, rectal bleeding, and pelvic pain, with fewer hospitalizations and treatment interruptions compared to chemoradiation alone.*

Newer findings: *This study shows that Pentoxifylline and Tocopherol effectively manage chemoradiation-induced toxicities, improve patient outcomes, and minimize treatment disruptions.*

Abbreviations: *CCRT – Concurrent Chemoradiation Therapy, HFNC – High-Flow Nasal Cannula, IMV – Invasive Mechanical Ventilation, ARDS – Acute Respiratory Distress Syndrome, VAP – Ventilator-Associated Pneumonia.*

INRODUCTION

Rectal cancer is a common malignancy, which has increased in the last decade which constitutes approximately 5% of all cancers. The term rectal cancer refers to a slowly developing cancer that begins as a tumour or tissue growth on the inner lining of the rectum. If this abnormal growth, known as polyp, eventually becomes cancerous, it can form a tumour on the wall of the rectum and subsequently grow into blood vessels or lymph vessels, increasing the chance of metastasis to other anatomical sites. Between 5% and 10% of the patients with rectal cancer are present with locally advanced rectal cancer (LARC). The Global burden of colorectal cancer (CRC) is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030. CRC incidence and mortality rates vary up to 10-fold worldwide, with distinct gradients across human development levels,

pointing towards widening disparities and an increasing burden in countries in transition. Generally, CRC incidence and mortality rates are still rising rapidly in many low-income and middle-income countries; stabilizing or decreasing trends tend to be seen in highly developed countries where rates remain among the highest in the world.[1] According to GLOBOCAN, carcinoma rectum is the 7th malignancy worldwide (3.8%) where 61% of them are male and 39% are female. Mortality rate is 3.2% worldwide in high or very high HDI countries and Southeast Asia age standardized incidence rate per 100000 is 8.3 and 5.0 for males and females respectively. CRC is the third commonest diagnosed cancer and the second leading cause of cancer-related mortality. According to the World Health Organization (WHO) database, there are 1.93 million estimated new CRC cases and 0.94 million CRC-related deaths in 2020. Regional estimates show that among half of the new cases, deaths and 5-year prevalent cases were found in Asia. Rectal Cancer is in 16th position in Bangladesh as per incidence and mortality rate .[2] Deaths in Bangladesh reached 4,534 or 0.63% of total deaths according to the latest WHO data published in 2020.

In 2016 there were an estimated 134,490 new colorectal cancer cases (70,820 in males and 63,670 in females) along with 49,190 colorectal cancer death (26,020 and 23,170 in male and females respectively). Colorectal cancer ranked third, only behind prostate cancer and lung cancer, for new cases in male (8% of all new cancer) and behind breast cancer and lung cancer for new cases in females (8% of all new cancer cases). Similarly, only lung cancer and prostate cancer are expected to claim more in the US. male lives than colorectal cancer in 2016 and only lung cancer and breast cancer are expected to take more US females lives (8% of total cancer death for both genders). Thus, rectal cancer remains a heavy burden on the global population. A sharp increase in the incidence of colorectal cancer in Asian developed countries may be attributable to economic growth and environmental factors such as the Western lifestyle. Colorectal cancer has clearly become an emerging health threat in Asia-Pacific regions and is dramatically increasing in its incidence. Prevention and treatment programs for colorectal cancer control should be actively implemented and evaluated in this region.[3] Multimodality treatments are available for curative intention. Concurrent chemo-radiation is a good treatment option. It is obvious that chemo-radiotherapy can reduce the distressing symptoms of patients as well as local control of tumour. Most cancer patients of this country come to tertiary level hospitals in advanced stages and with an age limit of 35-54 years. It is well known that less access to Screening and health care services, increasing average life expectancy, changes in lifestyle like consumption of processed meat, red meat, refined grains, starch and sugars, excessive alcohol intake and smoking are attributable to the occurrence of such diseases in the Developing world. Another risk factor is inflammatory bowel disease, which includes Crohn's disease and Ulcerative Colitis. Some of the inherited genetic disorders that can cause colorectal cancer include familial adenomatous polyposis and hereditary non-polyposis colon cancer; however, these represent less than 5% of cases. Approximately 20% of cases of CRC cancer are associated with newly diagnosed colorectal adenoma or invasive colorectal cancer. Therefore, it is recommended that all patients with colorectal cancer be required regarding their family history and considered for risk assessment.[4] Vast majority (over 95%) of Colorectal cancer are classified as adenocarcinoma. These begin in the mucus making glands lining the rectum. Other less-common cancers of the colorectal region include carcinoid tumours (which begin in hormone producing intestinal cells), gastrointestinal stromal tumours (which form in specialized colonic cells known as intestinal cells of Cajal), lymphomas (immune system cancers that form in the colon or rectum), and sarcomas (which typically begin in blood vessels but occasionally form in colorectal walls.[5]

Rectal cancer has the potential to produce significant pelvic morbidity including pain, bleeding, abdominal cramping, obstruction, hemorrhage, tenesmus and discharge. Systemic anti-mitotic treatment has prolonged the median survival of patients with advanced colorectal cancer for up to two years. Worldwide the treatment of rectal cancer can be aimed at cure or palliation. The decision on which aim to adopt depends on various factors, including the person's health and preferences, as well as the stage of the tumor. When CRC diagnosed early, surgery can be curative. As with chemotherapy, radiotherapy can be used as a neo-adjuvant for clinical stages T3 and T4 for rectal cancer. This results in downsizing or downstaging of the tumor, preparing it for surgical resection, and decreases local recurrence rates.

Enteritis and proctitis are the most relevant complications following chemoradiotherapy for carcinoma rectum. Chemo-radiation induced enteritis and proctitis resulting in bleeding, pain, abdominal cramping, mucoid discharge, fecal urgency and the incidence has been estimated between 5% to 30% after chemoradiotherapy. The pathogenesis of chemo-radiation enteritis and proctitis is characterized by inflammatory disease, end arteritis of arterioles, epithelial atrophy, vascular thrombi, ischemia, necrosis and excessive fibrosis. Chemo-radiation proctitis and enteritis is a relevant complication of pelvic irradiation, which is still mainly treated by supportive measures only. On the other hand, several studies on the treatment of chemo-radiation induced injury to other tissues indicated that treatment with Pentoxifylline and Tocopherol might be promising.[6] The phosphodiesterase inhibitor Pentoxifylline playing a role in inflammatory and fibrotic process. The combination treatment with Pentoxifylline and Tocopherol seems to have a benefit in patients with grade I–II proctitis and enteritis. This drug pentoxifylline and tocopherol are available anywhere. Pentoxifylline produces hemorheological effects and additionally is an immune modulator with activities on down regulation of several cytokines that are known to be mediators of inflammatory and fibrotic reactions. Pentoxifylline decreases fibrosis by reducing blood viscosity and improving erythrocyte flexibility, leading to increase blood flow and higher oxygenation. It may also decrease the inflammatory response and formation of oxygen radicals induced by radiation injury by inhibiting neutrophil activity and adhesion. Pentoxifylline has also shown to decrease fibroblast cellular matrix and collagen production by blocking the activity of TNF, decreasing production of interleukin (eg.1B) and stimulating collagenase activity. After irradiation radiation damage is mediated through reactive oxygen metabolites and tocopherol which has antioxidant properties may also be beneficial in the treatment of inflammatory and fibrotic process. Considering that Pentoxifylline and Tocopherol interfere with chemo-radiation induced damages, it is hypothesized that this treatment combination could improve chemo-radiation induced toxicities.

Aims and Objective

The aim of this study is to assess the effectiveness of Pentoxifylline and Tocopherol in reducing toxicities during preoperative concurrent chemoradiation for locally advanced rectal cancer. Specific objectives include evaluating treatment-related toxicities, comparing treatment interruptions, analyzing hospitalization rates due to complications, and determining the overall treatment response rates.

MATERIAL AND METHODS

Study Design

This study is a quasi-experimental design conducted to evaluate the efficacy of Pentoxifylline and Tocopherol in reducing toxicities during preoperative concurrent chemoradiation for locally advanced rectal cancer. The study was carried out at the Department of Radiation Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka, from November 2020 to October 2021. A purposive sampling technique was used to select 80 patients, divided into two arms: 40 patients received Pentoxifylline and Tocopherol (Arm A), and 40 patients received only concurrent chemoradiation (Arm B). The study aimed to assess treatment-related toxicities, complications, and treatment response.

Inclusion Criteria

Patients diagnosed with histopathologically confirmed adenocarcinoma of the rectum were included in the study. Only those with locally advanced rectal cancer, with an ECOG performance status of 0 to 2, and those planned for preoperative concurrent chemoradiation were eligible. Patients had to be capable of undergoing the planned chemoradiation regimen and willing to attend follow-up visits during and after the treatment period.

Exclusion Criteria

Patients aged below 21 or above 70 years were excluded from study. Additionally, those who had received prior chemotherapy or radiotherapy, or who suffered from serious concomitant illnesses such as severe heart disease, uncontrolled diabetes mellitus, hypertension, liver disease, renal disease, or inflammatory bowel disease, were also excluded. Patients who were unable to attend follow-up visits during the study period were not included in the study.

Data Collection

The data collection process involved obtaining informed written consent from all patients or their attendants before enrollment. A comprehensive history, physical examination, and

laboratory investigations were recorded for each participant. The patients' responses to the treatment were monitored from the start of concurrent chemoradiation through to 12 weeks after treatment. Data on treatment-related toxicities, hospitalization rates, and treatment interruptions were systematically documented. Data was collected through a pretested and semi-structured questionnaire designed for this purpose.

Data Analysis

The data were analyzed using SPSS version 26.0. Descriptive statistics were used to summarize patient characteristics and treatment outcomes. The independent sample t-test was applied for continuous variables to compare means between the two groups, while the Chi-square test was used for categorical variables to compare proportions. Statistical significance was set at $p < 0.05$. Data are presented as mean ± standard deviation for continuous variables and as percentages for categorical data.

Procedure

Patients meeting the inclusion criteria were enrolled after providing informed written consent. They were randomly assigned to either Arm A or Arm B based on purposive sampling. Arm A received Pentoxifylline (400 mg) and Tocopherol (400 mg) twice daily, along with preoperative concurrent chemoradiation, while Arm B received only concurrent chemoradiation. The treatment plan for both arms included the same chemotherapy and radiotherapy regimen. A toxicity assessment was done regularly during the treatment process and at 6 and 12 weeks after treatment. Adverse effects such as diarrhea, rectal bleeding, pelvic pain, and per rectal discharge were closely monitored. Hospitalization rates, length of hospital stay, and treatment interruptions were recorded as part of the safety profile assessment. The response to treatment was evaluated at the end of the study. Follow-up assessments were conducted at designated intervals to track any treatment-related complications. The results were then compared between the two arms to determine the impact of Pentoxifylline and Tocopherol in reducing toxicities and improving overall treatment outcomes.

Ethical Considerations

Ethical approval for the study was obtained from the institutional review board of NICRH. Informed consent was obtained from all participants or their guardians, ensuring that they were fully aware of the study procedures, potential risks, and benefits. Confidentiality of patient information was maintained throughout the study, and all procedures conformed to ethical guidelines for clinical research.

RESULTS

Table 1: Age Distribution of the Patients: (N=80)

Age Groups (Years)	Arm A n (%)	Arm B n (%)	*p*-value
21-30	12 (30)	8 (20)	0.595
31-40	6 (15)	10 (25)	
41-50	12 (30)	12(30)	
51-60	6 (15)	8 (20)	
61-70	4 (10)	2 (5)	
Total	**40 (100)**	**40 (100)**	
Mean(±SD) 42.8 (± 13.2) Years		**Mean(±SD)** 42.0 (±13.1) Years	

Table shows age of the patients was divided into 5 groups: 21 to 30, 31 to 40, 41-50, 51 to 60 and 61 to 70 years. Mean age of Arm A group was 42.8 (± 13.2) years and in Arm B group 42.0 (±13.1) years. t-test was done to measure of significance. But there was no significant relationship between the groups (p=0.595).

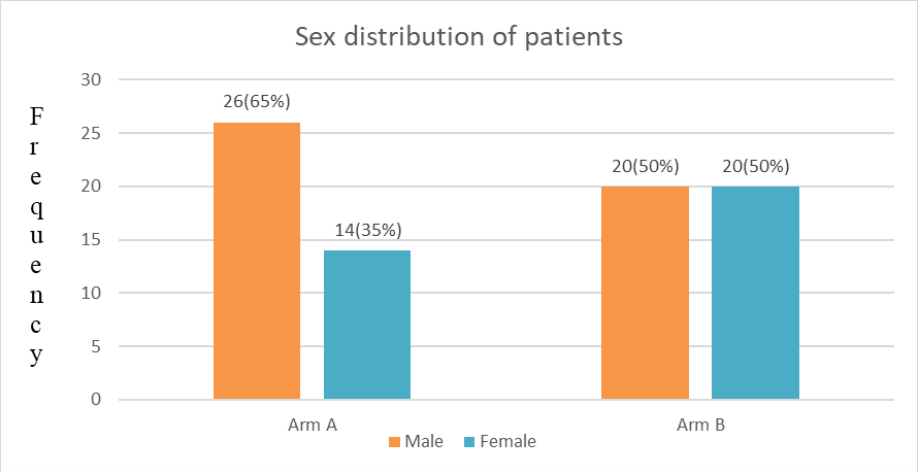

Figure 1: Sex Distribution of the Patients: (N=80)

From the bar diagram, Arm A group had male predominant (65%) patients. But in Arm B group both male and female were equal (50%) in number.

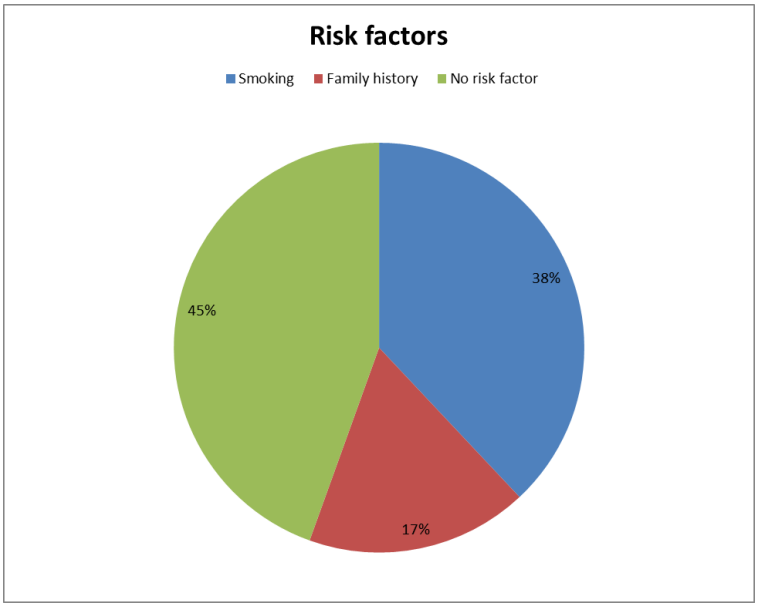

Figure 2: Distribution of Patients According to Risk Factors (N=80)

Figure shows the distribution of patients according to risk factors in both arms. Most of the patients (e.g. 38.0%) were smokers in both arms [15 (36.7%) in arm A and 16 (40.0%) in arm B]. Family history was detected in total 14 (17.5%) patients. (Smoking: Smoking is the inhalation of the smoke of burning tobacco encased in cigarettes, pipes, and cigars).

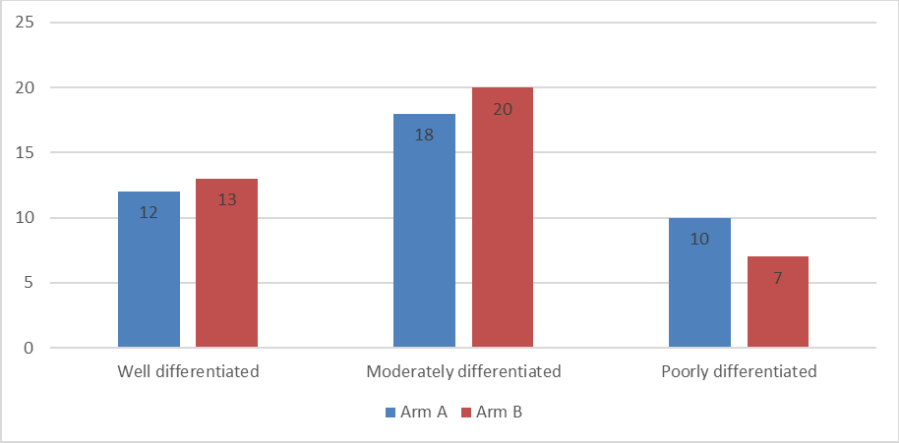

Figure 3: Bar Chart Showing the Grading of Tumour (N=80)

Figure shows the distribution of patients according to tumour grading. Well differentiated tumour was 12(30.0%) patients in Arm A and 13 (32.5%) in arm B. Moderate differentiated tumour was 18(45.0%) patients in Arm A and 20(50.0%) in arm B. Poor differentiated tumour was 10(25.0%) patients in Arm A and 7(17.5%) in arm B.

Table 2: Pretreatment Clinical Stage of the Patients in Both Arms: (N=80)

Stages of the disease	Arm A (n = 40)		Arm B (n = 40)		*p* value
	n	%	n	%	
Stage IIA & IIB	23	57.5	25	62..5	
Stage IIIA	17	42.5	14	35.0	0.824
Stage IIIB	0	0	1	2.5	

Table shows the pretreatment clinical stage of the patients in both arms. In this study 57.5% and 62.5% patients of Arm A and Arm B were Stage IIA & IIB, respectively in pre-treatment state. Though the p-value was not significant (>0.05).

Table 3: Distribution of Patients According to Physical Examination and Imaging Findings (N=80)

Findings	Group		Chi-square value	*p* value
	Arm-A (total = 40) n (%)	Arm-B (total = 40) n (%)		
DRE findings			0.048	0.976
Bleeding	35 (86.66)	36(90.0)		
Growth	40 (100.0)	39(96.7)		
Adhesion of growth with surrounding structure	36 (90.0)	37(93.3)		
MRI findings				
Growth	40(100.0)	40(100.0)	0.285	0.622
Lymph node involvement	17(42.5)	21(52.5)		

Digital rectal examinations and MRI were done for bleeding, growth and adhesion of growth with surrounding structure and lymph node status. P value reached from Fisher's exact test.

Table 4: Toxicities Assessment During 2nd Week of CCRT: (N=80)

Symptoms	Arm A n (%)	Arm B n (%)	*p* value
Diarrhoea			**0.9637**
Grade 0	17 (42.5)	15 (40)	
Grade I	18 (45)	18 (45)	
Grade II	5 (12.5)	5 (12.5)	
Grade III	0	2 (5)	
Rectal bleeding			**0.954**
Grade 0	19 (47.5)	18 (45)	
Grade I	14 (35)	14 (35)	
Grade II	7 (17.5)	8 (20)	
Pelvic pain			**0.185**
Grade 0	24 (60)	22 (55)	
Grade I	10 (25)	10 (25)	
Grade II	6 (15)	8 (25)	
Rectal discharge			**0.691**
Grade 0	23 (57.5)	20 (50)	
Grade I	10 (25)	10 (25)	
Grade II	7 (17.5)	10 (25)	
Skin Change			**0.958**
Grade 0	20 (50)	19 (47.5)	
Grade I	12 (30)	12 (30)	
Grade II	8 (20)	9 (22.5)	
Anaemia			**0.817**
Grade 0	6 (15)	5 (10)	
Grade I	27 (67.5)	27 (67.5)	
Grade II	7 (17.55)	8 (20.0)	

During 2nd week of CCRT, toxicities (Diarrhoea, rectal bleeding, pelvic pain, rectal discharge, skin change and anaemia) were lower in the patients in Arm A who received Pentoxifylline and Tocopherol. But the differences were not statistically significant (p>0.05).

Table 5: Toxicities Assessment During 4th Week of CCRT: (N=80)

Symptoms	Arm A n (%)	Arm B n (%)	*p* value
Diarrhoea			**<0.001**
Grade 0	20 (50)	5 (12.5)	
Grade I	17 (42.5)	17 (42.5)	
Grade II	3 (7.5)	16 (40)	
Grade III	0	2 (5)	
Rectal bleeding			**<0.001**
Grade 0	28 (70)	6 (15)	
Grade I	10 (25)	26 (65)	
Grade II	2 (5)	8 (20)	
Pelvic pain			**0.001**
Grade 0	34 (85)	20 (50)	
Grade I	6 (15)	10 (25)	
Grade II	0	10 (25)	
Rectal discharge			**0.001**
Grade 0	34 (85)	20 (50)	

Grade I	6 (15)	10 (25)	
Grade II	0	10 (25)	
Skin Change			**0.66**
Grade 0	17 (42.5)	14 (35)	
Grade I	15 (37.5)	19 (47.5)	
Grade II	8 (20)	7 (17.5)	
Anaemia			**0.449**
Grade 0	6 (15)	3 (7.5)	
Grade I	28 (70)	28 (70)	
Grade II	6 (15)	9 (22.5)	

During 4th week of CCRT, toxicities (Diarrhoea, rectal bleeding, pelvic pain, rectal discharge) were much lower in the patients in Arm A who received Pentoxifylline and Tocopherol. The difference was statistically significant ($p<0.05$). But difference was not statistically significant in skin change and anaemia ($p>0.05$).

Table 6: Toxicities Assessment During 6th Week of CCRT: (N=80)

Symptoms	**Arm A n (%)**	**Arm B n (%)**	***p* value**
Diarrhoea			**<0.001**
Grade 0	21 (52.5)	3 (7.5)	
Grade I	15 (37.5)	17 (42.5)	
Grade II	4 (10)	18 (45)	
Grade III	0	2 (5)	
Rectal bleeding			**<0.001**
Grade 0	20 (50)	5 (12.5)	
Grade I	17 (42.5)	23 (57.5)	
Grade II	3 (7.5)	12 (30)	
Pelvic pain			**0.0049**
Grade 0	30 (75)	17 (42.5)	
Grade I	8 (20)	12 (30)	
Grade II	2 (5)	11 (27.5)	
Rectal discharge			**0.0048**
Grade 0	32 (80)	20 (50)	
Grade I	7 (17.5)	10 (25)	
Grade II	1 (2.5)	10 (25)	
Skin Change			**0.586**
Grade 0	14 (35)	10 (25)	
Grade I	18 (45)	22 (48.8)	
Grade II	8 (20)	8 (20)	
Anaemia			**0.594**
Grade 0	8 (20)	5 (12.5)	
Grade I	27 (67.5)	28 (70)	
Grade II	5 (12.5)	7 (17.5)	

During 6th week of CCRT, toxicities (Diarrhoea, rectal bleeding, pelvic pain, rectal discharge) were much lower in the patients in Arm A who received Pentoxifylline and Tocopherol. The difference was statistically significant ($p<0.05$). but difference was not statistically significant in skin change and anaemia ($p>0.05$).

Table 7: Number of Patients with Treatment Interruption (N = 80).

Trait	Arm A	Arm B	Chi-square value	*p*-value
	N percentage	N percentage		
Number of patients with RT break	8 (20.0)	17 (42.5)	4.7	0.0294

RT=Radiotherapy

Table 8: Duration of Hospital Stay

Trait	Arm A (n=7)		Arm B (n=15)		t test	*p*-value
	Mean	Standard deviation	Mean	Standard deviation		
Duration of hospital stay (days)	5.3	±1.7	10.0	±1.9	-6.242	<0.001

This table XI shows that the number of patients required hospitalization due to complications was 7 (17.5%) in Arm A and 15(37.5%) in Arm B (statistically significant $p < 0.05$). This table XII shows that the Mean length of hospital stay was 5.3 ± 1.7 in Arm A and 10.0 ± 1.9 in Arm B (statistically significant $p < 0.05$).

Table 9: Distribution of the patients according to treatment response after 6 weeks of CCRT (N=80)

Response	Arm A n (%)	Arm B n (%)	*p* value
			0.371
Complete response	6 (15)	4 (10)	
Partial response	27 (67.5)	25 (62.5)	
Stable disease	6 (15)	6 (15)	
Progressive disease	1(2.5)	5 (12.5)	

Final follow up was done 6 weeks after completion of reatment and it was observed that 67.5% of patients had a partial response in Arm A and in Arm B 62.5% had a partial response. The overall treatment response was 65%. Statistical analysis revealed there was no significant difference but arithmetically this proven that Arm A patients had better response than Arm B. chi-square test was used to determine *p* value.

DICUSSION

Colorectal cancer (CRC) is the third most common cancer worldwide. CRC has been thought to be less common in Asia compared to Western countries. However, the incidence rates of CRC in Asia are high and there is an increasing trend in the Asian population. Furthermore, colorectal cancer accounts for the greatest number of all incidences of CRC in Asia .[7] Most of the patients in my study groups belonged to the age group 41-50. The mean age in Arm A 42.8(±13.2) and (±13.2). Similar result was observed in previous study Gou *et al*., Difference was not significant (p>0.05) between two Arms.[8] In Arm A group, majority was male (65%) and in Arm B group both male and female were equal (50%) in number. Among all patients' male and female ratio 1.35: 1. In Arm A male female ratio 1.8 :1 and In Arm B male female ratio 1:1. Study conducted by Attia *et al*., shows almost same observation.[9] Difference was not significant (P>0.05) between two Arms. According to socioeconomic status, the lower class 42% comprising the major percentage of the patients, which is followed by middle class 38% and remaining are upper class 20%. Socioeconomically patients are grouped into three classes. Hospital Cancer Registry Report 2015-2017 from NICRH found also this type of results in 2017. Difference was not significant (p>0.05) between two Arms.

Approximately 70% of CRC cases are sporadic cases which were influenced by environmental factors including dietary habits, physical activity, smoking and alcohol consumption.[10] Distribution of patients according to risk factors in both arms. Most of the patients (e.g., 30%) were smokers on both arms 12 (30%) in arm A and 12

(30.0%) in arm B. Family history was detected in total 12 (15%) patients. Study conducted by Libutti et al, (2015) showed similar observations. Difference was not significant (p>0.05) between two Arms. In this study 25 (62.5%) in Arm A and 21 (52.5%) in Arm B patients' ECOG performance status was 1. Study conducted by Hille *et al*., showed almost same observations. Difference was not significant (p>0.05) between two Arms. Among the patients, altered bowel habit and rectal symptoms (bleeding, pain, discharge) were the most clinical manifestation in both Arms, which were followed by pelvic pain and anaemia before starting treatment. In current study, toxicities were assessed by RTOG (Radiation therapy oncology group) of acute radiation morbidity criteria. In a study at BSMMU in Bangladesh by Alotaibi *et al*, found identical observation. Chemo-radiation induced toxicities mainly enteritis and proctitis are the most frequent complications of abdominal and pelvic radiation.[11] New treatment modalities may be devised to improve the outcome of patients who are affected with this complication.[12] It is recognized that patients may subsequently develop a range of GI side effects.[13] In this study, response was evaluated by RECIST (Response evaluation criteria in solid tumour) criteria. In the current study, as compared to previous symptoms during 4th and 6th week of CCRT, significant improvement was found in all Arm A participants. Diarrhoea, rectal bleeding, pelvic pain, rectal discharge was found lower in Arm A. differences were statistically significant (p<0.05) but in case of skin toxicity and anaemia the difference was not significant (p>0.05). In the final week of CCRT (6th week), according to RTOG toxicity assessment, 50% of patients having no symptoms of diarrhoea, 45% had mild symptoms and 5% had moderate symptoms and those were highly significant (p<0.001). Rectal discharge and pelvic pain were found mildly among 20% of patients (p<0.001). Highly significant (p<0.001) difference was found in Arm A patients in rectal bleeding, pelvic pain and rectal discharge compared to Arm B patients after 6 and 12 weeks follow up according to RTOG toxicity criteria. Most of the patients (80%) of Arm A had no symptoms of diarrhea followed by mild (15%) and moderate symptoms (5%) where more than half (55%) had mild symptoms and less than one fourth (15%) had moderate diarrhea in Arm B patients. Minimum (5%) patients complained about moderate symptoms in Arm A whenever (17.5%) of patients noticed moderate symptoms of rectal bleeding in Arm B. 90% of no symptoms of pelvic pain were seen in Arm A, but more than one third (40%) had mild symptoms of pelvic pain in Arm B, which was highly significant (p<0.001). Skin change, anaemia was found less symptomatic in Arm A compared to Arm B in this current study. The difference was not statistically significant (p>0.05).

Found in a study that efficacy of Pentoxifylline & Tocopherol in reduction of radiation toxicities during pelvic radiotherapy in 15/21 patients (71%) experienced a relief of their symptoms. A reduction from grade I/II to grade 0 toxicity was observed in seven and from grade II to grade I toxicity in eight patients. No improvement was seen in six patients. The median time for improvement with Pentoxifylline and Tocopherol treatment was 28 weeks. In three of the nine patients who were treated supportively only, deterioration of symptoms occurred. In this study, Arm B (without Pentoxyphilline and Tocopherol) patients had significantly more hospital admissions during the treatment period compared to Arm A. Number of patients required hospital admissions was 7 (17.5%) in Arm A and 15 (37.5%) in Arm B. Mean length of hospital stay was 5.3 ± 1.7 in Arm A and 10 ± 1.9 in Arm B. The difference was statistically significant in both arms (p value < 0.05). In Royal Brisbane and women's Hospital, Callaghan et *al*, conducted a retrospective cohort study. In health cost analysis evaluating average hospital stay was found significant when compared between intervention and control arm.[14, 15] My results also showed duration of hospital stay was significantly lower in study arm (Arm A). Patients in Arm A had significantly less mean hospital stay which translated into substantial cost saving for my institutions. In this study, 8 (20.0%) patients in Arm A and 17 (42.5%) patients in Arm B underwent treatment interruption due to acute toxicities which include abdominal pain, per rectal bleeding, diarrhoea, skin toxicity and weight loss. The mean duration of RT break was 4.1 ± 0.9 in Arm A and 6.7 ± 1.2 in Arm B. Weekly chemotherapy was held during radiotherapy break and restarted with radiotherapy. The difference between the two groups was statistically significant. Treatment interruption produces unwanted machine occupancy. In a low resource country like ours, unwanted machine occupancy produces radiotherapy delays of scheduled patients. Spijkervet et *al*, conducted a retrospective study, where they found 49.6% patients underwent treatment interruption because of side

effects. The mean duration was 4.8 days per patient.[16] Interruption, duration of interruption for toxicities and cumulative duration of treatment interruption for toxicity were significantly lower in Arm A group. Treatment response assessment by RECIST criteria after 6 weeks of CCRT showed in Arm A, Complete Response (CR) was 6 (15%) and Partial Response (PR) was 27 (67.5%) and in Arm B, CR was 4 (10%) and PR was 25 (62.5%). There were 6 (15%) from Arm A and 6 (15%) patients from Arm B had shown stable disease out of total 40 (100%) patients of each Arm. There was no significant difference in partial response and stable disease ($p>0.05$). Treatment response was further analyzed to determine the association with treatment interruptions. There was a significant association between treatment interruption and treatment response.

CONCLUSION

Aim of the study to assess efficacy of Pentoxifylline and Tocopherol in reduction of chemo-radiation induced toxicities in patients with locally advanced rectal cancer. From the findings of the study, it can be concluded that the patients who were treated with Pentoxifyilline and Tocopherol reduced chemo-radiation induced toxicities, decrease treatment break, decrease hospital admission. Treatment response also increased in patients who were treated with Pentoxifylline and Tocopherol. So, treatment with Pentoxifylline and Tocopherol may be a promising one with concurrent chemo-radiation in the treatment of locally advanced rectal cancer.

Recommendation

The following recommendations can be made in light of the study:

As symptoms of chemo-radiation induced injuries were improved with treatment of Pentoxifylline and Tocopherol than conventional symptomatic treatment. So, practice of this kind of treatment should be encouraged.

This was a small scale quasi experimental attempt. Further research may be conducted on a large scale before taking any policy decision.

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