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EFFICACY OF RACECADOTRIL COMPARED TO DIPHENOXYLATE IN ACUTE RADIATION ENTERITIS

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ABSTRACT

Introduction: Radiation enteritis is one of the most common and distressing complications of pelvic radiation. There are limited studies that have assessed the efficacy of antidiarrhoeals in radiation enteritis. This study was done to assess the efficacy of racecadotril versus diphenoxylate in acute radiation enteritis. **Methods:** This was a prospective open label randomized study.50 patients were recruited into the study with 25 patients in each group. They received either Tab. Racecadotril 100mg tid for 3 days or Tab. Diphenoxylate Hydrochloride 2.5 mg(+ atropine 0.025 mg) tid for 3 days as an add on to fluid supplementation. **Results**: The grade of radiation enteritis in both the groups were similar after 3 days of treatment with the drug (p=0.210).Only one patient in the racecadotril group required cessation of pelvic radiation due to hypokalemia. **Conclusion:** Racecadotril and diphenoxylate are both effective in treating radiation enteritis and are well tolerated. Further studies with racecadotril are warranted.

KEYWORDS: racecadotril, diphenoxylate, radiation enteritis, diarrhea.

INTRODUCTION

Radiation enteritis is one of the most feared complications of abdominal and pelvic radiation seen in 75 to 80%[1] of patients receiving pelvic radiation. Once it occurs, the process is relentless and may result occasionally in the patient's death. The small intestine is highly radiosensitive but the mobility of the small bowel protects it minimally from the effects of radiation damage. Due to its spontaneous resolution with cessation of radiation this distressing complaint has not gained much attention from researchers as well as clinical

professionals. The physical and mental overbearing on the patients needs to be taken into consideration and much importance should be given to this aspect of therapy as well.

Radiation-induced diarrhoea is thought to result from the disruption of immature intestinal stem cells leading to secretion of fluid into the lumen and inhibition of mucosal absorption by the villi, which is noticed by patients at the second week of radiation treatment (due to maximum tissue damage and inflammation) and characteristically peaks by the fourth to fifth week of starting radiation (when histological changes are stable or begin improving).[2]

Traditionally, these patients are managed symptomatically by fluid replacement and agents including antidiarrhoeal drugs such as diphenoxylate and loperamide. Racecadotril has proven to be an effective and safe antidiarrhoeal drug in acute diarrhea in all age groups however its efficacy in the field of radiation enteritis has not been explored. Thus, this study was done with an aim to assess the efficacy and tolerability of racecadotril versus the standard treatment diphenoxylate in acute radiation enteritis patients.

MATERIALS AND METHODS

The study was an open, prospective randomized trial that assigned 25 patients to each of the two treatment groups. The sample size was determined to detect a 30% difference between the two treatment groups in grade of radiation enteritis with α and β error of 0.05 and 0.1, respectively. The study protocol was approved by the Institutional Ethics Committee and informed consent was obtained from all participants.

Patients aged 18-75 years with histologically proven abdominal and pelvic malignancy without metastases beyond the regional lymph nodes, Karnofsky performance status > 60 and a white blood cell count of over 3,000/mm^3 were included into the study. Patients with grade 4 diarrhoea (as per Common Terminology Criteria version 4.0 grading for diarrhoea), uncontrolled diabetes and hypertension, planned whole-pelvis external irradiation>50Gy, history of prior abdominal surgery, pelvic inflammatory disease, diverticulitis, inflammatory bowel disease, history of taking opioid analgesics and other antidiarrhoeal agents and pregnant and lactating women were excluded from the study.

Patients were randomly assigned to receive either Tab. Racecadotril 100 mg tid, plus iv fluids/ORS solution or Tab. Diphenoxylate 2.5 mg(+ atropine 0.025 mg)1 tablet tid daily,

plus iv fluids/ORS solution. Randomisation was done using computer generated randomization tables.

The primary outcome variable was grade of radiation enteritis after 3 days of therapy. If the patient had four or more diarrhoeas daily after the third day; the drug treatment was extended to 5 days. If four or more diarrhoeas were observed at the 6^{th} day; the antidiarrhoeal drug and radiation were both discontinued. The incidence of cessation of pelvic radiation was then recorded and rescue treatment as per standard clinical practice was initiated.

Each patient was also interviewed by medical and nursing staff during the course of antidiarrhoeal treatment and adverse events were asked for. Serum electrolytes were recorded every alternate day following initiation of drug treatment.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD and results on categorical measurements are presented as Number (%). P values of 0.05 and less were considered significant. Chi-square test has been used to find the significance of study parameters on categorical scale between two or more groups. The analyses were performed blindly by an independent statistician who did not know the nature of the treatment arms.

RESULTS

50 patients with ARE were recruited into the study, 25 each in the racecadotril and the diphenoxylate group. The baseline characteristics are listed in Table 1. Seven patients developed radiation enteritis at 2 weeks of radiation therapy and the rest developed it at 3 or more weeks of starting radiation therapy. The arms were balanced with regard to age, gender, primary tumour, concomitant chemotherapeutic agent and grade of radiation enteritis.

10 and 15 of the 25 patients in the diphenoxylate group respectively whereas 6 and 18 patients in the racecadotril group had Grade 1 and Grade 2 radiation enteritis respectively after 3 days of therapy($p=0.210$ between the two groups) (Table 2). One patient in the racecadotril group with carcinoma rectum receiving concomitant 5-FU continued having Grade 3 diarrhoea despite therapy. Because of hypokalemia, this patient required cessation of radiation treatment for a day (Fig. 1). Both study drugs were well tolerated by all patients with minor adverse events noted i.e. thirst and headache; deemed to be not related to the study drugs.

Table 1. Baseline characteristics of patients

Characteristic	Octreotide	Diphenoxylate	P value
Age(years)	51.76 ± 9.11	54.80 ± 8.67	0.233
Gender (female)	25	23	0.149
Primary tumour Cervix	23	22	0.492
Rectum	1	2	
Anal Canal	1	1	
Concomitant Chemotherapeutic agent Cisplatin	23	22	0.551
5-FU	2	3	
Diarrhoea Grade 2	9	16	0.390
3	12	13	

Table 2: Comparative evaluation of grade of radiation enteritis in two groups of study subjects

Drug	Grade of Radiation enteritis Day 0		Grade of Radiation enteritis Day 3		
	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Diphenoxylate	9	16	10	15	0
Racecadotril	12	13	6	18	1

P=0.210 at 3 days between the two groups.

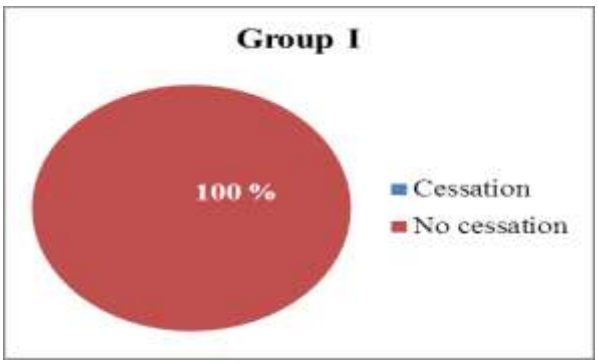
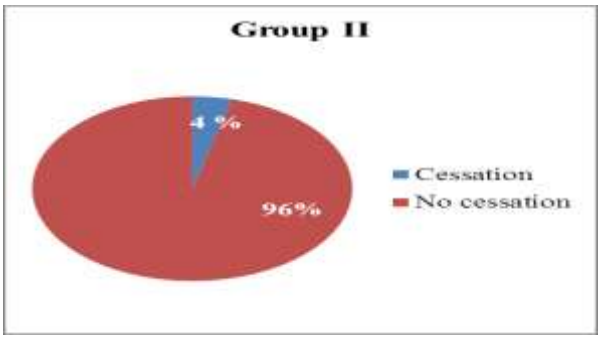


Fig. 1: Comparison of cessation of pelvic radiotherapy in the two treatment groups



P=0.312 between the two groups

DISCUSSION

Radiation enteritis is a distressing complication of pelvic radiotherapy. Histopathologic studies have shown that radiation produces acute damage to the intestinal mucosa characterised by inflammation or cell death including mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscess formation and swelling of the endothelial lining of arterioles.[3] A shift in the balance of absorptive and secretory cells and destruction of the brush border enzymes involved in the terminal digestion of carbohydrates, proteins, fats and bile salts leads to abnormal absorption and secretion of fluids and electrolytes. Additionally, opportunistic infections and epithelial cell necrosis can initiate local inflammatory responses along with radiation induced release of eicosanoids and free radicals. At the same time an almost identical process of intestinal injury can occur with the concomitant use of certain chemotherapeutic agents such as 5- FU, cisplatin, methotrexate, doxorubicin, hydroxyurea, cytosine arabinoside and irinotecan.[4] It is evident that acute radiation enteritis has a multifactorial etiology with a complex pathogenesis and only a multifaceted approach can relieve the symptoms of radiation induced diarrhea. The most common treatment approach is to use opioid agonists which reduce the discomfort and inconvenience of frequent bowel movements.

Racecadotril, an enkephalinase inhibitor, with a predominant antisecretory activity has been shown to reduce both the frequency and duration of acute diarrhoea of presumed infectious origin in randomised, placebo-controlled studies in both adults and children.[5,6] Racecadotril recipients had a significantly shorter duration of diarrhoea and a reduced requirement for oral rehydration solution compared to placebo recipients. When compared to loperamide, racecadotril appeared to have similar efficacy for the treatment of adults and children with acute non infectious diarrhoea in several double-blind comparative trials.[7,8] Racecadotril (100 to 200mg 3 times daily for 2 to 4 weeks) compared to placebo was found to be superior in relieving chronic diarrhoea in patients with HIV infection[9] and irinotecan induced delayed diarrhoea, when used along with loperamide.[10] Also, a systematic review stated that antisecretory agents, such as racecadotril, seem to be as effective as antimotility agents at improving symptoms of diarrhoea in patients from resource poor countries and cause fewer adverse effects.[11] Thus, racecadotril has proved to be a cost effective option in all types of diarrhoea. Its role in radiation enteritis has however not been investigated.

In an earlier randomized controlled study, octreotide, a somatostatin analogue with predominant antisecretory activity, was more effective than diphenoxylate and atropine in controlling ARE and eliminated the need for radiotherapy interruptions.[12] However, the need to give octreotide injections subcutaneously thrice daily and its high cost casts doubt on its use, particularly in developing countries. Thus, this study was done to compare the efficacy of antisecretory drug, racecadotril compared to diphenoxylate in acute radiation enteritis.

In the present study, at baseline all the patients had comparable characteristics. A predominance of females was observed with carcinoma cervix being the primary tumour diagnosed which can be substantiated by the fact that carcinoma cervix is the most common cancer observed in either sex in India.[13] Most patients developed radiation enteritis at or after the third week of starting radiation therapy. This trend was also observed in an earlier study.[11]

The results reveal similar response in terms of grade of radiation enteritis to drug treatment. Both the drugs were well tolerated with one patient in the racecadotril arm requiring radiation cessation due to no change in grade of diarrhoea and hypokalemia. Because no similar study was done before, it is not possible to compare the results with results of previous studies.

The strengths of this study are it is the first double blind randomized controlled trial to compare the efficacy of racecadotril as against conventional opioid therapy. The limitations of the study are first, the inability to do a diagnosis wise and chemotherapeutic agent wise subgroup analysis due to the asymmetric distribution in both the treatment groups. However, this could be expected as cervical cancer is the most prevalent cancer in India. Second, the duration of the follow up was short. At the same time, previous randomized trials have also used a minimum 3 day period for evaluating the response to treatment. This study paves the way for future studies to confirm the benefits of racecadotril in ARE and investigate the use of combination therapies of racecadotril and diphenoxylate and assess whether these effectively control ARE as against the individual drugs by tackling the two major mechanisms involved in acute radiation enteritis.

CONCLUSION

Both racecadotril and diphenoxylate are effective in the treatment of ARE and are well tolerated. Further studies to assess the effectiveness of racecadotril in reducing radiation induced gastrointestinal toxicity will be of value for investigators.

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