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Original Research Article

Evaluation of efficacy and safety of diphenoxylate hydrochloride and atropine sulphate in patient with acute radiation or chemotherapy induced diarrhea

Shrikant Khare[1]*, Dilip Nikam[2], Abhishek Singh[3], Laxman Pandey[4]

[1]Department of Radiation Oncology, Signus Hospital, Nashik, Maharashtra, India
[2]Department of Radiation Oncology, Bombay Hospital and Medical Research Center, Mumbai, Maharashtra, India
[3]Department of Radiation Oncology, Gangashill Cancer Institute, Bareilly, Uttar Pradesh, India
[4]Department of Radiation Oncology, Rohilkhand Cancer Institute, Bareilly, Uttar Pradesh, India

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***Correspondence:**
Dr. Shrikant Khare,
E-mail: kharedrshrikant@gmail.com

ABSTRACT

Background: Chemoradiotherapy (CRT)-induced diarrhea poses significant challenges for cancer patients, impacting both quality of life and treatment efficacy. Current management strategies often involve symptomatic relief with medications such as lomotil and loperamide, but limited data exist on the efficacy of lomotil for management of CRT-induced diarrhea. This study aimed to evaluate the efficacy and safety of lomotil in managing acute CRT-induced diarrhea.
Methods: A cross-sectional observational trial was conducted at 25 Indian healthcare centers having medical records of adult patients with cancer who had received lomotil for the treatment of CRT-induced diarrhea. Adult patients (aged ≥18 years) with confirmed diagnosis of cancer, who were experiencing CRT-induced diarrhea of grade II or grade III severity were included in this study. Demographic information and treatment history were collected. Moreover, data related to stool frequency, stool consistency, abdominal cramp, and occurrence of blood or mucus were collected at baseline, day 1, day 2, day 3, 2nd week, 3rd week, and 4th week.
Results: A total of 177 patients were included in this study. Of these 30.51% underwent radiotherapy, while 26.55% received both chemotherapy and radiotherapy in combination. Post-lomotil treatment, diarrhea incidence declined significantly by week 4 [pre-treatment to week 4: 3.58 to 0.42; P<0.001]. The presence of blood or mucus decreased significantly from baseline to week 4 (0.25 to 0.05; p<0.01). The overall global assessment for improvement showed that a majority of the patients (80.79%) experienced improvement.
Conclusions: Lomotil demonstrated efficacy in reducing CRT-induced diarrhea incidence and symptoms, with minimal adverse effects.

Keywords: Improvement, Quality of life, Mucus, Stool frequency

INTRODUCTION

Chemoradiotherapy (CRT)-induced diarrhea is a significant concern for patients undergoing cancer treatment, particularly those receiving treatments with bolus fluorouracil (5-FU) and irinotecan.[1] Several studies indicate that up to 49% of patients may experience some degree of diarrhea during CRT, with majority of patients facing severe episodes (grade 3 and 4).[2-4] This side effect

not only compromises patients' quality of life but also interferes with the efficacy of anti-cancer treatment.[5,6]

The etiology of CRT-induced diarrhea is multifaceted, involving disruptions to the gut microbiota, mucosal cells' permeability, and intestinal motility. Additionally, CRT alters intestinal microflora composition, affecting various gut functions, including immune responses and barrier integrity maintenance.[7] Such disturbances in gastrointestinal function not only lead to symptomatic discomfort but also pose risks of severe complications such as dehydration, electrolyte imbalances, renal issues, malnutrition, and increased susceptibility to infections.[8]

Traditionally, these patients are managed symptomatically by fluid replacement and agents including antidiarrheal drugs such as diphenoxylate and loperamide. Management of CRT-induced diarrhea typically involves symptomatic relief with medications like loperamide and diphenoxylate. However, there's limited data supporting the efficacy of diphenoxylate and atropine compared to loperamide.[9]

The synergetic effect of diphenoxylate and atropine sulfate weakens gastrointestinal motility and causes constipation by reducing the content of diphenoxylate.[10] It reduces stool weight, frequency of bowel movements, urgency and faecal incontinence in acute and chronic diarrhea.[11] Given the clinical challengesand the lack of comprehensive data, it's important to evaluate the effectiveness and safety of medications like lomotil (diphenoxylate hydrochloride and atropine sulphate) in managing acute radiation or CRT-induced diarrhea. While clinical trials provide essential insights, observational studies offer a broader perspective on drug performance in diverse patient populations, shedding light on its impact on disease progression, quality of life, and safety. This study aims to bridge the gap between controlled clinical settings and real-world clinical practice, providing valuable insights into the role of lomotil as a primary treatment option for CRT-induced diarrhea.

METHODS

Study design

A cross-sectional observational trial was conducted over a period of 1 month (from December 2023 to January 2024) at 25 Indian healthcare centers having medical records of adult patients with cancer who had received lomotil (diphenoxylate and atropine sulphate) for the treatment of CRT-induced diarrhea.

Inclusion criteria

Adult patients (aged ≥18 years) with confirmed diagnosis of cancer of either sex, who were experiencing CRT-induced diarrhea of grade II or grade III severity (defined as having 4 to 6 stools per day) were included in this study. Additionally, patients without fever, with a minimum white blood cell count of 3000/mm³, and exclusion of other potential causes of diarrhea were also included in this study.

Exclusion criteria

Exclusion criteria include individuals with grade 4 diarrhea (more than 10 stools per day) or those requiring immediate hospitalization, as well as those with incomplete medical records. Pregnant or breastfeeding women were also excluded from the study.

All participants in this study were asked to sign an informed consent form prior to study enrolment. The informed consent process was conducted by trained research staff. Prior to participation, participants received an overview of the study objectives and methodologies. It was emphasized that participation was entirely voluntary. This approach was adopted to minimize the potential risk of participation bias and guarantee the authenticity of individual perspectives. In order to uphold participant confidentiality, all collected data were anonymized, and any identifying information was removed during theanalysis phase. Sample size calculation was not conducted in this study. Study included all eligible patients within the available data ensuring a comprehensive analysis of the available population.

Ethical consideration

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Ethics Committee of Human Care Independent Ethics Committee (Reg No. ECR/276/Indt/MH/2017/RR-20). All study investigators and research staff involved in the conduct of the study was trained in the ethical conduct of human subject’s research, including the protection of participant rights, privacy, and confidentiality. All participants' personal information and data was kept strictly confidential and was only accessed by authorized study personnel to ensure anonymity in data collection and analysis.

Endpoints

The primary endpoint of the study was to assess the complete resolution of diarrhea or change of bowel action details of bowel action (frequency, stool consistency, abdominal pain, occurrence of blood or mucus), from baseline to 4 weeks.

Data collection

The study collected a variety of data encompassing demographic information such as age, sex, types of cancer, history of previous surgeries, duration of diarrhea prior to study enrollment, and severity of diarrhea. Additionally, adverse reactions and treatment-related

complications, and overall improvement as assessed by physicians were also assessed. Data related to stool frequency, stool consistency, abdominal cramp, occurrence of blood or mucus were collected at baseline, day 1, day 2, day 3, 2nd week, 3rd week, and 4th week. Data was collected using paper forms and electronic case report forms (eCRFs). All study data was managed according to Good Clinical Practice guidelines and applicable laws and regulations. The data was entered into a secure electronic database and was monitored by trained research staff for accuracy and completeness.

Sample size

Given the observational study no formal sample size calculation was conducted. Instead, the study was aimed to include all eligible cases within the available data or within a predetermined timeframe, ensuring a comprehensive analysis of the available population.

Safety reporting

Safety reporting is an important aspect of this study. Adverse events (AEs) were monitored throughout the study and reported in accordance with applicable laws and regulations. All AEs and serious AEs were recorded in the study database, and the investigators were responsible for assessing the severity, relationship to the study treatment, and expectedness of each event. If an adverse event or serious adverse event occurs, the study personnel was providing appropriate medical care and follow-up as needed. Overall, safety reporting was conducted in a timely and thorough manner to ensure the safety and well-being of study participants.

Statistical analysis

Statistical analysis was assessed using Statistical Package for Social Sciences (SPSS) software version 23.0. The comparison between the baseline and subsequent follow-ups was done using a paired sample t-test. Statistical significance was considered at a two-sided alpha level of 0.05.

RESULTS

Total 177 patients were included in this study out of which majority of patients were men (55.37%). Majority of patients had head and neck carcinoma (31.64%), breast cancer (19.77%), and colorectal carcinoma (11.29%). Total 30.51% underwent radiotherapy, while 26.55% received both chemotherapy and radiotherapy in combination. The mean radiotherapy dose was 48.31 Gy. The majority of patients (33.89%) had a history of diarrhea for duration of 7 days prior to their enrollment in the study. Grade 2 diarrhea was observed in 98 patients (55.37%), while grade 3 diarrhea occurred in 79 patients (44.63%) (Table 1).

Table 1: Demographic characteristics.

Characteristics	No. patients (n=177)
Age (years), mean (SD)	48.99 (10.97)
Sex	
Men	98 (55.37)
Women	79 (44.63)
Cancer type	
Head and neck carcinoma	56 (31.64)
Breast cancer	35 (19.77)
Colorectal carcinoma	20 (11.29)
Advanced renal cell carcinoma	12 (6.78)
Acute myeloid leukemia	12 (6.78)
Non-small cell lung cancer	11 (6.21)
Acute lymphocytic leukemia	8 (4.52)
Nasopharyngeal carcinoma/ esophageal cancer	8 (4.52)
Esophageal cancer	8 (4.52)
Advanced non-small cell lung cancer	4 (2.26)
Cervical cancer	3 (1.69)
Cancer treatment	
Radiotherapy	54 (30.51)
Chemotherapy and radiotherapy	47 (26.55)
Chemotherapy	8 (4.52)
5-FU-based chemotherapy	8 (4.52)
HDC HSCT conditioning regimen	8 (4.52)
Radiotherapy or HDC HSCT conditioning regimen	8 (4.52)
5-FU (bolus)	4 (2.26)
5-FU infusion/cisplatin or doxorubicin	4 (2.26)
Capecitabine	4 (2.26)
Chemotherapy (FOLFOX-4)	4 (2.26)
Cyclophosphamide-based conditioning regimen	4 (2.26)
Docetaxel/paclitaxel	4 (2.26)
m-TOR inhibitors	4 (2.26)
Pralatrexate	4 (2.26)
Pralatrexate +radiotherapy	4 (2.26)
Sorafenib/sunitinib	4 (2.26)
Targeted agents anti-EGFR-antibodies	4 (2.26)
RT dose (Gy), mean (SD)	48.31 (23.89)
Past history of surgery	40 (22.59)
Days of diarrhea before study entry	
3	20 (11.29)
4	19 (10.73)
5	19 (10.73)
6	40 (22.59)
7	60 (33.89)
8	19 (10.73)
Diarrhea grade	
Grade 2	98 (55.37)
Grade 3	79 (44.63)

Data presented as n (%), unless otherwise specified.
HDC HSCT, high-dose chemotherapy with hematopoietic stem-cell transplantation; RT, radiotherapy; SD, standard deviation

Post-lomotil treatment, the incidence of diarrhea showed an initial rise from baseline to day 1 (3.58 vs. 3.67), however exhibited a notable decline by week 4, with frequencies decreasing significantly from 3.58 to 0.42 (p<0.001). The change in mean stool consistency from baseline to post-treatment (pre- vs. post-treatment: 3.67 vs. 0.10; p<0.001) was significant. Moreover, the presence of blood or mucus decreased significantly from baseline to week 4, dropping from 0.25 to 0.05; p<0.01 (Table 2).

Table 2: Treatment outcomes.

Parameters	Frequency	Stool consistency	Abdominal pain	Occurrence of blood or mucus
Baseline	3.58 (0.54)	3.67 (0.47)	2.69 (0.69)	0.25 (0.53)
Day 1	3.67 (0.47)	3.00 (0.00)	2.29 (0.45)	0.11 (0.38)
P value	0.001	<0.001	<0.001	<0.001
Day 2	2.99 (0.47)	2.16 (0.67)	0.74 (0.06)	0.05 (0.21)
P value	<0.001	<0.001	<0.001	<0.001
Day 3	2.01 (1.13)	1.22 (0.85)	1.14 (0.65)	0.02 (0.15)
P value	<0.001	<0.001	<0.001	<0.001
Week 2	1.68 (0.81)	0.40 (0.75)	0.45 (0.49)	0.02 (0.15)
P value	<0.001	<0.001	<0.001	<0.001
Week 3	1.02 (0.72)	0.08 (0.28)	0.18 (0.38)	0.02 (0.15)
P value	<0.001	<0.001	<0.001	<0.001
Week 4	0.42 (0.58)	0.10 (0.30)	0.18 (0.38)	0.05 (0.21)
P value	<0.001	<0.001	<0.001	<0.001

Data presented as mean (SD). All follow-up data were compared with baseline data

Adverse drug reaction was observed among 11.29% of patients while 40.11% of patients had treatment related complications. The overall global assessment for improvement showed that a majority of the patients (80.79%) experienced improvement, while only 4.52% of patients experienced worsened symptoms (Table 3).

Table 3: Safety outcomes.

Parameters	Number of patients (n=177)
Adverse drug reaction	20 (11.29)
Complications	71 (40.11)
Overall improvement by physician's assessment	
Improved	143 (80.79)
Remain undeterminable	23 (12.99)
Worsened	8 (4.52)

Data presented as n (%)

DISCUSSION

Clinically, CRT-induced intestinal damage is termed to as radiation enteropathy (RE), and diarrhea. The CRT induced diarrhea is the most common RE-related symptom. Histopathologic studies have revealed that radiation exposure initiates acute alterations in the intestinal mucosa, marked by inflammatory responses and mucosal cell death, and swelling of the endothelial lining of arterioles.[12] It is evident that CRT induced diarrhea 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 strategy often involves the administration of opioid agonists, aiming to reduce the discomfort and inconvenience associated with frequent bowel movements.[13] Several compounds such as loperamide, diphenoxylate and atropine, and tincture of opium are currently used as antidiarrheal agents and have shown excellent safety records.[14] However, clinical trials evaluating the efficacy of these agents in CRT induced diarrhea are lacking.

The present cross-sectional observational trial assessed the efficacy and safety of lomotil (diphenoxylate hydrochloride and atropine sulphate) in patient with acute CRT-induced diarrhea. The key observation of the study were i) majority of patients underwent radiotherapy and chemotherapy and radiotherapy in combination; ii) grade 2 diarrhea was observed in most of patients; iii) Post-lomotil treatment, the incidence of diarrhea exhibited a notable decline by week 4; iv) The mean stool consistency was decreased from baseline; v) The presence of blood or mucus decreased significantly from baseline to week 4; vi) The overall global assessment for improvement showed improvement after lomotil therapy.

Diphenoxylate and atropinesulphate are the most frequently used opioids in diarrhea management. Diphenoxylate, an opioid analgesic, that acts on the presynaptic opioid receptors in the enteric nervous system blocking the release of acetylcholine within the synaptic cleft. Consequently, it restrains the motility and secretory functions of the enteric nervous system. This mechanism results in a reduction of segmental contractions and extends the transit time of gastrointestinal contents. It has been shown to reduce both the frequency and duration of acute diarrhea of presumed infectious origin.[14-16] Atropine is a competitive

inhibitor of acetylcholine receptors to prevent patients from misusing diphenoxylate. In several comparative trials, lomotil appeared to have similar efficacy to loperamide for the treatment of critically ill patients with acute non-infectious diarrhea.[17-19] Diphenoxylate and atropine, compared to placebo were found to be superior inrelieving diarrhea.[19] Thus, lomotil might be a better option in all types of diarrhea. However, its role in CRT induced diarrhea has however not been investigated.

Similar to loperamide, diphenoxylate inhibits intestinal motility by stimulating opioid receptors in the intestine.[20] Furthermore, the addition of atropine to diphenoxylate also inhibit intestinal peristalsis.[21] However, limited efficacy data support the use of diphenoxylateand atropine compared to loperamide for the treatment of CRT-induced diarrhea. Findings from one double-blind study comparing these agents suggest that loperamide might offer greater effectiveness.[22] However, a previous comparative analysis revealed that 42% of patients in the loperamide group needed 2 to 3 tablets to manage diarrhea, while only 23% of patients in the diphenoxylate and atropine group achieved control with the same dosage suggesting effectiveness of dipheoxylate and atropine over loperamide.[23] Palmer et al conducted a double-blind cross-over study on efficacy of loperamide (4.6 mg), codeine (103.5 mg) and diphenoxylate (12.5 mg) in the treatment of chronic diarrhea. The results showed that theeffectiveness of diphenoxylate in terms of in stool frequency, consistency, urgency, and incontinence was comparable to that of loperamide and codeine.[15] Similarly, in patients with chronic diarrhea and fecal incontinence, diphenoxylate and atropine led to a reduction in both stool frequency and volume compared to the placebo group.[24]

Recently published study on animal model reported that diphenoxylate was identified as a superior inducer of constipation compared to loperamide.[16] In another recent study, the efficacy of racecadotril as against diphenoxylate (n = 25) and atropine sulphate (n = 25) among patients with radiation enteritis. The groups were comparable in terms of primary tumor, concomitant chemotherapeutic agent, and grade of radiation enteritis. After three days of therapy, 10 patients in the diphenoxylate group had grade 1 radiation enteritis, while 15 had grade 2. In comparison, 6 patients in the racecadotril group had grade 1 radiation enteritis, and 18 had grade 2 diarrhea. However, one patient in the racecadotril group continued to have grade 3 diarrhea despite treatment, leading to cessation of radiation treatment.[25] Similarly, in the present study post-lomotil treatment, exhibited a notable decline incidence of diarrhea by week 4, with frequencies decreasing significantly from 3.58 to 0.42 ($p<0.001$). Additionally, the change in mean stool consistency from baseline to post-treatment was significant. Overall, these findings suggest that diphenoxylate in combination with atropine, may be a viable option for managing diarrhea, including CRT-induced diarrhea, and could potentially alleviate symptoms.

Loperamide and diphenoxylate and atropine are generally associated with limited risks of drug-drug interactions.[20] Gawron and Bielefeldt, et al, utilized the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System database (FAERS) to examine pancreatitis following treatment with eluxadoline and compared with other medications such as loperamide, diphenoxylate and atropine, oxycodone, and rifaximin. Their findings indicated that pancreatitis accounted for a small percentage of AEs reported for diphenoxylate and atropine (0.43%) compared to eluxadoline (16.4%) and rifaximin (0.96%). Moreover, the majority ofpancreatitis events were associated witheluxadoline, while fewer associated it with loperamide, suggesting a higher perceived risk with eluxadoline compared to diphenoxylate and atropine.[26] Similarly, Suvarna et al who comparatively evaluated the racecadotril and diphenoxylate in acute radiation enteritis noted that both medications were well tolerated, with minor AEs such as thirst and headache, which were not attributed to the study drugs.[25] Consistently, present study also revealed minimum treatment related AEs. In contrast to this previous study observedhigher side effect with diphenoxylate than those with loperamide.[15] Overall, while diphenoxylate and atropine appears to have a generally favorable safety profile, further research is warranted to fully understand its comparative safety and efficacy in various clinical contexts.

Additionally, Hirsh et al, highlighted the efficacy of targeting the epidermal growth factor receptor (EGFR) signaling pathway in treatment, leading to enhanced clinical outcomes. However, these treatments were accompanied by adverse effects including diarrhea. As a result, the authors recommended the proactive use of loperamide or diphenoxylate-atropine as antidiarrheal agents prior to patients beginning EGFR therapy.[27]

An inherent limitation of this study is the unavailability of recent literature related to the efficacy of lomotilin CRT-induced diarrhea. Consequently, the analysis relies on literature from previous years, which may not fully capture the most current perspectives in this area. This scarcity of up-to-date literature may hinder the extrapolation of results to the current clinical landscape. Future research endeavors would benefit from addressing this limitation through the inclusion of more recent data to enhance the robustness and relevance of findings.

CONCLUSION

Post-lomotil treatment significantly reduced CRT-induced diarrhea incidence, improved stool consistency, and minimized blood or mucus presence, with minimal adverse effects. Further research may be warranted to explore optimal dosing regimens and potential strategies

to minimize adverse effects while maximizing treatment benefits.

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