

# A Prospective Randomized Controlled Trial to Study the Role of Sulfasalazine in the Prevention of Acute Gastrointestinal Toxicities in Patients of Carcinoma of the Cervix Receiving Concurrent Chemoradiation

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## Abstract



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## Keywords

- cervical carcinoma
- chemoradiation
- diarrhea
- sulfasalazine
- acute gastrointestinal toxicities

The present study aimed to evaluate the effectiveness of sulfasalazine in preventing acute gastrointestinal (GI) toxicities in patients with cervical carcinoma receiving concurrent chemoradiation. This prospective randomized controlled study was conducted at the Department of Radiotherapy from November 2016 to April 2018. A total of 60 eligible patients (30 in arm A and 30 in arm B) were enrolled in the study. Patients in arm A received 5,000 cGy of external beam radiotherapy (EBRT) in 25 fractions concurrently with chemotherapy using cisplatin (40 mg/m<sup>2</sup> weekly) and tablet sulfasalazine (1 g twice a day). Patients in arm B received 5,000 cGy of EBRT in 25 fractions concurrently with chemotherapy using cisplatin (40 mg/m<sup>2</sup> weekly) without any prophylactic medication. The acute GI toxicities assessed in this study included diarrhea, abdominal pain, tenesmus, and rectal bleeding. The chi-squared test was employed to compare the toxicity grades in the two arms. The collected data were analyzed using Statistical Package for Social Sciences (SPSS) version 21, with statistical significance considered at  $p < 0.05$ . The results showed a significant decrease in the incidence of grade 2 or higher diarrhea in the study arm compared to the control arm. Additionally, there was a decrease in the incidence of grade 1 or higher abdominal pain in the study arm. A decrease in the incidence of grade 1 or higher tenesmus was also observed, although the difference was not statistically significant. Rectal bleeding decreased significantly. Sulfasalazine was found to be a cost-effective and safe method for reducing the incidence of radiation-induced acute GI toxicities in cervical carcinoma patients undergoing radiotherapy.

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## Introduction

In India, cervical cancer accounted for 9.4% of all cancers and 18.3% (123,907) of new cases in 2020. It still is among the most common cancers in India and a leading cause of cancer-related deaths in women in low- and middle-income countries.<sup>1</sup> External beam radiotherapy (EBRT) to the pelvis along with concurrent chemotherapy followed by brachytherapy is the standard of care in locally advanced cervical carcinoma.<sup>2</sup>

Pelvic irradiation causes mucosal damage to normal gut tissue, both small and large intestines, which fall within the treatment field leading to bile acid malabsorption, carbohydrate intolerances, and small bowel bacterial overgrowth.<sup>3</sup>

Radiation enteritis refers to radiation therapy-induced injury to the intestinal epithelium.

In some patients, radiation enteritis may be so severe that it may necessitate treatment interruption, prolonging treatment time, thus reducing the therapeutic benefit.<sup>4</sup>

Antidiarrheal agents are commonly used with some efficacy in the treatment of this problem. Some patients have severe diarrhea despite the medications. These agents are not used as prophylaxis as they can cause constipation.

Aminosalicylates, particularly sulfasalazine, were used by Rauch and Weiland to prevent acute radiation-induced diarrhea.<sup>5</sup> The rationale for using sulfasalazine was that radiation-induced diarrhea mainly occurs due to increased synthesis of nuclear regulating proteins that regulate cytokines and have secondary effect on eicosanoids as postulated by Mennie et al.<sup>6</sup> Sulfasalazine reduces the synthesis of eicosanoids.

The aim of this study was to evaluate the effectiveness of sulfasalazine in prevention of acute gastrointestinal (GI) toxicities in cervical carcinoma patients receiving concurrent chemoradiation.

## Materials and Methods

A prospective randomized controlled trial was undertaken at the Department of Radiotherapy, GSL Medical College and General Hospital, from November 2016 to April 2018 after obtaining approval from the institutional ethical committee.

### Study Sample

All the patients who fulfilled the inclusion criteria were included in the study.

### Inclusion Criteria

- Histopathologically confirmed locally advanced nonmetastatic squamous cell carcinomas of the cervix.
- Age up to 70 years.
- Karnofsky performance status score of at least 70%.
- Hematological parameters with total leukocyte count of greater than 4,000 cells/mm<sup>3</sup> and platelet counts of >150,000/mm<sup>3</sup>.
- Renal parameters with serum creatinine less than 1.5 mg/dL.
- Minimum radiation dose of 45 Gy with conventional fractionation.

### Exclusion Criteria

- Metastasis beyond the pelvic lymph nodes.
- History of prior chemotherapy or radiotherapy to the pelvic region.
- Patients with abnormal cardiac function, renal, hematological parameters, or comorbid illness.
- Patients with pregnancy and lactation.
- Lack of functioning rectum.
- Known salicylate hypersensitivity.

### Study Design

We conducted a prospective two-arm randomized controlled trial. Simple randomization with odd number patients in arm A and even number patients in arm B was done.

Patients in **arm A** received a radiation dose of 5,000 cGy in 25 fractions with concomitant chemotherapy with injection cisplatin 40 mg/m<sup>2</sup> weekly along with tablet sulfasalazine 1 g twice daily.

Patients in **Arm B** received a radiation dose of 5,000 cGy in 25 fractions with concomitant chemotherapy with injection cisplatin 40 mg/m<sup>2</sup> weekly without sulfasalazine.

### Radiotherapy Planning

Radiotherapy (RT) was planned by four-field box technique (anteroposterior [AP], posteroanterior [PA], and two laterals) using the three-dimensional conformal radiotherapy (3DCRT) technique.

EBRT was delivered to a dose of 50 Gy in 25 fractions at 2 Gy/d. This was followed by three applications of high dose rate (HDR) intracavitary brachytherapy of 7 Gy/fraction per week prescribing dose to point A.

### Chemotherapy Administration

- Patients were administered cisplatin chemotherapy weekly (40 mg/m<sup>2</sup>) during EBRT with adequate hydration and antiemetic premedication.
- RT was delivered within 1 hour of cisplatin administration.

### Monitoring

- Assessment acute GI toxicities was done weekly during EBRT according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in all patients.
  - Severity of diarrhea and duration.
  - Abdominal cramping.
  - Rectal bleeding.
  - Tenesmus.
- Patients were counseled to maintain adequate hydration, protein-calorie intake, and personal hygiene during the entire course of treatment.
- Diarrhea was managed conservatively with lactobacillus and loperamide for noninfective etiology. In case of an infective cause, appropriate antibiotics were administered.

### Statistical Analysis

All descriptive data were presented in mean, range, percentage, and frequency. A chi-squared test was performed to

**Table 1** Showing patient and disease characteristics in both arms

	Arm	
	A	B
<b>Age (y)</b>		
25–35	00	02
36–45	06	06
46–55	16	11
56–65	08	11
<b>Stage</b>		
IIA	01	03
IIB	17	12
IIIA	01	02
IIIB	11	13
<b>KPS</b>		
70	8	8
80	17	18
90	5	4

Abbreviation: KPS, Karnofsky performance status.

compare the toxicity grading in the two groups. Collected data were analyzed using Statistical Package for Social Sciences (SPSS) version 21. A *p*-value of less than 0.05 was considered statistically significant.

## Results

In this study, the age range of the patients was between 28 and 65 years. The mean age of the patients was 51.46 years in

arm A and 51.63 years in arm B. The basic characteristics and demographic data of patients in both arms were found to be similar. The majority of patients in the study were illiterate and were of low socioeconomic status. Many of the patients were of postmenopausal age. The staging of the patients was done according to the 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system and the majority of patients belonged to stage IIB. Most of the patients around 75% in this study had a performance status score of  $\geq 80$  ([Table 1](#)).

In the study, the EBRT duration range was between 33 and 44 days. The mean duration was 35.5 days in arm A and 39.5 days in arm B. More than 85% of patients in both arms received five cycles of concurrent weekly cisplatin. A minimum of four cycles of chemotherapy was administered in both arms.

In this study, the weekly assessment of GI toxicities was noted in all the patients. The highest grade of each type of toxicity as per CTCAE version 4 was recorded for assessment and is represented in [Table 2](#). The acute GI toxicities assessed in this study were diarrhea, abdominal pain, tenesmus, and rectal bleeding. There was a significant decrease in the incidence of grade 2 or higher diarrhea in the study arm in comparison with the control arm, and there was also a decrease in the incidence of grade 1 or higher abdominal pain in the study arm. There was also a decrease in the incidence of grade 1 or higher tenesmus, but the difference was not significant. Rectal bleeding also decreased significantly.

## Discussion

This study was conducted on 60 patients with locally advanced cervical carcinoma treated with pelvic radiotherapy with

**Table 2** Comparison of toxicities between both arms

Parameter	Grade of toxicity	Arm A, N (%)	Arm B, N (%)	<i>p</i> value
Diarrhea	0	3 (10)	0 (0)	0.001
	1	17 (56.7)	7 (23.3)	
	2	10 (33.3)	15 (50)	
	3	0 (0)	8 (26.7)	
Abdominal pain	0	11 (36.7)	2 (6.7)	0.006
	1	15 (50)	16 (53.3)	
	2	04 (13.3)	12 (40)	
	3	00 (0)	00 (0)	
Tenesmus	0	15 (50)	11 (36.7)	0.573
	1	10 (33.3)	11 (36.7)	
	2	05 (16.7)	07 (23.3)	
	3	00 (0)	01 (3.3)	
Rectal bleeding	0	29 (96.7)	20 (66.7)	0.005
	1	00 (0)	09 (30)	
	2	01 (3.3)	01 (3.3)	
	3	00 (0)	00 (0)	

concurrent chemotherapy followed by brachytherapy to assess whether sulfasalazine reduces acute GI toxicities.

Radiation enteritis can be divided into acute and chronic enteritis according to the time and course of symptoms. Acute radiation enteritis usually occurs during radiotherapy or within 3 months after the initiation of treatment. It presents as diarrhea, mucous discharge, abdominal pain or cramping, tenesmus and in some cases rectal bleeding. It usually starts during the second week and continues till the last week of radiation and can occur in about 75 to 80% of patients receiving pelvic radiotherapy. Radiation tolerance of small bowel is a dose-limiting factor because of early adverse effects.<sup>7</sup>

Chronic symptoms such as fecal incontinence, urgency, rectal bleeding, flatulence, and abdominal pain may follow acute GI symptoms with an incidence of approximately 2 to 20%.<sup>8</sup>

Many interventions, surgical techniques, and pharmacological and nonpharmacological methods were tried to reduce or prevent radiation-induced acute GI effects.

Surgical procedures, displacing the small intestine from the irradiated field, with endogenous material like omentum or hydrogel injection or spacer or endorectal balloons were tried to prevent or decrease the incidence of acute GI toxicities.<sup>9,10</sup>

Several pharmacological agents such as aminosaliclates, sucralfate, amifostine, steroid enema, and bile acid sequestrants were tested for prophylaxis. Nonpharmacological interventions concentrating on dietary modifications such as addition of probiotics, protein, and high-fiber diet were also tested.<sup>11</sup>

Radiation-induced GI toxicities can be reduced by techniques like placing the patient in prone or following the full urinary bladder protocol or using belly boards. These techniques help displace the small gut from the radiation field.<sup>12,13</sup>

The efficacy of different oral 5-aminosalicylic acid (5-ASA) formulations to prevent acute radiation enteropathy has been studied by three randomized controlled trials.<sup>14–16</sup> None of them showed positive results; moreover, two trials showed a worsening of diarrhea.<sup>15,16</sup>

The difference in drug formulations and their side effects resulted in variability of results. Mesalazine contains only 5-ASA. There is no carrier molecule. So it may not be effectively deposited in the terminal part of the small intestine or the colon. Olsalazine consists of two molecules of 5-ASA coupled with an azo bond. This azo bond is split in the colon. So no separate carrier is needed. By inhibiting water and electrolyte absorption in the small intestine and also by decreasing the transit time through the bowel, it aggravated the diarrhea.

Sulfasalazine is a 5-ASA compound with sulfapyridine linked by an azo bond. Sulfapyridine is a carrier molecule. The azo bond is broken by colonic bacteria by azoreductase releasing the active molecule, that is, 5-ASA. It exerts an anti-inflammatory effect by inhibiting lipoxygenase and cyclooxygenase enzymes, and thus reduces the production of prostaglandin and leukotriene and other mediators such as cytokines and platelet activation factor. Another proposed mechanism of the action of 5-ASA is scavenging of free radicals.

These unique properties of sulfasalazine and its differences from other 5-ASA congeners prompted us to choose sulfasalazine in our study.

In our study, 1g of sulfasalazine twice daily was employed, which was identical to the studies done Pal et al<sup>17</sup> and Miller et al,<sup>18</sup> and Kiliç et al.<sup>19</sup> The comparison between the studies is represented in [Table 3](#). Mennie et al<sup>6</sup> administered 972 mg of aspirin as sodium acetylsalicylate in an effervescent antacid buffer at pH 6 to 7 (3 Alka-Seltzer tablets dissolved in water) or the equivalent effervescent antacid buffer without aspirin (3 control tablets) four times a day before meals. Baughan et al<sup>15</sup> used 5-ASA 800 mg three times a day, while Resbeut et al<sup>14</sup> used 4 g of 5-ASA daily. Martenson et al<sup>16</sup> utilized olsalazine 250 mg, two pills twice daily, in their study.

All the patients in our study were diagnosed with just cervical cancer, which was similar with the findings of Mennie et al,<sup>6</sup> Pal et al,<sup>17</sup> Baughan et al,<sup>15</sup> and Resbeut et al.<sup>14</sup>

Martenson et al<sup>16</sup> evaluated patients who had cancer of the rectum, bladder, prostate, cervix, and uterus. Miller et al<sup>18</sup> investigated patients with cancer of the anal margin,

**Table 3** Similar studies using sulfasalazine for prevention of acute radiation induced GI toxicities

Study	Type of study	No. of patients	Type of malignancy	Results
Present study	RCT	60	Cervical carcinoma	Statistically significant reduction was found in severity and incidence of diarrhea, abdominal pain, and rectal bleeding
Pal et al <sup>17</sup>	RCT	98	Cervical carcinoma	Statistically significant reduction in grade 2 or higher GI toxicities in the experimental arm
Miller et al <sup>18</sup>	RCT	84	Any pelvic malignancy requiring RT	No significant difference in diarrhea severity between the sulfasalazine and placebo groups
Kiliç et al <sup>19</sup>	RCT	87	Any pelvic malignancy requiring RT	Significant decrease in the rate of all grades of diarrhea was noted between the groups receiving placebo and sulfasalazine

Abbreviations: GI, gastrointestinal; RCT, randomized controlled trial; RT, radiotherapy.

colon, rectum, endometrium, ovary, prostate, uterus, and vaginal vault. The intervention began at the start of radiotherapy and was continued daily throughout radiotherapy treatment.

Other factors that may influence the risk of radiation enteritis includes chemotherapy, previous abdominal surgery, smoking, coexisting medical conditions (diabetes, hypertension, and HIV, etc.), genetic factors, and psychological issues.

### Chemotherapy

In our study, all the patients received at least four cycles of concurrent cisplatin during the course of EBRT, which was identical to the study by Pal et al.<sup>17</sup> Concurrent 5-fluorouracil (5-FU) was given to some patients in a study by Martenson et al.<sup>16</sup> Miller et al.<sup>18</sup> studied patients who had radiation with or without 5-FU, capecitabine, or oxaliplatin. Kiliç et al.<sup>19</sup> and Resbeut et al.<sup>14</sup> conducted experiments in which no systemic chemotherapy was administered.

In our study, acute GI toxicities like diarrhea, abdominal pain, tenesmus, and rectal bleeding were assessed, which was similar to the studies by Miller et al.<sup>18</sup>

### Diarrhea

In our study, 33.3% of the patients had a grade 2 or higher diarrhea, compared to 76.7% of control patients, which was statistically significant ( $p = 0.001$ ). Pal et al.<sup>17</sup> found 19.14% in the study arm and 41.6% in the control arm ( $p = 0.017$ ). Mennie et al.<sup>6</sup> found that 12 of 14 individuals in the study arm improved from acetylsalicylate. Baughan et al.<sup>15</sup> found that 91.2% of 5-ASA patients had diarrhea, compared to 73.7% of placebo patients ( $p = 0.070$ ). Resbeut et al.<sup>14</sup> found that 70.4% of the trial subjects had a grade 1 or higher diarrhea compared to 65.7% of placebo individuals ( $p = 0.14$ ). Martenson et al.<sup>16</sup> found a grade 3 or higher diarrhea to be more common in the olsalazine group (60 vs. 14%;  $p = 0.0036$ ). Kiliç et al.<sup>19</sup> found that 7% of patients in the trial arm had a grade 3 or higher diarrhea compared to 30% in the placebo arm ( $p = 0.038$ ). Miller et al.<sup>18</sup> found 44% of study participants had a grade 2 or greater diarrhea compared to 41% of placebo participants ( $p = 0.44$ ).

### Abdominal Pain

In our study, 63.3% of patients in the study arm had a grade 1 or higher abdominal pain, compared to 93.3% in the control arm ( $p = 0.006$ ). Resbeut et al.<sup>14</sup> found that the patients in the study arm reported less abdominal pain than the placebo arm patients (34 vs. 51%,  $p = 0.048$ ). Martenson et al.<sup>16</sup> found that 24% of olsalazine patients had a grade 2 or higher stomach pain, compared to 11% of placebo patients ( $p = 0.084$ ). Miller et al.<sup>18</sup> found a grade 2 or higher stomach pain in the study arm (14 vs. 10%,  $p = 0.30$ ).

### Tenesmus

Fifty percent of patients in the study arm had a grade 1 or greater tenesmus, compared to 63.3% of control arm patients ( $p = 0.573$ ). Martenson et al.<sup>16</sup> found a significant decrease in the incidence of tenesmus in olsalazine arm compared to placebo ( $p = 0.033$ ). Miller et al.<sup>18</sup> found that a grade 2 or

higher tenesmus was more common in the study arm (22 vs. 7%,  $p = 0.23$ ).

### Rectal Bleeding

In this study, 3.3% of patients in the study arm had a grade 1 or higher rectal bleeding, compared to 33.3% in the control arm ( $p = 0.005$ ). There was no significant difference in maximum severity and the duration of rectal bleeding in sulfasalazine arm compared to placebo arm in the study by Miller et al. Martenson et al.<sup>16</sup> found 26 versus 32% grade 1 or greater rectal hemorrhage in the study and control arms, respectively ( $p = 0.595$ ).

The discrepancies in outcomes of other studies compared to our study can be attributed to several factors. First, different drug formulations of aminosalicylates used in studies have distinct pharmacokinetics, mechanisms of action, and side effect profiles, all of which can influence the outcomes. Second, radiation dose is one of the major determinant of toxicities. In our study, a dose of 50 Gy was given, while Martenson et al.<sup>16</sup> and Miller et al.<sup>18</sup> used higher doses as the study population included other pelvic malignancies like prostate and colon cancers.

One of the limitations of the above-mentioned studies and our study is the technique of radiation used to deliver EBRT. Today, many advanced techniques like intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) are available in which the small bowel can be contoured and given a constraint dose, so that we can limit the dose delivered to that organ without compromise in target coverage and thereby decrease the incidence of acute GI toxicities.

Another limitation of our study is the small group of patients. Further, to establish the role of sulfasalazine in preventing acute GI toxicities, multiple randomized trials with a larger sample sizes are required.

### Conclusion

In this study, the treatment group experienced fewer cases of abdominal discomfort of grade 1 or higher and diarrhea of grade 2 or higher than the control group. During the follow-up visits, no unfavorable effects of sulfasalazine were observed. It can be concluded that sulfasalazine was successful in reducing the incidence of radiation-induced acute GI toxicities, which is probably brought on by GI irritation and inflammation.

### Funding

None.

### Conflict of Interest

None declared.

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