Original Article

A prospective randomized controlled trial to study the role of sulfasalazine in prevention of acute gastrointestinal toxicity associated with concurrent chemoradiation in carcinoma cervix

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ABSTRACT

Background: The primary aim of the study was to evaluate the effectiveness of sulfasalazine in reducing the incidence of acute radiation-induced enteritis in carcinoma cervix patients receiving pelvic external beam radiotherapy along with concurrent cisplatin-based chemotherapy. **Materials and Methods:** Between November 2011 and July 2012 a total of 98 patients of locoregionally advanced carcinoma of cervix (49 each in study and control arms) were enrolled in this study. Patients in both the arms were treated with whole pelvis external beam radiotherapy with total dose of 50 Gy in conventional fractionation. Along with this inj. cisplatin was given concurrently at the dose of 40 mg/m^2 of body surface area every week during radiation for 5 weeks. Concurrent chemoradiation was followed by brachytherapy after a gap of 2 weeks. Patients in the study arm also received tablet sulfasalazine 1,000 mg orally twice daily from the day of starting of radiotherapy to 1 week after completion of treatment. Weekly follow-up of all patients to assess acute toxicities was done using common toxicity criteria version 4.0 (CTC v4.0) toxicity scores. Data analysis was carried out by SPSS version 20.0 software. **Results:** Incidence of grade II or higher grade, lower gastrointestinal toxicity was 19.14% (09/47) in study arm and 41.66% (20/48) in control arm which was statistically significant ($P = 0.017$). **Conclusion:** The study shows that sulfasalazine can significantly reduce the acute radiation-induced diarrhea (ARID) in patients undergoing whole pelvis external beam radiotherapy for carcinoma cervix. The drug is safe, cheap, and readily available.

Key words: Chemoradiation, diarrhoea, sulfasalazine

INTRODUCTION

Radiation therapy is the mainstay of treatment in various common gynecological malignancies like cervical and endometrial carcinoma, gastrointestinal malignancy such as anal and rectal carcinoma, and genitourinary malignancy like carcinoma of urinary bladder and prostate. For these cancers, patients are often subjected to pelvic irradiation in primary or adjuvant setting. Concurrent chemotherapy along with pelvic irradiation is the standard of care in carcinoma cervix stage IIB to IVA.[1,2] Pelvic irradiation causes mucosal damage to normal gut tissue;[3] both small and large intestine which fall within the treatment field; leading to fat malabsorption, leakage of albumin, and hypermotility. Radiation tolerance of small bowel is a dose limiting factor because of early adverse effect.[4,5] These patients often present with diarrhea and abdominal cramping termed as acute radiation enteritis (ARE), starting during 2nd and continuing to 3rd week of pelvic irradiation.[4] These side effects occur in about 75-80% of patients receiving pelvic radiotherapy. In patients receiving concurrent chemotherapy, the gastrointestinal toxicity is more severe in grade as anticipated. In some of the patients these side effects are so severe that we have to withhold radiation therapy in the middle of the treatment,

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leading to prolongation of treatment time, thus reducing the therapeutic benefit.[6]

This radiation-induced gut toxicity can be reduced by techniques like treating the patients in prone position or treating the patients with full urinary bladder. These techniques help to displace the small gut from the radiation field.[7,8] In some studies, it is seen that this radiation-induced diarrhea can be prevented by use of sulfasalazine 1 gm orally twice daily. The rationale for using sulfasalazine is that this radiation-induced diarrhea mainly occurs due to increased synthesis of nuclear regulating proteins that regulate cytokines and have secondary effect on eicosanoids.[9] Sulfasalazine reduces the synthesis of eicosanoids. So our aim in this present clinical trial is to explore the role of sulfasalazine in concurrent chemoradiation-induced diarrhea. We have also noticed that there is paucity of recent research publications addressing the effectiveness of sulfasalazine in prevention of concurrent chemoradiation-induced diarrhea.

MATERIALS AND METHODS

The entire study was conducted in the Department of Radiotherapy, Medical College Hospital, Kolkata between November 2011 and July 2012. Total 98 patients, belonging to the age range 18-70 years and sufficing the following criteria were included in this study: Attending the outpatient department with histologically proven squamous cell carcinoma (SCC) of cervix; Karnofsky performance status (KPS) more than 60; normal hematological, renal, and hepatic function. Informed consent was taken from all the patients. Patients with pregnancy and lactation, history of prior chemotherapy or radiotherapy to the pelvic region, uncontrolled comorbid conditions, and with evidence of distant metastasis were excluded from the study. Patients were randomly allocated to arm A (study arm) and arm B (control arm) who were planned for radical radiation therapy with concurrent chemotherapy; every other patient was recruited in the study arm. Patients on study arm were prescribed sulfasalazine 1,000 mg twice daily as oral medication from the day of starting of radiotherapy and continue till 1 week after completion of treatment while the control population were prescribed placebo.

Patients in both the arms were treated with external beam radiotherapy (EBRT) with conventional 2 Gy/fraction, 5 days a week for 5 weeks with total dose of 50 Gy with standard anteroposterior-posteroanterior (AP-PA) or four-field box technique using Telecobalt unit THERATRON 780C (Theratronics), CT-simulator (Brilliance CT 16-slice configuration, Philips Health Care), and ASHA 3D Planning System (TPS). Cisplatin were given concomitantly at a dose of 40 mg/m^2 of body surface area on every week during radiation for 5 weeks. After EBRT all patients received intracavitary brachytherapy (7-9 Gy per fraction to a total dose of 18-24 Gy) using Gamma Med Plus machine (Varian Medical Systems International India Pvt. Ltd).

Patients were followed-up every week to assess acute toxicities from the start of treatment to 4 weeks after completion of chemoradiation using CTC v4.0 [Table 1]. Level of significance will be calculated by Chi-square test. *P* values of 0.05 or less is considered to be significant. Data analysis was carried out by SPSS version 20.0 software.

RESULTS

Total 98 patients were studied and their characteristics are given in Table 2. Two patients from the test arm and one patient from control arm discontinued treatment midway due to unknown reasons. One patient in the

Table 1: Common toxicity criteria version 4.0 (diarrhea)

Grade 0	None
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline
Grade 3	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline, limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Table 2: Pretreatment patient characteristics

Characteristics	Study group %	Control group %
Number of cases	49	49
Age distribution (years)		
Minimum	33	35
Maximum	70	70
Mean	56	57
Distribution according to parity		
Para≤1	12 (24.5)	11 (22.4)
Para 2-3	27 (55.1)	28 (57.1)
Para≥4	10 (20.4)	10 (20.4)
Distribution according to performance status (KPS)		
60-70	6 (12.24)	7 (14.28)
70-80	25 (51.02)	23 (46.9)
>80	18 (36.73)	19 (38.77)
Distribution according to menstrual status		
Premenopausal	7 (14.3)	8 (16.3)
Postmenopausal	42 (85.7)	41 (83.7)
Distribution according to FIGO staging		
II B	24 (49)	23 (46.9)
III A	11 (22.4)	12 (24.5)
III B	12 (24.5)	12 (24.5)
IV A	2 (4)	2 (4)

KPS: Karnofsky performance status, FIGO: International federation of gynecology and obstetrics

control arm required hospital admission and parenteral support. Other adverse effects viz. renal, hematological, hepatic and dermatological toxicities were comparable in both arms. Most of the cases of acute radiation-induced diarrhea (ARID) occurred from third week of radiation onwards in both the arms.

Table 3 and Figure 1 describe the grades of lower gastrointestinal toxicities in two arms. The incidence of overall (Grade I-IV) lower gastrointestinal toxicity was 44.68% (21/47) in treatment arm and 75% (36/48) in control arm which was statistically significant ($P = 0.0025$). It is seen that incidence of Grade II or more lower gastrointestinal toxicity was 19.14% (09/47) in treatment arm and 41.66% (20/48) in control arm ($P = 0.017$). No Grade IV toxicity was found in study arm.

DISCUSSION

Pelvic radiotherapy is often associated with ARID which mainly starts around 3rd week of radiation. Radiation causes irritation and inflammation of gastrointestinal tract. There is excess production of prostaglandin, thromboxane, and leukotriene. They also affect water and electrolyte absorption and contractility of the gut. The excess production of prostaglandin as a cause of diarrhea during pelvic radiation was postulated by Mennie *et al*.[10]

One study by Resbeut *et al*.,[6] showed that mesalazine (5-aminosalicylic acid) is ineffective to reduce the rate of radiation-induced diarrhea. Another study by Martenson *et al*.,[11] showed worsening of symptoms after using olsalazine. But two studies, one by Rauch *et al*.,[12] and Kilic *et al*.,[13] showed decrease in incidence of ARID after use of sulfasalazine. The different results with different formulations of 5-aminosalicylic acid may be due to difference in drug formulation and also due to difference in side effect profile.

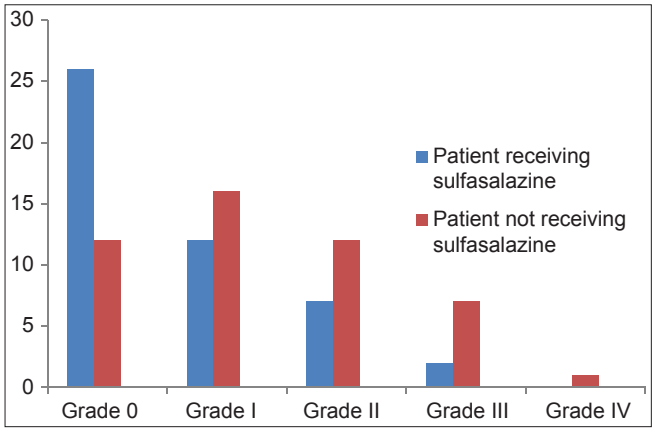

Figure 1: Comparison of toxicities of different grades in two arms

Mesalazine contains only 5-aminosalicylic acid. There is no carrier molecule. So it may not be effectively deposited in the terminal part of small intestine or the colon. Olsalazine consists of two molecules of 5-aminosalicylic acid coupled by azo bond. This azo bond is split in the colon. So no separate carrier is needed. But it may aggravate diarrhea by inhibiting water and electrolyte absorption in small intestine and also by decreasing transit time through bowel. However, sulfasalazine is a 5-aminosalicylic acid compound with sulfapyridine linked by an azo bond. This sulfapyridine is only a carrier molecule. The azo bond is broken by colonic bacteria by azoreductase releasing the active molecule, that is, 5-aminosalicylic acid.[9,14] It exerts an anti-inflammatory effect by inhibiting lipooxygenase and cyclooxygenase enzymes, and thus reduces production of prostaglandin and leukotriene and other mediators such as cytokines and platelet activation factor. Besides, scavenging of free radicals has also been attributed to 5-aminosalicylic acid as a proposed mechanism of action.[15]

These unique properties of sulfasalazine and its differences from other 5-aminosalicylic acid congeners prompted us to choose sulfasalazine in our study to prevent ARID. As ARID mainly results from irritation and inflammation of the gut, we have got promising results by using sulfasalazine to reduce the incidence of the same. Grade II or higher grade diarrhea were significantly less in the sulfasalazine arm and the findings were validated statistically. Sulfasalazine is a cheap and effective method to reduce the incidence of ARID. The patients are on routine follow-up to assess any change in disease response and late toxicity profiles as well.

In conclusion, our analysis reveals that administration of sulfasalazine reduces lower gastrointestinal toxicity of pelvic radiation and concurrent chemotherapy. Further clinical trials with greater number of patients will be of value for investigators who want to reduce treatment toxicity as an endpoint in concurrent pelvic chemoradiotherapy.

Table 3: Distribution according to grade of lower gastrointestinal toxicity

	Grade-0 (%)	Grade-I (%)	Grade-II (%)	Grade-III (%)	Grade-IV (%)
Patients receiving sulfasalazine	26 (55.3)	12 (25.53)	7 (14.9)	2 (4.25)	0 (0.0)
Patients not receiving sulfasalazine	12 (25.0)	16 (33.3)	12 (25.0)	7 (14.6)	1 (2.08)

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