Original Article

Role of glutamine versus placebo in prevention of acute gastrointestinal toxicity in pelvic radiotherapy: A randomized control study

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ABSTRACT

Context: Nausea, vomiting, diarrhoea, abdominal cramping, ano-proctitis are common acute gastrointestinal (GI) toxicities during pelvic radiotherapy (RT), having important impact on treatment outcome. Glutamine has a major role in mucosal growth and function. This phase III study is conducted to evaluate the role of prophylactic glutamine supplementation in prevention of acute GI toxicities during pelvic RT. **Materials and Methods:** Eighty five nonmetastatic patients with pelvic malignancy needing pelvic RT are included in this double blind randomized control trial. During RT 42 patients (Arm A) received 10 g glutamine oral supplementation 1 h before every RT fraction. Forty three patients received glycine as placebo (Arm B) in same schedule. Patients were assessed weekly for common acute RT induced GI toxicities. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.02. **Results:** Two arms were well balanced with all baseline parameters. Median age was 57. 56.47% (n = 48) patients had cervical cancer. There was no significant difference between two arms in grade wise incidence of any of the GI toxicities. Trends of diarrhoea during weekly assessments also similar in both arms. **Conclusion:** There is no significant beneficial effect of glutamine during pelvic RT. As per our study data and our dose schedule glutamine should not be indicated in pelvic RT.

Key words: Gastrointestinal toxicity, glutamine, pelvic radiotherapy

INTRODUCTION

Pelvic radiation therapy (RT) is used either as primary or adjuvant treatment in gynecological, gastrointestinal (GI) and genitourinary malignancies. Radical RT aims to cure the patient of their cancer but carries a risk for normal tissues around the tumor. During their 5 or 6 weeks course of treatment, approximately 80% of patients will develop GI symptoms which are partly caused by acute GI inflammation.[1] Acute GI side effects of pelvic RT include nausea, diarrhoea, abdominal cramping, rectal discomfort, and occasionally rectal bleeding, which may be caused by transient enteroproctitis. Patients with haemorrhoids may experience discomfort earlier than other patients. Diarrhoea, a very frequent symptom, is not only uncomfortable but can also cause dehydration and nutrients mal-absorption.[2] GI symptoms potentially alter quality of life of patients. Severe symptoms may require temporary or permanent cessation of RT before completion of the planned RT program.

Radiotherapy initially causes mucosal changes characterized by inflammation or cell death, but subsequently persistent cytokine activation in the sub mucosa leads to progressive ischemia, fibrosis and loss of stem cells.[3] These ischemic and fibrotic changes potentially cause impairment of GI physiological function (s). Chemotherapy increases the sensitivity of noncancerous tissues to damage from RT.

Diarrhoea and abdominal cramping can be controlled with the oral administration of diphenoxylate hydrochloride, loperamide, atropine sulphate etc., Proctitis and rectal discomfort can be alleviated by small enemas with

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hydrocortisone and antinflammatory and or steroid suppositories. A low-residue diet with no grease or spices and increased fibre in the stool (psyllium, polycarbophil) usually help to decrease GI symptoms.[4]

Glutamine plays an important role in the support of mucosal growth and function. Malignancy produces a state of physiologic stress that is characterized by a relative deficiency of glutamine, a condition that is further exacerbated by the effects of cancer treatment. Glutamine deficiency may impact on normal tissue tolerance to antitumor treatment, and may lead to dose reductions and compromised treatment outcome. Providing supplemental glutamine during cancer treatment has the potential to abrogate treatment-related toxicity.[5-7] In animal models, glutamine supplementation before or after whole abdominal RT appears to inhibit bacterial translocation and decreases the likelihood of both acute and chronic toxic radiation effects on the lower intestine. But this benefit was not evident in different clinical studies with pelvic RT. There were no significant differences in the incidence, amount, or maximum severity of diarrhoea.[5,8-10]

Our study aims at evaluating role of glutamine supplementation during pelvic RT in prevention of acute GI toxicities.

MATERIALS AND METHODS

Patients

This two arm Phase III double blind placebo controlled randomized study was done in a tertiary hospital from December 2011 to April 2013. Patient with nonmetastatic pelvic malignancy who needed pelvic RT (radical/adjuvant) were included in the study after getting written consent. Eligible subjects were having age range 18-75, years histologically confirmed squamous or adenocarcinoma. Patients having inflammatory bowel disease, prior abdomino-perineal resection, history of prior RT, pregnancy and severe comorbidities are excluded from the study.

Radiation therapy

Patients underwent whole pelvis RT with/out concurrent chemotherapy with four field arrangement. Upper border of the field did not extend beyond L4-L5 vertebra interspace. Lower border did not extend beyond 2 cm below obturator foramina. Treatment was given with Cobalt 60 machine (Theratron 780 C, Best Theratronics Ltd., Ottawa, Ontario, Canada). Total dose was between 45 and 50 Gy with 2 Gy per fraction and treatment was given 5 days a week. Patients were included from the 2nd day of radiation.

From the 2nd day of radiation patients were randomly assigned to receive glutamine (Arm A) or placebo (glycine) (Arm B). Before randomization patients baseline parameters were noted like age, sex, site of cancer, use of concurrent chemotherapy. Glutamine sachet containing 10 g glutamine granules dissolved in 100 ml of fruit juice was given to the patient every day 1 h prior radiation. Arm B also received placebo in same schedule.

Evaluation of toxicities

Patients were interviewed and examined for GI toxicities at baseline (1 week prior RT), weekly during RT and post treatment (1 week post-RT). Interviews were done by one prior trained radiation oncologist. Toxicities were graded and recorded according to Common Terminology Criteria for Adverse Events version 4.02 (CTCAE version 4.02). (vide Table 1)[11] Each toxicity was graded from 0 to 5.

Table 1: Major acute gastrointestinal toxicity grading according to CTCAE (version 4.02)

Symptoms	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Nausea loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 h	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN[a] indicated 24 h	Life-threatening consequences	Death
Vomiting	Vomiting 1 episode in 24 h	2–5 episodes in 24 h; IV fluids indicated <24 h	6 episodes in 24 h; IV fluids, or TPN indicated 24 h	Life-threatening consequences	Death
Enteritis (inflammation of the small bowel)	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis	Death
Diarrhoea	Increase of<4 stools per day over baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24 h	Increase of 7 stools per day over baseline; incontinence; IV fluids 24 h; hospitalization	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Distension/ abdominal bloating	Asymptomatic	Symptomatic, but not interfering with GI function	Distension symptomatic, interfering with GI function	-	-
Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL[b]; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death

[a]TPN: Total parenteral nutrition, [b]ADL: Activities of daily living, IV: Intravenous, GI: Gastrointestinal, CTCAE: Common terminology criteria for adverse events

Statistical analysis

The study was planned to include 90 patients with 45 patients distributed in each group. The study had a power of 0.8 and confidence interval of 95% to detect an improvement in which the GI toxicity of 75% of the glutamine-treated patients decreased by one grade compared with the patients treated with placebo. Type 1 error was fixed to 5%. Patient with more than 7 days gap in RT were planned to exclude from the study. Interim analysis was planned after 50% patient accrual to find out whether the Arm A is more toxic than Arm B. If it is so, study was designed to stop accrual in Arm A.

The unpaired Student's *t*-test or one-way analysis of variance was used to analyze continuous variables between groups. The Chi-square test or Fisher's exact test was used for comparison of categorical variables. Statistical analyses were performed using the Statistical Package for Social Sciences software version 19 (SPSS, Chicago, IL, USA). Results were considered statistically significant at $P = 0.05$.

RESULTS

Patient characteristics

During May 2012 to April 2013 91 eligible patients were enrolled in this study and randomly assigned to either Arm A or Arm B (46 patients and 45 patients respectively). During the course of the study 6 patients were excluded from analysis (4 patients did not complete radiation and 2 patients had more than 7 days gap during radiation (11 and 8 days). Final statistical evaluation was done with 85 patients (42 and 43 patients in Arm A and Arm B respectively). The patient characteristics are shown in Table 2. The differences between the two treatment groups were not statistically significant (Pearson Chi-square two-tailed asymptotic significance >0.05). Commonly occurring toxicities were reported, that is, nausea, vomiting, enteritis, abdominal bloating/distension, anal incontinence and proctitits. Maximum toxicity grade occurred at any observation was considered as quantal end point for each patient. Incidences of different toxicity grades are compared in Table 3. No significant difference was found between the two arms with regard to any toxicity event.

Patterns of toxicities in different weekly assessments were also analyzed. For any event most frequent grade in any weekly observation was taken into analytical consideration. Grades are compared between two groups. No statistical difference was noted on Chi-square test. Figure 1 depicts the graphical comparison of two arms during weekly assessments of diarrhoea.

Table 2: Distribution of baseline characteristics of the patients

Baseline factors	Arm A (glutamine) (*n*=42) (%)	Arm B (placebo) (*n*=43) (%)	*P* value
Age (years)			0.603
Mean	57.2±8.14	56.2±9.6	
Median	57	56	
Sex			
Male	15 (35.8)	14 (32.6)	0.670
Female	27 (64.2)	29 (67.4)	
Site			
Cervix	23 (54.8)	25 (58.1)	0.979
Rectum	10 (23.8)	8 (18.6)	
Endometrium	4 (09.5)	4 (09.3)	
Prostate	2 (04.8)	2 (04.7)	
Others	3 (07.1)	4 (09.3)	
Chemotherapy			
Yes	36 (85.7)	36 (83.8)	0.519
No	6 (14.3)	7 (16.2)	
Delay in RT*			
Yes	36 (85.7)	38 (88.37)	0.483
No	6 (14.3)	5 (11.63)	

*Includes only <7 days gap. RT: Radiotherapy

Table 3: Toxicity patterns comparison between two groups

Toxicities (grade wise)*	Arm A (glutamine) *n*=42 (%)	Arm B (placebo) *n*=43 (%)	*P* value
Nausea			
No nausea	5 (11)	2 (04.65)	0.413
1	33 (78.57)	38 (88.37)	
2	4 (09.52)	3 (06.97)	
Vomiting			
No vomiting	10 (23.8)	12 (27.9)	0.910
1	27 (64.28)	2660.46)	
2	5 (11.9)	5 (11.62)	
Enteritis			
No enteritis	7 (16.67)	9 (20.93)	0.875
1	18 (42.85)	17 (39.43)	
2	17 (40.47)	17 (39.53)	
Diarrhea			
No diarrhoea	11 (26.19)	10 (23.26)	0.668
1	8 (19.04)	10 (23.26)	
2	15 (35.71)	16 (37.20)	
3	6 (14.29)	7 (16.67)	
4	2 (04.77)	0	
Distension/ abdominal bloating			
No distension/ abdominal bloating	9 (21.4)	6 (13.95)	0.610
1	15 (35.71)	15 (34.89)	
2	18 (42.85)	22 (51.16)	
Proctitis			
No proctitis	10 (23.80)	17 (39.53)	0.249
1	28 (66.67)	24 (55.81)	
2	4 (09.52)	2 (04.76)	

*CTCAE grading (version 4.02). CTCAE: Common terminology criteria for adverse events

DISCUSSION

Radical RT to pelvic cancers carries a risk of complications to normal tissues around the tumour. Acute complications affecting the GI tract occur in approximately 80% of patients.[1,12] Acute symptoms include diarrhoea, abdominal pain, tenesmus or nausea that usually start during the 2nd or 3rd week of a course of radical RT and resolve within a fortnight of completion of RT. GI symptoms potentially alter quality of life of patients. Severe symptoms may require temporary or permanent cessation of RT before completion of the planned RT program.[1,2,12,13] Acute

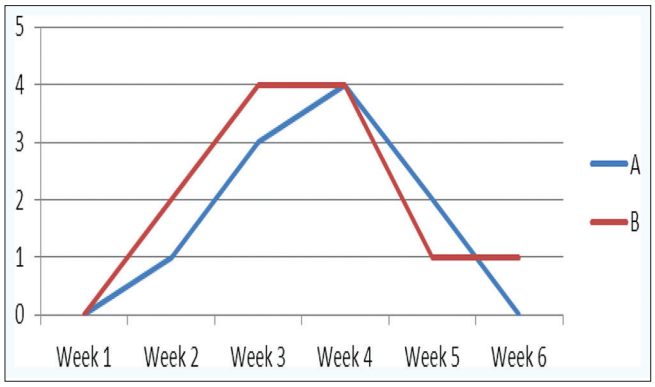

Figure 1: Comparison of diarrhoea grade in two study arms on weekly assessments

toxicities are usually mild in majority of cases. The severity of acute bowel toxicity may predetermine the degree of chronic bowel changes.[14] Therefore, early intervention to prevent or reduce acute toxicity may be worthwhile in the long-term.

Radiotherapy damages tissue by series of biochemical events inside the cell. Free radicals are formed and disrupt DNA, preventing replication, transcription and protein synthesis. When chemotherapy is added, the risk to normal tissues may be enhanced. RT alone or in combination with chemotherapy ultimately leads to inflammatory damage of gut mucosa and sub mucosa with ischemic and fibrotic changes. These changes potentially cause impairment of GI physiological function (s).[15] Majority of acute adverse effects of pelvic RT are related to lack of mucosal integrity from chemotherapy- or RT-induced damage of oral and gut epithelium. Any agent that could reduce such adverse effects would have good implications.

Glutathione (GSH), a by-product of glutamine metabolism, protects against oxidant injury in normal tissues. The gut is a major organ of GSH synthesis, which can be increased three-fold by the provision of supplemental glutamine. In the presence of oxidative stress, glutamine is rate limiting for GSH synthesis.[16,17] Cancer is a state of relative glutamine deficiency. This can have a negative impact on the function of host tissues that are dependent upon adequate stores of glutamine for optimal functioning (e.g. intestinal epithelial cells and lymphocytes).[7,18] Furthermore, the extent of normal tissue damage from radiation or chemotherapy may be influenced by the presence of adequate tissue glutamine stores. These facts support a possible therapeutic role for glutamine in the prevention of host normal tissue toxicity during cancer treatment.

There are very few evidences regarding the role of glutamine in prevention of radiation/chemotherapy induced gut mucosa damage.[5,8,10,19-23]

In order to determine the effects of glutamine on the intestine three studies have been done with animal model.[5,8,19] In a study by O'Dwyer *et al*. showed that glutamine enriched nutrition protects against atrophy of mice intestinal mucosa.[5] Other two studies were randomized control study with mice to evaluate the effects of prophylactic use of glutamine-enriched elemental diet, administered before whole-abdominal radiation on gut mucosal changes. Among these, Klimberg *et al*. found that glutamine exerts a protective effect on the small bowel mucosa by supporting crypt cell proliferation effect on accelerate healing of the acutely radiated bowel.[19] In the second investigation Jensen *et al.* tried to evaluate effect of oral glutamine supplementation on the development of RT induced chronic enteropathy in rat. Injury scores in glutamine and RT arm were similar to those of un-irradiated bowel and significantly different from placebo arm. There was 10-fold decrease in gross thickening and fibrosis in irradiated rat gut on addition of glutamine than placebo.[8]

Three studies tried to evaluate prophylactic role of oral glutamine on acute radiation injury of the gut in pelvic RT. None of them showed any advantages of adding glutamine.[10,22,23]

A study by Membrive Conejo *et al.* evaluated the effect of L-glutamine in the prevention of induced enteritis after pelvic RT. Incidence of diarrhoea observed was similar to published series in which glutamine is not administered. Administration of glutamine to patients during pelvic RT did not prevent the incidence of enteritis (diarrhoea) neither in RT alone nor in concomitant chemo-RT.[22]

North Central Cancer Treatment Group (NCCTG) did a similar randomized control study. There was no significant difference in incidence of diarrhoea and maximum grade of diarrhea. They also found no difference in quality of life scores between glutamine arm and placebo arm also.[10]

A very recent study by Vidal-Casariego *et al*. similar to previous study by NCCTG has been published which also showed similar results.[23] Unlike the previous two studies[10,22] the researchers in this study used clinical and biochemical parameters for assessment for radiation induced enteritis. Interestingly the authors noted more toxicity events in glutamine arm than placebo arm as per clinical end points. They also measured fecal calprotectin for mucosal inflammation and citrulline for mucosal integrity. But there was no difference in the results.[23]

Daniele *et al*. did a randomized control study with colorectal cancer patients to find out beneficial role of glutamine in adjuvant chemotherapy (5-flurouracil and folinic acid) induced intestinal toxicity. Bit similarly they found no

difference in the clinical parameters (daily diarrhoea score) and biochemical parameters (D-xylose urinary excretion and cellobiose-mannitol ratio) between oral glutamine arm and placebo arm.[20]

In three studies glutamine showed a beneficial role during RT. In a randomized study by Topkan *et al*. during concurrent chemo-RT of locally advanced nonsmall carcinoma of lung ,oral glutamine supplementation reduced weight loss, undue treatment delay and acute and chronic esophagitis.[21] Similar beneficial results are observed in concurrent chemo-RT of head neck cancer in the study by Huang *et al*.[24] Glutamine reduced the incidence of oral mucositis. Third interesting study done by Richards *et al*.[25] evaluated its role in prevention of entreocolitis in RT of prostate cancer. Authors assessed clinical endoscopic and histo-pathological comparison between glutamine and placebo group. They found no difference in intestinal events between two arms. But the histological changes are less marked in the glutamine arm.

In the present study we also tried to evaluate the role of oral glutamine supplementation in pelvic RT induced enteritis. We used 10 g glutamine granules. Total dose of glutamine was similar to studies by Kozelsky *et al*.[10] and Anderson *et al*.[26] But we used one time daily dosing schedule due to logistic reasons unlike twice or thrice daily dosing used by Kozelsky *et al*.[10] and Anderson *et al*.[26] In this present randomized control study only CTCAE clinical toxicity grading was used for toxicity evaluation. We did not use any biochemical, endoscopic and histological end points for comparison.

In our study incidence of all toxicities (CTCAE Grade 2 onwards) like nausea, vomiting, diarrhea, abdominal distension, enteritis and proctitis in placebo arm are similar with previous reported studies.[10,22,23] Also similar to other studies[10,21-23] there is no difference of toxicity events between glutamine and placebo arm in any grade. Mean dose of RT for occurrence of diarrhea and enteritis are similar in both arms and also corroborating the results of previous studies.[22] Trends of changes in diarrhoea grades are also comparable in both arms supporting the study by Kozelsky *et al*.[10]

Results regarding role of glutamine are variable and conflicting. One of the main reason may be the fact that exact patho-physiological changes (type of change, onset, duration etc.) in GI tracts during pelvic RT are not fully known.[15] Secondly, all the studies used different dose schedules of glutamine. Optimum dose, timing and its relationship with clinical outcome is unknown.[10] We followed the schedules of Kozelsky *et al*.[10] and Anderson *et al*.[26] But many other studies used much higher dose. Topkan *et al*.[21] and Vidal-Casariego *et al*.[23] reported 30 g/day in different divided doses. But interestingly though we used lower dose of glutamine incidence of diarrhoea events of present study was similar to reported incidences of the studies using higher doses.[10,23] Thirdly very few studies noted the exact pathological changes.[8,23,25] Most of the studies assessed only clinical parameters like ours. In the present study we used CTCAE toxicity tool which is very objective one having the disadvantage of excluding the subjective component. This may be one of the limitations of our study.

CONCLUSION

Glutamine oral supplementation during pelvic RT is well tolerated. But it showed no benefit in preventing occurrence and severity of common radiation induced acute GI toxicities. There is no recommended dose schedule published yet. Studies using higher dose of glutamine have different results. As per our study data and our dose schedule glutamine should not be indicated in pelvic RT.

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