Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 5, Suppl 4, 2012 ISSN - 0974-2441

Research Article

EFFICACY AND SAFETY OF ORAL GLUTAMINE IN RADIATION INDUCED ORAL MUCOSITIS IN PATIENTS WITH HEAD AND NECK CANCER

S.SARUMATHY*[1], A.M.ISMAIL[2], A.PALANISAMY[1]

[1] Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy; Elayampalayam, Tiruchengode - 637 205, Tamilnadu, India; [2] Department of Pharmacy Practice, Periyar College of Pharmaceutical sciences for Girls, Tiruchirappalli – 620 021, Tamilnadu, India; Email: saruprabakar@gmail.com

Received: 28 August 2012, Revised and Accepted: 11 October 2012

ABSTRACT

Aim To determine the efficacy and safety of oral glutamine in the treatment of radiation induced oral mucositis in patients with head and neck cancer.

Method 26 Head and neck cancer patients who were receiving radiotherapy (RT) were randomized to glutamine (Group A, n = 11) and negative control groups (Group B, n = 15), respectively, from June 2009 to January 2010. Group A patients swished the glutamine solution (5g glutamine dissolved in 75 ml of water, twice daily) for 1 minute. Oral mucositis was graded daily fraction at each day of treatment till the completion of therapy. The study groups were compared for the oral mucositis development using the WHO scale. The adverse events due to radiation or glutamine treatment were also assessed.

Results Patients in the age group of 51-60 years were in a higher risk of being affected with head and neck cancer. The mean grade of maximum mucositis was 2 and 2.93 in group A and group B, respectively. The onset of grade 1 and grade 2 mucositis was delayed in Group A compared to Group B. The adverse events were found to be mild to moderate in group A.

Conclusion Glutamine significantly delayed the onset of oral mucositis and reduced the incidence and severity of grade 3 mucositis.

Keywords: Radiotherapy, Oral Mucositis, Glutamine, Head and Neck Cancer

INTRODUCTION

Oral mucositis is a common side effect of cancer therapies, particularly radiation therapy for head and neck cancer and various forms of chemotherapy. Nearly all patients with advanced disease require adjuvant radiotherapy, preoperatively or postoperatively.[1] Oral mucositis manifests first by thinning of oral tissues leading to erythema. As these tissues continue to thin, ulceration eventually occurs. At this stage the primary symptom of severe debilitating oral pain will occur[2]. Hospitalizations are common because patients lose the ability to take anything by mouth due to severe pain and must have alimentation support during this period[1]. Pain management usually requires potent narcotic analgesia. Patients who become neutropenic and develop severe mucositis are at greatly increased risk for the spread of oral organisms, through oral ulceration, into the systemic circulation, resulting in life-threatening systemic infection[3,4]. Several studies reported about the reduction of oral mucositis during radiotherapy [5–9]. Glutamine is an essential amino acid that is critical to the regulation of protein synthesis, respiratory fueling, and nitrogen shuttling. It has been shown to reduce gastrointestinal mucositis in animals receiving chemotherapy[10]. AES-14, which is glutamine in a vehicle that greatly increases its uptake, has recently been shown to decrease grade 2 or higher mucositis in patients receiving chemotherapy for solid tumors[11]. In a pilot study, oral glutamine significantly reduced the duration and severity of objective oral mucositis in patients receiving 50 Gray (Gy)/25 fractions of radiotherapy[12]. Thus we conducted a pilot study, to assess the efficacy and safety of glutamine in patients who were scheduled to receive the radiotherapy of 2Gy/fraction for 5 weeks and more than 5 weeks.

METHOD

The study was carried out with the approval of the Institutional Ethics Committee and the consent was obtained from all the patients involved in the study. Patients visiting the oncology department from June 2009 to January 2010 with head and neck cancer receiving radiotherapy of 2 Gy/day fraction of radiotherapy for 5 weeks and/or more than 5 weeks with the ability to tolerate solid food were included into this study. Patients with any mucositis or oral and throat pain prior to starting radiotherapy, pregnant or lactating women and patients with any co-morbidities such as hepatic encephalopathy, kidney failure, seizure disorders, depressive disorders were excluded.

Patients were sequentially randomized to two treatment groups: Group A, who received 5 g glutamine dissolved in 75 ml of water, twice daily doses and group B, negative control. Group A patients swished the solution for 1 minute and expectorated before meals in the morning and same in the evening. The rinse was used throughout the radiotherapy treatment period. Patients received the prescribed fractions such as 50, 60 and 66 Gy at 2 Gy/RT fraction daily, 5 days a week, with a 2 days lapse period in between the radiotherapy. Patient education was also provided at the initial (base) level about head and neck cancers, radiotherapy treatment, oral mucositis, medication use, storage and diet enforcement. Then patients were examined by the radiation oncologists on each day of radiotherapy treatment.

Oral mucositis was assessed using the WHO scale[13] at daily fraction of the radiotherapy on each day of the treatment. The severity of oral mucositis was graded as follows, Grade 0: presence of no mucositis, Grade 1: presence of soreness and erythema, patients can eat solid foods, Grade 2: presence of ulcers and erythema, patients can take only soft foods, Grade 3: presence of ulcers and extensive erythema, patients can take only liquid foods, Grade 4: alimentation is not possible. Certain parameters were documented from the beginning until to the end of the treatment: Age, gender, social habits, diagnosis and length of radiation therapy. Mean maximum grade of mucositis, and mean fraction number of Grade 1–3 mucositis were compared by the student t test. $P < 0.05$ was considered to indicate the statistical significance. Graph Pad In stat prism software package was used in the statistical analysis. Adverse events for both the study groups were measured during the radiotherapy treatment.

RESULTS

From the oncology department 26 head and neck cancer patients who received the radiation therapy for 5 weeks and more than 5 weeks were selected. Out of these selected 26 patients, 11 patients (group A) were asked to swish the glutamine suspension for the treatment of radiation-induced oral mucositis and 15 patients were treated as negative control group (group B). The distribution of patients according to age, gender, social habits was seen to be similar between the study groups as shown in Table 1. The diagnosis, tumor differentiation and treatment parameters for the comparison groups were shown in Table 2. From the Table 3, the duration or number of RT fractions of mucositis as determined by using WHO scale was found to be 10.55 and 7.6 fractions for grade 1, 10.81 and 9.0 fractions for grade 2; 0 and 9.40 fractions for grade 3, of group A and group B patients respectively.

There was a statistically significant difference ($P<0.05$) between the duration of grade 1, grade 2 and grade 3 mucositis in both the study groups. The mean fraction number of the onset of grade 1 and grade 2 mucositis in the glutamine group was 7.72 and 18.27 fractions, respectively. The mean fraction number of the onset of grade 1 and grade 2 mucositis in the control group was 5.27 and 12.87 fractions, respectively. Glutamine was found to delay the onset of grade 1 and grade 2 mucositis of 2.45 and 5.4 fractions, respectively. There was no development of grade 3 mucositis in the glutamine group patients. The mean maximum grade of mucositis was found to be 2 and 2.93, for group A and group B patients, respectively. From the Table 4, the adverse events analysis revealed that in group A, 27 % of patients had edema, 18% of patients with infection, 27% of patients with dysphagia, 18% of patients with nausea, 82% of patients with taste loss, 36% of patients with RT-pain and 27% of patients with cough. In Group B, 33% of patients with edema, 20% of patients with infection, 26% of patients with dysphagia, 33% of patients with nausea, 86% of patients with taste loss, 40% of patients with RT-pain and 33% of patients with cough.

DISCUSSION

Oral mucositis has significant clinical implications in patients receiving radiation therapy for treatment of head and neck cancer. It may cause severe pain and dysfunction that interfere with swallowing and speech and lead to serious consequences such as weight loss. More importantly, radiation-associated mucositis can have significant implications on tumor control or cure, if treatment has to be interrupted to allow for healing or the dose and volume have to be reduced. There are no established measures for treatment of oral mucositis. A study showed that oral care to remove potential sources of infection provided in conjunction with cancer therapy is necessary to prevent serious complications, including rampant decay and osteo radio necrosis with radiation therapy and potentially life threatening infections and bleeding with chemotherapy[14]. Certain studies had shown that the use of topical antimicrobial lozenge containing polymyxin, tobramycin, and amphotericin B reduced oral mucositis with radiation therapy[5,15]. Two hematopoietic growth factors—granulocyte colony stimulating factor (GCSF) and granulocyte macrophage colony stimulating factor (GMCSF)—have been employed extensively to lessen mucositis [16, 17]. But these growth factors are expensive and would lead to economic burden to the patients.

Glutamine is an essential amino acid that is critical to the regulation of protein synthesis, respiratory fueling, and nitrogen shuttling[18]. Under great stress such as when humans suffer from disease, trauma, or are subjected to harsh drugs such as chemotherapy or radiotherapy, the body exhausts its supply to glutamine. In these cases glutamine supplementation can help the body maintain the necessary quantities of glutamine to maintain healthy metabolic function. Glutamine is primarily produced in the muscles and appears to play an important part in keeping them functioning normally, particularly in the digestive system. It is also used by white blood cells and contributes to normal immune-system function. Individuals with muscle-wasting and immune-system related illnesses (such as cancer or AIDS) who may be incapable of manufacturing their own supply of glutamine may benefit from glutamine supplements taken along with other amino acids[19]. It has been reported already about the reduction of gastrointestinal mucositis in animals receiving chemotherapy[10]. In human trials, AES-14, which is glutamine in a vehicle that greatly increases its uptake, has been shown to decrease grade 2 or higher mucositis in patients receiving chemotherapy for solid tumors[11]. It may be used to alleviate the oral mucositis induced by cytotoxic chemotherapy/radiotherapy in cancer patients[10, 12]. Thus we conducted a pilot study to determine the efficacy in prevention of radiation induced oral mucositis.

Table 1: Baseline parameters

Baseline Parameters	Group A (glutamine treated group, n =11)	Group B (negative control group, n = 15)	Total Percentage of Patients (%)
Age	54.18 ± 11.69	52.80 ± 10.02	
Male	9 (81%)	11 (73.3 %)	77
Female	2 (19%)	4 (27.7 %)	23
Presence of Social habits	8 (73 %)	13 (87 %)	81
Smoking	2	1	12
Smoking and alcohol use	2	2	15
Tobacco chewers	3	9	46
Betel nut chewers	1	1	8
None	3	2	19

Table 2: Diagnosis and Treatment parameters

Treatment Parameters	Group A (n = 11)	Group B (n = 15)
Diagnosis		
Oral cavity cancer	5	11
Oropharyngeal cancer	4	1
Nasopharyngeal cancer	2	1
Laryngeal cancer	0	2
Tumor differentiation		
Well	6	7
Moderate	3	4
Poor	1	1
Others	1	3
Radiotherapy treatment (gys)		
50 gy	2	1
60 gy	10	5
66 gy	0	8

In this study more number of male patients was found to be affected with head and neck cancers. Among the study population tobacco chewers were in a higher proportion. Most of the patients were having oral cavity cancer. From our analysis it was seen that the onset of grade 1 mucositis was 7.27 and 5.27 fractions for group A and B respectively, the onset of grade 2 mucositis was 18.27 and 12.87 fractions for group A and B respectively, the onset of grade 3 mucositis was 21.87 fractions for group B patients. There was no development of grade 3 mucositis in group A patients. This showed that there was delay in the onset of grade 1 (2.45 fractions) and grade 2 mucositis (5.4 fractions), respectively between the study groups. The mean maximum grade of mucositis was found to be 2 and 2.93, for group A and group B patients, respectively. There was no significant difference in the adverse events between the study groups. Therefore glutamine was found to be safe and effective in the treatment of radiation induced oral mucositis.

Table 3: The onset and development of mucositis at various duration or No. of RT fractions.

Variables	Group A(n = 11)	Group B (n =15)	P Value
Duration or No. of RT fractions of mucositis			
Grade 0	7.72	5.27	*0.0001
Grade1	10.55	7.6	*0.0001
Grade 2	10.81	9.0	*0.0341
Grade 3	0	9.40	*0.0001
Onset of grade 1 mucositis	7.27	5.27	
Onset of grade 2 mucositis	18.27	12.87	
Onset of grade 3 mucositis	nil	21.87	
Mean grade of maximum mucositis	2	2.93	

Table 4: Adverse events for both group A and group B patients

Type of Adverse Event	Group A (n = 11) in Percentage	Group B (n = 15) in Percentage
Edema	27	33
Infection	18	20
Dysphagia	27	26
Nausea	18	33
Taste loss	82	86
RT-pain	36	40
Cough	27	33

CONCLUSION

Oral glutamine significantly delayed the onset of oral mucositis and also reduced the incidence and severity of grade 3 oral mucositis. So the present study emphasizes the supplementary therapy of glutamine in order to delay and/or reduce the oral mucositis in patients with head and neck cancers undergoing radiation therapy. Thus the present study claims conformation of these findings in larger sample size in future.

REFERENCES

1. Spencer W.R. Cancer therapy related oral mucositis Journal of Dental Education 2005;69(8):919-29
2. Epstein JB, Schubert MM. Oropharyngeal mucositis in cancer therapy. Oncology 2003;17(12):1767-76.
3. Ruescher TJ, Sodeifi A, Scrivani SJ, Kaban LB, Sonis ST. The impact of mucositis on hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematolgic malignancies. Cancer 1998;82(11):2275–81.
4. Redding SW, Marr KA, Kirkpatrick WR, Coco BJ, Patterson TF. Candida glabrata sepsis secondary to oral colonization in bone marrow transplantation. Med Mycol 2004;42:479–81
5. Okuno SH, Foote RL, Loprinzi CL, et al. A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation- induced mucositis. Cancer 1997;79:2193–9.
6. Meredith R, Salter M, Kim R, et al. Sucralfate for radiation mucositis: Results of a double-blind randomized trial. Int J Radiat Oncol Biol Phys 1997;37:275–9.
7. Symonds RP, McIlroy P, Khorrami J, et al. The reduction of radiation mucositis by selective decontamination antibiotic pastilles: A placebo-controlled double-blind trial. Br J Cancer 1996;74:312–7.
8. Kannan V, Bapsy PP, Anantha N, et al. Efficacy and safety of granulocyte macrophage-colony stimulating factor (GM-CSF) on the frequency and severity of radiation mucositis in patients with head and neck carcinoma. Int J Radiat Oncol Biol Phys 1997;37:1005–10.
9. Abitbol AA, Sridhar KS, Lewin AA, et al. Hyperfractionated radiation therapy and 5-fluorouracil, cisplatin, and mitomycin-C (1/2 granulocyte-colony stimulating factor) in the treatment of patients with locally advanced head and neck carcinoma. Cancer 1997;80:266–76.
10. Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer 1998; 83:1433–9.
11. Peterson D, Petit R. Phase III study: AES-14 in chemotherapy patients at risk for mucositis [abstract 2917]. Prog Proc Am Soc Clin Oncol 2003; 22:725.
12. E.-Y.Huang et al. Oral glutamine to alleviate radiation induced oral mucositis: a pilot randomized trial. Int.J. Radiation Oncology Biol Phys 2000;46:535-9.
13. World Health organization. Handbook for reporting results of cancer treatment. Geneva: World Health organization, 1979, pp 15-22.
14. Rankin KV, Jones DJ, Redding SW. Oral health in cancer therapy. Texas Cancer Council, 2004;2:43-52.
15. Symonds RP, McIlroy P, Khorrami J, Paul J, Pyper E, Alcock SR, et al. The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo controlled double-blind trial. Br J Cancer 1996;4:312-7.
16. Ibrahim EM, al-Mulhim FA. Effect of granulocyte-macrophage colony-stimulating factor on chemotherapy-induced oral mucositis in non-neutropenic cancer patients. Medical Oncology 1997;14(1):47-51.
17. Nicolatou O, Sotiropoulou-Lontou A, Skarlatos J, Kyprianou K, Kolitsi G, Dardoufas K. A pilot study of the effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients during X-radiation therapy: a preliminary report. Int J Radiat Oncol Biol Phys 1998; 42:551-6.
18. Lacey J & Wilmore D: Is glutamine a conditionally essential acid? Nutr Rev 1990;48(8):297-307.
19. Jones, C., Palmer, T. E. & Griffiths, R. D. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition 1999;15:108-115.