Efficacy of Oral Glutamine Supplementation for Prevention of Mucositis Associated with BEAM Conditioning in Bone Marrow Transplant

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SETTING-Bone marrow transplant unit in Tata Memorial Hospital

ABSTRACT

OBJECTIVE-To determine whether oral glutamine supplementation reduces the grade of oral mucositis in Autologous BMT with BEAM conditioning chemotherapy.

METHODOLOGY-28 consecutive patients of autologous transplant receiving BEAM conditioning are equally divided in 2 groups 14 patients in each group. Glutamine supplementation of 20g/day dissolved in 200ml water was given to the study group patients twice a day from post transplant day +1 to day +23 and the grading of oral mucositis and diarrhea for both the study and control groups was tabulated daily according to WHO scale of grading for oral mucositis.

RESULTS-The study and the control groups were clinically similar. The incidence of grade 2 4 mucositis is significantly less in the study group ($p = 0.006$). Diarrhea wasn't statistically significant between the study and the control groups ($p = 0.866$)

CONCLUSION- Patients receiving oral Glutamine supplementation after Bone marrow transplant had significantly lesser grade of oral mucositis and related morbidity.

KEY WORDS- Glutamine, BEAM, Mucositis, Autologous bone marrow transplant

INTRODUCTION

Use of bone marrow transplantation (BMT) to treat malignant and non-malignant disease has increased dramatically during the past decade (Mogul, 2000; Slavin, 2000). Patients may undergo allogeneic BMT, in which cells for transplant are derived from HLA-matched donors, or autologous BMT, in which cells for transplant are derived from the patient. The most commonly used method to obtain cells for BMT is ex vivo mobilization of stem cells from peripheral blood using colony-stimulating growth factors (Mogul, 2000; Slavin, 2000). Administration of high doses of chemotherapy (often including bulsulfan, cyclophosphamide, and/or etoposide ARA-C), with or without total body irradiation

(TBI), is a feature of most BMT protocols for malignancy. These regimens are designed to ablate the underlying malignant cells, but may cause adverse gastrointestinal complications including nausea, vomiting, inflammation of the oral and esophageal mucosa (mucositis), abdominal pain and diarrhea (Blijlevens et al. 2000; Jonas et al. 2000).

Nonmyeloablative stem cell allogeneic transplantation (NST) is also undergoing clinical investigation for malignant and non-malignant disease (e.g. induction of organ allograft tolerance or genetic disorders) and is associated with less gastrointestinal toxicity (Slavin, 2000). However, for malignant diseases, the efficacy of NST remains to be defined and high-dose cytotoxic therapy remains the standard of care in BMT protocols (Mogul, 2000; Slavin, 2000). Adverse gastrointestinal effects associated with high dose chemotherapy given prior to BMT may decrease spontaneous food intake, disrupt the gastrointestinal mucosal barrier and interfere with nutrient transport and absorption (Blijlevens et al. 2000). In addition, marked body protein wasting, immune system suppression and oxidative stress occur after BMT, despite administration of conventional nutrition support (Mogul, 2000; Slavin, 2000; Jonas et al. 2000; Durken et al. 1995).

Although parenteral nutrition (PN) and oral nutrient supplements are commonly prescribed, the efficacy of nutrition support in BMT patients still remains unclear (Weisdorf et al. 1987; Ziegler et al. 1990; Klein &Koretz, 1994). This is due to the small number of well-designed randomized clinical trials and rapid changing conditioning and growth factor regimens, which makes controlled studies of nutrition support difficult. Thus, administration of specialized nutrition varies widely among BMT centers worldwide.

An increasing number of clinical investigations have focused on supplementation of specialized enteral and parenteral nutrition with the amino acid glutamine to improve the efficacy of nutritional support (reviewed in Darmaun, 2000; Griffiths, 1999; Ziegler et al. 2000; Wilmore &Shabert, 1998; Ziegler et al. 2000). This interest derives from strong evidence in animal models and an increasing number of clinical trials in cancer and noncancer patients demonstrating benefits of glutamine supplementation in certain catabolic states, including patients following chemotherapy, trauma and sepsis.

Glutamine has protein-anabolic effects and is used as a major fuel or substrate by cells of both the gut epithelium and the immune system (Darmaun, 2000; Griffiths, 1999; Ziegler et al. 2000; Wilmore &Shabert, 1998; Ziegler et al. 2000). These effects may be particularly advantageous in patients

undergoing BMT, who exhibit body protein wasting, immunodeficiency, mucositis and gut mucosal injury. In critically ill and post-operative patients, nutritional formulations supplemented with either free L-glutamine or glutamine dipeptides (glycyl-glutamine or alanyl-glutamine) have been shown to improve nitrogen balance, decrease the incidence of infection, diminish length of hospital stay, improve immune functions and reduce hospital costs.

Effect of glutamine supplementation on mucositis after high-dose chemotherapy alone or in BMT regimens

Mucositis or inflammation of the oral mucosa is a painful and dose-limiting complication that occurs after high-dose chemotherapy (Blijlevens et al. 2000). The management of oral mucositis and the inflammation that also affects esophageal, gastric and intestinal mucosa varies from center to center and optimal treatments are still not clarified (Biron et al. 2000; Rosenthal et al. 2000). Therapies in practice and those under investigation are directed at inflammatory, epithelial, ulcerative and healing phases of mucositis (Blijlevens et al. 2000; Biron et al. 2000; Rosenthal et al. 2000). Therapies under investigation include cryotherapy, cytoprotection (e.g. with prostaglandin E2), epithelial cell protective factors and agents that may accelerate epithelial restitution (growth factors) and use of antiseptics and antibiotics to decrease secondary infection of denuded mucosal (Blijlevens et al. 2000; Biron et al. 2000; Rosenthal et al. 2000). intravenous and/or oral L-glutamine did not influence incidence or severity of mucositis after BMT.

However, other studies indicate potential benefits of oral glutamine in BMTassociated mucositis (Anderson et al. 1998a; Cockerham et al. 2000). In a randomized, prospective, double-blind clinical trial, Anderson et al. (1998a) evaluated effects of oral L-glutamine in 193 patients undergoing allogeneic or autologous BMT.

Most subjects had hematologous malignancies but 32 % had solid tumors and 9 % were transplanted for inherited diseases. The pediatric and adult subjects were matched for clinical demographics and BMT regimen and randomized to either oral L-glutamine or oral glycine (1:0 g/m2 per dose) to swish-and-swallow four times daily. The study amino acids were given from hospital admission until 28 days post-BMT. In patients undergoing autologous BMT ðn ¼ 87Þ; glutamine use was associated with significantly less mouth pain and less difficulty eating and decreased opiate requirements (Anderson et al. 1998a). The number of patients not requiring morphine for pain was greater in the glutamine group than in controls (53 v. 31 %, P¼0:04). When morphine was given, the duration of administration was approximately 50 % less with glutamine treatment (5 v. 10 days,

P¼0:005). These beneficial effects were not observed in allogeneic BMT patients (comprised of both matched donors and unrelated donors). There were no differences between groups in graft-versus-host disease or the incidence of infections overall. However, seven viral infections developed in placebo patients versus none in those receiving glutamine (Anderson et al. 1998a). Further, in autologous BMT patients, glutamine use was associated with a significant improvement in the 28-day survival rate (100 v. 93 % survival, P¼0:006) but not in the 100-day survival rate (87 v. 81 % P¼0:18) (Anderson et al. 1998a). In a recent retrospective analysis of twenty-one consecutive patients receiving high-dose paclitaxel and melphalan with autologous BMT for metastatic breast cancer, an oral L-glutamine suspension (24 g/d) was given as a swish-and-swallow (4 g/dose 6 times daily) beginning at the onset of chemotherapy 7 days prior to BMT (Cockerham et al. 2000). Results showed that the group given glutamine demonstrated significantly fewer days of mucositis, a lower maximum grade of mucositis and required fewer days of parenteral morphine for oral pain relief (Cockerham et al. 2000). Several studies have been published on effects of oral glutamine in non-BMT patients receiving chemotherapy alone, with mixed results.

In a crossover study of patients receiving 5-fluorouracil (5-FU) for intestinal cancer, oral glutamine (16 g/day) had no measurable effect on the incidence or severity of mucositis (Jebb et al. 1994). Bozzetti et al. (1997) studied sixty-five patients with advanced breast cancer being treated with doxifluridine. Subjects received either L-glutamine orally (30 g/day) or malto dextrine as the control for eight consecutive days during intervals before chemotherapy courses. There were no differences between groups in either doxifluridine induced diarrhea or in tumor response (Bozzetti et al. 1997). In a double-blind randomized study of patients receiving 5-FU-based chemotherapy regimens for various cancers by Okuno et al. (1999) patients received oral glutamine (4 g swish and swallow twice daily) or placebo for 14 days beginning on the first day of chemotherapy (sixty-eight patients/group). There were no significant differences or substantial trends in the mucositis scores between the two study arms (Okuno et al. 1999).

In contrast to these information, additional data indicates that glutamine administration can decrease gastrointestinal toxicity to chemotherapy in cancer patients (Anderson et al. 1998b; Muscaritoli et al. 1997; Daniele et al. 2001). In a double-blind, crossover study of twenty-four pediatric and adult patients receiving doxorubicine chemotherapy for solid cancers, Anderson et al. (1998) showed that twice daily oral administration of L-

glutamine (2.0 g/m2 per dose) versus glycine significantly decreased the duration of mucositis and also the severity of oral pain. In an unblinded study of fourteen patients with acute leukemia receiving high-dose combination chemotherapy, oral glutamine given at a dose of 18 g/day begun 3 days prior to chemotherapy induction significantly decreased the duration and severity of diarrhea and requirements for antifungal agents (Muscaritoli et al. 1997).

Finally, Daniele et al. (2001) recently investigated seventy chemotherapy-naive patients with colorectal cancer randomly assigned to either oral glutamine (18 g/day) or placebo before the first cycle of a five-day course 5-FU and folinic acid. Treatment was continued for 15 consecutive days starting 5 days prior to chemotherapy. Results showed that patients receiving oral glutamine had a significantly improved D-xylose absorption and cellobiose-mannitol urinary excretion, indicating improved gut absorptive and barrier function compared to controls (Daniele et al. 2001). Glutamine also significantly decreased the severity of diarrhea and the need for loperamide therapy for diarrhea. Thus, oral glutamine in this setting had a protective effect on 5-FU-induced diarrhea and abnormal intestinal function following chemotherapy (Daniele et al. 2001).

METHODOLOGY

A prospective cohort interventional study was conducted on 28 consecutive patients of autologous transplant receiving BEAM conditioning. BEAM stands for(Busulphan, etopside ARA-C and melphalan) these drugs are given before transplants to damage the bone marrow completely so that new cells can be transplanted to stem cell transplant. These patients are equally divided in 2 groups 14 in control group who does not received the glutamine and 14 in the study group who received glutamine supplementation these patients are in the age group of 25-60yrs were included in the study group based on the the inclusion and exclusion criteria which includes subject diagnosed with hematological malignancy undergoing autologous transplant receiving BEAM conditioning regimen and with no renal dysfunction

INTERVENTION

Glutamine supplementation of 20g/day which is 15gm sachet(10gm of L-glutamine) dissolve in 200ml water was given to the study group patients twice a day from post transplant day +1 to day +23 after giving the glutamine supplementation the in-charge sister used to sign in the drug sheet as it is given and the grading of oral mucositis and diarrhea for both the study and control groups was tabulated daily, based on WHO scale of grading for oral mucositis and CTCAE grading of diarrhea(Table no.1-2)

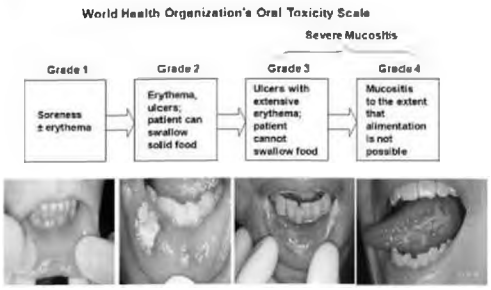


Table 1- WHO grading scale of mucositis

	Grade	*CTCAE description*
1	Mild	Increase of fewer than 4 stools per day over baseline
2	Moderate	Increase of 4–6 stools per day over baseline
3	Severe	Increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; limits self-care activities of daily living
4	Life-threatening	Life-threatening consequences; urgent intervention indicated
5	Death	Death

CTCAE = *Common Terminology Criteria for Adverse Events* (version 4.03)[27].

Table-2 grade of diarrhea CTCAE

DATA COLLECTION

A tabular proforma was formed for bone marrow transplant unit which is being filled by the dietician everyday with collaboration with unit doctors and consultants, proforma contains the baseline height, weight, body mass index , known co morbidities, vitamin B12, folic acid and vitamin D status of each patient. The nutritional assessment tool used was SGA subjective global assesment. The calories and protein intake of each patient were calculated by the researcher on daily basis during the rounds from -4 day to +23 post transplant days

We also record the grade of mucositis, dysphagia, diarrhea, opiate use, and Total parenteral use

The data was recorded in the patients file during hospitalization. Post discharge this data was entered in the excel sheet

MEASUREMENTS

The anthropometric measurements such as Height, weight and BMI were used in the study; weight was monitored on daily basis to check fluid balance.

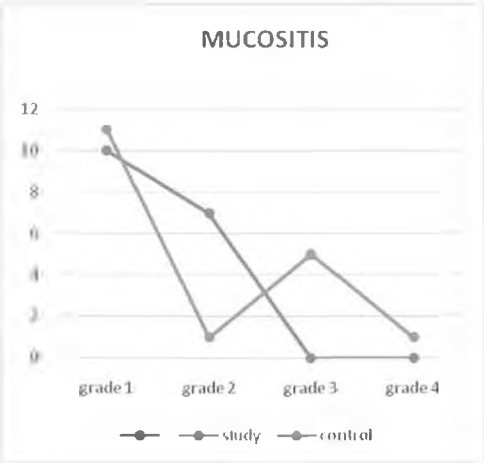
STATISTICAL ANALYSIS

The statistical analysis was done by using Man Whitney test to compare the differences in the grades of oral mucositis and diarrhea, between the study and the control groups.

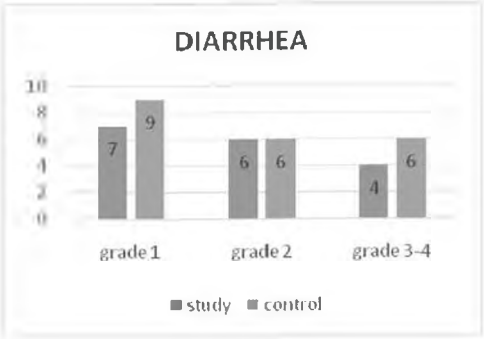
RESULTS

The study group and the control groups were clinically similar. The incidence of mucositis in the control and study groups are as follows 10 patients developed grade 1 mucositis in control group whereas 11 patients developed grade 1 mucositis in the study group. The incidence of grade 2 mucositis in the study group was more, as 7 patients developed grade 2 mucositis when compared to the control group where only 1 patient developed grade 2 mucositis .It is also noticed that Grade 3 mucositis is not seen in study group but in control group 5 patients developed grade 3 mucositis and were initiated on a liquid diet with partial parenteral nutrition. Incidence of grade 4 mucositis was seen in one patient

in the control group but there were no incidence of grade 4 mucositis was reported in the study group .The incidence of grade 3 and 4 mucositis was significantly less in the study group (p = 0.006).Among the 14 patients in the study group only 4 had grade 3 diarrhea whereas in the control group 6 patients had grade 3 diarrhea. The incidence of grade 3 - 4 diarrhea was not statistically significant between the study and the control groups(p value =0.866) .In patients undergoing autologous BMT (*n* = 14), glutamine use was associated with significantly less mouth pain and decreased opiate requirements between both the groups. None in the study group were on total parenteral nutrition(TPN) , whereas in the control group 6 patients were on TPN out of the 14 patients. The length of hospital stay was also less in the study group when compared to the control group.



GRAPH-1 Grade of mucositis in study and control group



Graph 2- grade of diarrhea in study and control group

DISCUSSION

Mucositis is the common problem in patient undergoing autologous stem cell transplant which can lead to poor oral intake of calories and protein, pain in mouth more opiate use and use of total parenteral nutrition which can increase the length of hospital stay and cost of the treatment it also affects the quality of life during transplant. use of oral glutamine of 20gm/day has shown a significant and a positive result in decreasing the grade and severity of oral mucositis and less use of TPN during transplant. patient was able to take food orally during transplant as the data on oral glutamine use in transplant in India is not being studied so far and international data is also very controversial this type of pilot study has increased the scope of using glutamine supplementation for the benefit of transplant patient more studies are required in this field to assess the efficacy of oral glutamine supplementation in other field of oncology as well which large population

CONCLUSION

Patients receiving oral Glutamine supplementation after Bone marrow transplant had significantly lesser grade of oral mucositis and related morbidity.

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