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Enteral/Oral Glutamine Supplementation in Patients Following Abdominal Surgery

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Abstract

The objective of this investigation was to study the effect of enteral/oral glutamine supplementation in patients following abdominal surgery on plasma glutamine levels, rate of infection and Length Of Hospitalization (LOS). A randomized control trial was used and the patients were randomly divided into two groups namely experimental and control with 15 participants each. Glutamine supplement (0.5g/kg) was administered (oral and enteral) to the experimental group for a period of 5 days post-surgery immediately after the feeding began. In both the feeding groups the plasma glutamine levels were analyzed spectrophotometrically using a glutamine determination kit on day 1 following surgery and day 6 (post 5 days of feeding). For statistical analysis t test and Chi square test were used. The study was carried out in Topiwala National Medical College and BYL Nair Hospital, Mumbai, India. There was a significant difference in the baseline plasma glutamine levels in both the groups ($p<0.05$). And on day 6 the plasma glutamine analysis revealed significant higher levels in the experimental group as compared to the control group. The incidence of infection in the control group was found to be almost twice that in the experimental group considering the role of glutamine in combating infection. Also the length of hospitalization was found to be slightly higher in the control group as compared to the experimental group. The present study has provided evidence that the supplementation of enteral glutamine in post-operative patients decreases the incidence of post-surgical infection, shortening of hospital stay and reduction in the overall hospital costs.

Keywords: *Glutamine supplementation, post-operative patients, oral and enteral feed*

Introduction

'Protein energy malnutrition' a major problem in the management of post-operative patients was long recognized by Hiram O Studley, an American surgeon way back in 1936, as he observed that weight loss was a significant predictor of surgical risk among his patients suffering from peptic ulcer disease[1]. According to 'gut origin

of sepsis' hypothesis the leaky gut is an essential factor in developing septic complications with the concept of bacterial translocation as demonstrated *in vitro* and *in vivo* studies[2]. In addition, nutritional depletion is associated with increased intestinal permeability and a decrease in villous height[3].

Post operative nutritional supplementation has been known to improve the quality of life, nutritional status and morbidity of patients[4].Hence 'malnutrition matters' and 'nutrition is the cutting edge in surgery'[5].Enteral nutrition has been known to bring about reduction in infectious complications in post major abdominal surgery[6]. Previous systematic reviews and meta-analysis have suggested that immune nutrition in critically ill have been associated with reduced hospital stay, infection rate and inflammatory response[7]. Any catabolic stressful condition results in 50% loss of glutamine from the muscles and it is of utmost importance to deliver adequate amounts of glutamine to maintain the integrity of intestinal mucosa, to preserve the muscle glutamine pool and to improve overall nitrogen economy during conditions of stress[8].Glutamine is known to be a precursor of protein synthesis and the mucosal and the immune cells in the body utilize this particular immunonutrient as an energy source in almost all the tissues. Also glutamine is involved in a large number of metabolic pathways[9].

One of the major procedures which results in severe depletion of glutamine from the skeletal muscles, bringing about muscle loss immunosuppression thus resulting in increased risk for postoperative infection and sepsis is surgery[10,11]. Various studies have indicated that glutamine supplementation in postoperative patients bring about improvement in their clinical outcome and also their intestinal permeability[9-14]. However a conclusive data on this aspect has not been explored much in India.

As noted in the review of Jan Wernerman, the recommendation from ESPEN and ASPEN/SCCM is to add Intra Venous (IV) glutamine supplementation when Total Parenteral Nutrition (TPN) is given to critically ill patients[15,16]. In all guidelines, this is given a level A recommendation. Meta analyses have identified a dose of 0.3-0.5g/kg/d in parenteral nutrition to normalize plasma glutamine concentration in almost all critically ill patients[15,17,18]. However no sufficient data has been obtained on the enteral glutamine requirement in post-surgery patients. Hence this study attempts to understand the effect of glutamine supplementation in patients following abdominal surgery on plasma glutamine levels, length of hospitalization and rate of infection.

Materials and Methods

This was a randomized controlled trial wherein 30 participants following

abdominal surgery belonging to the age group of 20-55 years were recruited from the surgery ward of BYL Nair Hospital using purposive sampling technique. The patient characteristics are given in Table I.

Exclusion criteria

Patients with co morbidities such as: type I diabetes and type II diabetes on insulin management, renal diseases (creatinine concentration > 2.5mg/dl), cardiac disorders (Class III or IV), hepatic disease (total bilirubin concentration > 3 mg/dl), autoimmune diseases, chronic use of steroids (30 mg or more for more than a month), chronic obstructive pulmonary disease (partial pressure of carbon dioxide (PCO_2) > 375kPa or 50mm Hg) and pregnant women.

Withdrawal criteria

Non-compliance with the blood test.

Ethical approval

The study was approved by the Independent Ethics committee at BYL Nair Charitable Trust. Thirty consenting participants were randomly assigned into two groups preoperatively namely: control (diet) group and experimental (diet + supplement) group.

Dietary management

Gastrostomy and jejunostomy tubes were placed during the surgery for post-operative nutrition support. However 10% of the participants were given oral feeds directly in post-surgery as they showed tolerance for the same.

The nutrition formula of both the groups were closely matched for energy and protein content. Feeding for either group began at strength of 1200kcal/day further advancing it on a daily basis towards the goal caloric requirement of 35-40 kcal/kg body weight. Goal nutrition also provided 1.5 g protein/kg body weight/day. The experimental group was given 0.5 g glutamine/day for a period of 5 days. Tube feeding tolerance for the participants on the same was done by daily recording of nausea, vomiting or diarrhoea.

Glutamine supplement

Meta gluta ZS® glutamine granules were used in the study. Each sachet contained 10g glutamine. The supplement was weighed as per the dosage requirement of 0.5g/kg body weight for each patient using a digital weighing scale.

Route of administration

The supplement was given in divided doses throughout the day. 10g of the glutamine from the supplement (Meta Gluta ZS®) was mixed in 180ml of water and given orally and enterally for the patients where oral feed was not possible.

Mode of study

The study protocol was divided into 4 sections:

1. Post-operative day 1 assessment of plasma glutamine levels
2. The primary study period of 5 post-operative enteral feeding days
3. Reassessment of plasma glutamine levels on day 6 of feeding
4. Follow up and tracking the incidence of infection and length of hospitalization till the patient was discharged.

Laboratory analysis

Venous plasma glutamine was measured at baseline for post-operative day 1 and day 6 of feeding. Blood samples were collected in heparinized tubes and were stored at -70 degree Celsius. Plasma samples were first deproteinized and then run in the glutamine determination kit. The glutamine determination kit was procured from Sigma Aldrich and a total of four kits were required for the study. The method was standardized on Anlytek at the department of Clinical Pharmacology, BYL Nair Hospital. The determination of glutamine was done on the basis of the protocol provided with the kit. The samples were analyzed for both glutamine and endogenous glutamate levels. The absolute glutamine levels were then calculated.

Statistical analysis

Continuous data were summarized as mean ± SD. Independent t test was used to compare the two groups with respect to Body Mass Index (BMI), age, calories and proteins received by day 5 and length of hospitalization. The difference in incidence of infection between the two groups was analyzed using the Chi square test and the differences in plasma glutamine levels on day 6 were analyzed using independent t test. Paired t test was used to compare the plasma glutamine levels within the group pre and post supplementation

Results and Discussion

A total of 30 patients following abdominal surgery were recruited in the present study and were randomly

TABLE I
Characteristics of Patients

Details	Control group (Diet group)	Experimental group (Diet+supplement group)
Age	38.0 ± 13.45 years	39.4 ± 12.33 years
BMI	23.3 ± 6.76 kg/m^2	21.7 ± 2.98 kg/m^2
Male	8	10
Female	7	5
N (Sample size)	15	15

TABLE II
Mean Calories and Protein Distribution in the Two Groups

Group	Control group (N=15)	Experimental group (N=15)	't' value
Mean calories (kcal)	1602 ± 296.70	1585.33 ± 236.57	0.042[NS]
Mean protein (g/d)	65.26 ± 10.25	61.93 ± 14.39	0.223 [NS]

NS - Not significant

divided into two groups namely control group and experimental group. The participants mainly belonged to the lower socio economic class. Patient characteristics are listed in Table I. The nutrition formulas of both the groups were closely matched for energy and protein content. Feeding for either group began at strength of 1200kcal/day further advancing it on a daily basis towards the goal caloric requirement of 35-40kcal/kg body weight. Goal nutrition also provided 1.2-1.5g protein/kg body weight/day. The caloric and protein distribution achieved as on day 5 have been listed in Table II. The surgical procedures followed by both the groups are given in Figure 1.

Plasma glutamine values

The experimental group was given 0.5g/kg body weight glutamine per day for a period of 5 days beginning from the

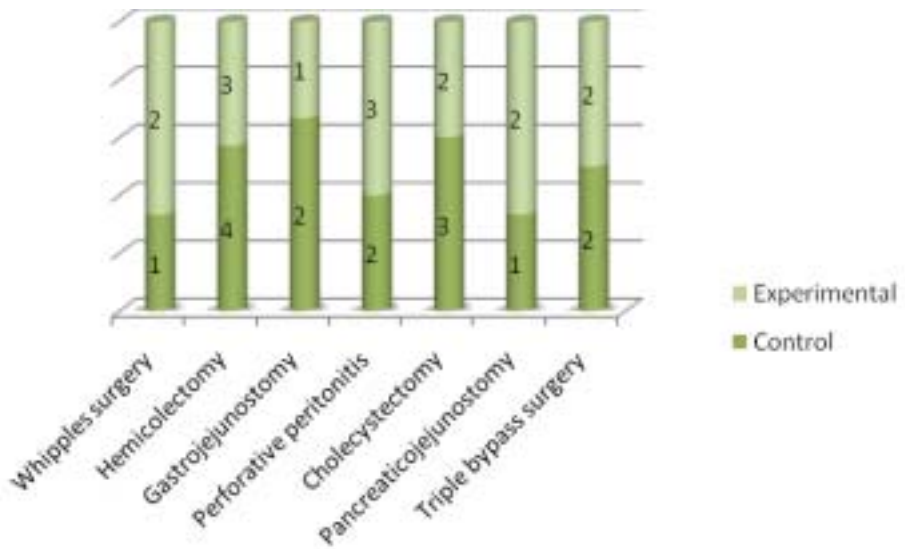

Figure 1
Types of surgery in two groups

TABLE III

Change in Mean Plasma Glutamine Levels in Experimental and Control Groups

Group	Baseline mean plasma glutamine levels (post-operative day 1) (µmoles/L)	Day 6 - Mean plasma glutamine levels (µmoles/L)	t value	
			Day 1 vs Day 6	Exptl. vs Control
Control group (N=15)	111.94 ± 77	177.40 ± 80.86	4.028**	2.744**
Experimental group (N=15)	167.34 ± 77.98	304 ± 77.19	6.756**	

** Significant at one % level

start of the feeding period. The venous blood samples of the participants in the control and the experimental group were analyzed for the plasma glutamine values on post-operative day 1 followed by enteral feeding and 5 days of glutamine supplementation and day 6 of feeding.

A significant increase in the plasma glutamine values of both groups as compared to day 1 was observed in both the groups. However as shown in Table III the increment was significantly more in the experimental group as compared to the control group.

Length of hospitalization

The average length of hospitalization was 19.8 ± 13.1 days in the experimental group and 25.13 ± 15.13 days in the control group. The length of hospitalization with glutamine supplementation was significantly shortened in experiment with a p-value 0.05.

Incidence of infection

About 53.3% of the participants in the control group were reported to have secondary infection post-surgery as compared to only 26.66% in the experimental group as shown in

TABLE IV

Hospitalization and Incidence of Infection in Control vs Experimental Group

Group	Length of hospitalization (days)	t value	Incidence of infection	χ^2 value
Control group (N=15)	25.13 ± 15.13	1.024*	53.30%	2.36*
Experimental group (N=15)	19.8 ± 13.1		26.60%	

* Significant at five % level

Table IV. The differences in the rate of infection among the two groups were significant different with a p-value $p<0.05$ as seen in Table IV.

Nutrition support has been widely used in the area of surgery, where the benefit on patients' prognosis is evident. Surgical site infections and wound and tissue dehiscence are well-known postoperative complications in gastrointestinal surgery[19]. Thus an appropriate and feasible nutrition support strategy is necessary and beneficial for patients' prognosis.

Several researchers have analyzed the role of glutamine post-surgery[20-24]. Dechelotte *et al*[25] evaluated the absorption and metabolic effects of enterally administered glutamine using stable-isotope methods in healthy subjects. Plasma glutamine showed a dose dependent increase and they concluded that glutamine is effectively absorbed by the jejunum.

A meta-analysis including 9 randomized, controlled clinical trials, with a total of 373 patients undergoing abdominal surgery, concluded that administration of parenteral nutrition supplemented with glutamine (20-40 g/day) has a beneficial effect on nitrogen balance, reduces hospital length of stay and infectious complications[21]. Oguz conducted a study in postoperative patients with colorectal cancer, where enteral nutrition vs enteral nutrition supplemented with parenteral glutamine was administered, in a total of 109 patients, concluding that glutamine supplements reduce the number of postoperative complications and hospital stay[23].

Kumar[24] compared in patients with peritonitis and abdominal injuries the administration of enteral glutamine (45 g/day) versus conventional EN without finding benefits in the glutamine group.

Jan Wernerman[26] mentioned that in postoperative patients, a daily IV glutamine dose of 20 g attenuates the decrease otherwise seen in skeletal muscle. This dose was originally chosen from a calculation of the decline in the free glutamine pool. Researchers in the ASPEN position paper on parenteral nutrition for glutamine supplementation have stated the probability of parenteral nutrition glutamine supplementation being better over enteral administration of glutamine in surgical and critically ill patients[27].

However parenteral nutrition generally proves to be very expensive and is not affordable for the lower socio economic group. Hence keeping this in mind in the present study oral glutamine supplements were used at a dosage of 0.5g/kg body weight for a period of 5 days and it was observed that plasma glutamine levels on day 6 of feeding showed a significant increase as compared to day 0 in both the groups. This could be due to the increased

proteins1.2-1.5g protein / kg body weight was supplied through the diet as protein consumption also has a direct correlation with the glutamine levels.

However as shown in Table III the increment was significantly more in the experimental group as compared to the control group. Similar finding was observed in a study done on patients receiving intravenous glutamine supplementation following elective abdominal surgery[28].

The incidence of infection in the control group was found to be almost twice that in the experimental group (53.3% *vs* 26.6%) considering the role of glutamine in combating infection. Also the length of hospitalization was found to be significantly higher in the control group as compared to the experimental group (25.13±15.13 day's *vs* 19.8±13.1 days).

In the present study due to limitations in the size of the samples a great significant value could not be obtained. It was noted that Kumar et al[24] also expressed the same concern of the sample size being low as he observed a similar phenomenon with regard to the incidence of infection and length of hospitalization when abdominal trauma patients in a hospital setting in Delhi were supplemented with 45g oral glutamine/d.

A similar study done on burn patients in China[29] displayed normalization of the plasma glutamine levels after oral glutamine supplementation (0.5g/kg body weight) for 14 days.

Conclusion

Hence the fact that glutamine does help in reducing the rate of infection cannot be denied. As observed in the present study, the experimental group did far better than the control in terms of length of hospitalization and incidence of infection. However since no such guidelines for oral glutamine supplementation in patients following abdominal surgery is available we need to confirm this finding with larger population groups.

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