

## Original Article

# Early Parenteral Supplementation with Glutamine Dipeptide for Acute Myeloid Leukaemia Patients Receiving High Dose Chemotherapy

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## Abstract

**Background:** Glutamine dipeptide (Gln) is one of conditionally essential amino acids that have a crucial role in cancer.

**Objectives:** The aim of this study was to investigate the effects of early Gln supplementation in patients with acute myeloid leukemia (AML) receiving intensive chemotherapy, but without bone marrow transplant and regardless of receiving parenteral nutrition.

**Methods:** A randomized control trial was carried out and included 46 AML patients who received high dose chemotherapy. Their ages ranged between 17-65 years. AML patients were randomly allocated as intervention group (Gln group; n=23) and control group (n=23). Gln group received intravenous supplementation with Gln (40 gm) from day 1 to day 5 of chemotherapy, while the patients in the control group received 40 gm per day of a standard amino acid mixture. Clinical end points included the body weight, body mass index, length of hospital stay, days of neutropenia, superoxide anion generation and length of neutropenic fever and serum albumin difference. White blood cells and absolute neutrophil count were done every second day till ANC reached >500 $\mu$ l then superoxide anion generation was measured.

**Results:** Weight loss, length of hospital stay, the mean days of neutropenia and neutropenic fever were significantly lower in the Gln group, whereas the mean superoxide anion generation was found higher comparing to the control group (50 ng/L vs 43ng/L respectively). Complications other than febrile neutropenia were significantly less common in Gln group. Gln supplementation has resulted in significant improvement in serum total protein and serum albumin.

**Conclusion:** This trial suggested that early Gln supplementation regardless receiving parenteral nutrition enhances neutrophil function, maintains nutritional status and decreases hospital stay.

**Key words:** Glutamine dipeptide; acute myeloid leukaemia; malnutrition; chemotherapy

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## INTRODUCTION

Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow. Nutrition is an important aspect of patient care in acute myeloid leukemia.<sup>(1)</sup> According to National Cancer Registry Program of Egypt the total number of estimated incident cases of myeloid leukemia cases was 1125 in 2013 and is expected to increase approximately to 2412 in 2050.<sup>(2)</sup> Malnutrition results

from the 'parasitic' metabolism of the tumor at the expense of the host, and from more and more aggressive cancer therapies. Nutrition in chronic critical illness is essential to ensure the restoration of muscle strength and immune status, both of which are necessary to attain optimal function and survival.<sup>(3)</sup> Acute myeloid leukemia patients who are treated with multiple chemotherapy cycles suffered to prolonged periods of bone marrow suppression and marked reduction in neutrophil count (Neutropenia: defined as an absolute neutrophil count less than 500 / $\mu$ L in the peripheral blood). Febrile neutropenia (FN) is an

oncologic emergency that occurs when a patient develops a fever while being neutropenic with or without any other overt signs or symptoms of infection. FN mainly occurs due to the myelosuppressive side effects of most chemotherapies. Fever within this context is defined as a single temperature of greater than or equal to 38.3°C (101°F) or a temperature of greater than or equal to 38°C (100.4°F) for one hour.<sup>(4)</sup>

Glutamine (Gln) is a conditional-essential amino acid, and an essential energy source.<sup>(5)</sup> Glutamine is important for rapidly dividing immune cells, for maintaining gut barrier function, and for synthesis of the endogenous antioxidant, glutathione. Healthy subjects have an endogenous glutamine production of 50-80 g/day. Most of the de novo glutamine synthesis takes place in skeletal muscle.<sup>(6)</sup> Gln metabolism is significantly altered in critical illnesses. The lower levels of Gln have been associated with impaired tissue healing, immune dysfunction and increased mortality.<sup>(7)</sup> However, A meta-analysis involving 1645 critically ill patients showed a significant decrease in mortality in patients receiving supplemental Gln.<sup>(8)</sup>

The American Society for Parenteral and Enteral Nutrition (ASPEN)<sup>(9)</sup> has published an exhaustive review on the use of Gln in parenteral nutrition. It warned that the potential beneficial effect of Gln supplementation remain unclear and concluded that Gln supplementation should be further investigated in the areas of timing and dosing. Finally, few studies have evaluated the effect of supplemental Gln on neutrophil functions, such as superoxide anion generation (SAG) in leukemic patients. This has raised a question about whether Gln supplementation in AML patients would have a beneficial effect on neutrophil function, and whether such supplementation would reduce the incidence of infection, stomatitis and diarrhea, all of which are common side-effects of chemotherapy.<sup>(10,11)</sup>

Consequently, the present trial was set to investigate the effect of early supplementation of Gln dipeptide on neutropenia and FN as side effects of chemotherapy, patient's immunity as indicated by neutrophil recovery, neutrophil SAG and length of hospital stay (LOS) upon admission in AML patients receiving chemotherapy.

## METHODS

A randomized controlled clinical trial was carried out at the Hematology Department of the Alexandria University Main Hospital from October 2014 to May 2015. The study was designed to comprise two groups of AML patients: an intervention group that will receive Gln dipeptide supplementation (Gln group) and a control group. Using Med. Calc. Software<sup>(7)</sup>, the

sample size was calculated using a power of 80% to detect a significant difference of superoxide anion generation (SAG) between the Gln group and the control group equal to 5.4 nmol/106 neutrophils per 10 minutes with SD=3.2 and 1.5 respectively. The minimal required sample was found to be 40 patients.

Forty six patients with AML from both gender aged 17-65 years and scheduled to receive myelosuppressive chemotherapy were included in the study. Patients with sepsis, pregnancy, liver (serum glutamic oxalacetic transaminase > 100 IU/l) or renal failure (serum creatinine > 2.5 mg/dl), or patients who had previously received other commercial Gln supplement products within 1 month of the start of the study were excluded. Patients were allocated at random into 2 equal groups (using Graph Pad-quick Calcs software) each comprising 23 patients.

The study comprised 3 phases:

### Phase I: Preliminary Nutritional assessment

A predesigned interview questionnaire was completed for each patient before starting Gln supplementation. It covered data about socio-demographics, medical history and dietary habits using a 24 hour dietary recall method. Egyptian food composition table was used to analyze the food consumed to get the dietary composition in terms of energy and macronutrients.<sup>(12)</sup> Height and weight were measured and body mass indices (BMI) were calculated.<sup>(13,14)</sup> Energy and protein requirements were estimated<sup>(15)</sup> then calculation of nutrient adequacy was done using the appropriate method.<sup>(16)</sup> On admission, routine clinical chemistry (including serum albumin and total protein measurement), and complete blood counts [including differential white blood count and absolute neutrophil count (ANC)] were evaluated.<sup>(17)</sup>

### Phase II: Intervention phase

The Gln group received a supplement of 40 gm Gln dipeptide (Dipeptiven®; Fresenius Kabi, Alexandria, Egypt) in a dose of 200 ml containing 13.46 g% of Gln for 5 days of the chemotherapy cycle. Each bottle of dipeptiven® (100 ml) was diluted in 250 ml normal saline 0.9% and infused over 4-6 hours twice daily; while the control group receive 40 g/day of a standard amino acid mixture (Aminoven® 10%; Fresenius Kabi, Alexandria, Egypt) twice daily for 5 days.

### Phase III: Follow up phase

White blood cells and ANC count were done every second day for monitoring of chemotherapy side effects, and till ANC reached >500 $\mu$ l. SAG was measured when ANC recovered to reach >500  $\mu$ l using ELISA Kit (Glory Science Co., Ltd, Del Rio, USA). Total protein, serum albumin levels, urea, creatinine, uric acid levels, liver enzymes, hemoglobin level and RBCs counts were done twice weekly.<sup>(17,18)</sup> Patients were monitored until hospital discharge for

the development of chemotherapy related side effects such as oral mucositis, diarrhoea, FN and days of neutropenia. Weight measurements and BMI calculation were repeated before patients' discharge. Dates from admission to discharge were recorded for each patient to determine length of hospital stay (LOS). The use of granulocyte-colony stimulating factor (G-CSF) for both groups which is another factor with potential effects on neutrophil recovery was recorded.

### Statistical analysis

Data were coded and analyzed with the Statistical Package for Social Sciences (SPSS, version 16; SPSS Inc., Chicago, USA).. All statistical analysis was done using two-tailed tests. A P-value less than or equal to 0.05 was considered to be significant. Descriptive statistics included the mean with standard deviation and percent to describe the scale and categorical data, respectively. Chi square and Fisher's Exact test using Monte Carlo method were used for comparison between qualitative variables. Student t-test of significance was used for comparison between mean changes in both groups, and paired t-test was used for comparison between data before and after neutrophil recovery. Finally, Pearson's correlation coefficient was applied to detect the relation between certain variables.

### Ethical statement

The researcher sought the approval of the Ethics Committee of the High Institute of Public Health and a written permission from the Head of Hematology Department for conducting the study. The study procedure conformed to the international research guidelines, the ethical guidelines of the 1975 Declaration of Helsinki and Guidelines of the International Conference on Harmonization for Good Clinical Practice. A written consent was obtained from all the study participants after elaboration on the study aim and concerns. Anonymity and confidentiality were guaranteed and maintained.

## RESULTS

**Preliminary Assessment:** Table 1 shows the baseline characteristics and chemotherapy regimen for the two study groups. Randomization has guaranteed that patients in both groups were almost matched regarding the same geographical area with essentially similar socio-economic background. There was no significant difference in the mean age and gender of the patients from both groups. Furthermore, both groups were comparable in terms of non use of (G-CSF) (78.3% vs 74%). Chemotherapy regimens consisted of low dose Cytarabine for seven days and Doxorubicin for three days (3+7), high dose Cytarabine for three days

(HIDAC), high dose Cytarabine for three days and Vepside for three days (HIDAC+vep), high dose Cytarabine for three days and Novantrone for three days (hAM). The distribution of chemotherapy regimens between the two groups was not significantly different (Mcp= 0.414). The nutritional value of the patient's daily diet was similar in both groups. The mean energy intake by Gln group was 2088.63±639.574 kcal/day and 1946.9±634.255 kcal/day for the control group. The mean protein intake by Gln group was 89.76±38.52 g/day and 95.83±34.10 g/day for the control group. More than half of the Gln group and the control group (56.5% and 52.2% respectively) were taking less than their daily energy needs, while about 56.5% of the Gln group and 34.8% of control group were taking less than their daily needs of protein, with no significant difference between them.

**Anthropometric and Clinical Data:** the mean weight of patients on admission was 78.47±19.7 Kg & 72.00±13.12 kg among the Gln group and the control group respectively. There was a significant difference in weight loss during the treatment period between the two groups (Table 2). Loss of body weight in the Gln group was less severe compared to the control group where the mean weight difference for Gln group was -0.52±1.675 kg comparing to -4.09±1.73 kg for control group and the difference was statistically significant. Likewise, the mean BMI difference for the Gln group was -0.363±0.8551 and -0.808±0.8161 for the control group although the difference was not statistically significant. Significant changes in serum albumin or serum total protein concentrations during treatment were found. The mean serum total protein difference of the Gln group was increased by 0.6 ±0.375g/dl whereas it was significantly decreased (-0.41 ±0.917g/dl) in the control group. On the other hand, the mean serum albumin decreased in both groups but to a lesser extent in the Gln group, with a statistically significant difference between the two groups (Table 2). The supplementation of glutamine dipeptide in a dose of up to 0.7 gm/kg/day (40 gm glutamine dipeptide) for patients with normal renal and hepatic function (no increase in renal or hepatic functions) did not result in any side effect as been demonstrated through laboratory analysis (Table 3).

**Incidence of FN, LOS and Neutrophil activity:** Patients in the Gln group experienced less FN episodes compared to the control group (39% vs 56.5% respectively), although the difference was not statistically significant ( $\chi^2=0.797$ , P =0.372, 95% CI). Also, the duration of hospital stay (mean of 21 days in Gln group vs 28 in the control group), days of neutropenia (11 and 15 days respectively) and length of neutropenic fever in days (2.1 and 5.15 days

respectively) were significantly shorter compared to those in the control group. A comparison of levels of SAG (with or without G-CSF administration) between the AML patients given Gln and the AML control

group revealed that the overall levels of SAG were higher in the Gln group than in the control group, although the difference was not significantly significant (Table 4).

**Table (1): Baseline characteristics of acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls**

Chemotherapy Protocols	Group				Test of Significance	
	Glutamine (n = 23)		Control (n = 23)		Test	P
	No	%	No	%		
Low dose Cytarabine for seven days and Doxorubicin for three days (3+7)	11	47.8	6	26.1		
HIDAC	8	34.8	10	43.5	2.979 <sup>1</sup>	0.414
HIDAC+vep	2	8.7	2	8.7		
hAM	2	8.7	5	21.7		
Age (years)	30±1.624		30±1.595		-0.086 <sup>2</sup>	0.931
Male/female (n)	17/6		17/6			1.000 <sup>3</sup>
Use of G-CSF subcutaneous injection (No. of cycles)						
None	18	78.3	17	73.9		
One time	2	8.7	1	4.3	4.141 <sup>1</sup>	0.300
Two times	1	4.3	4	17.4		
Three times	2	8.7	0	0.00		
Six times	0	0.00	1	4.3		
Mean total energy Intake (Kcal)	2088.63±639.57		1946.9±634.25		0.755 <sup>2</sup>	0.454
Inadequacy of total energy intake (< 100% of calculated requirements)	13	56.5	12	52.2	0.088 <sup>3</sup>	0.767
Mean Protein Intake (g/d)	89.76±38.518		95.83±34.104		-0.565 <sup>2</sup>	0.575
Mean CHO Intake (g/d)	300.182±92.37		275.31±95.95		0.896 <sup>2</sup>	0.375
Mean Fat Intake (g/d)	59.32±31.221		54.05±35.00		0.540 <sup>2</sup>	0.592
Inadequate protein intake (< 100% of calculated requirements)	13	56.5	8	34.8	2.190 <sup>3</sup>	0.139

<sup>1</sup>Monte-Carlo Exact Test.

<sup>2</sup>Independent student t-test

<sup>3</sup>Chi-square test

**Table (2): Comparison of weight, BMI, serum total protein and serum albumin in acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls**

Parameters	Group		Student t-test		
	Glutamine (n=23)	Control (n=23)			
Weight (kg)	Baseline	78.47 ±19.7	72.00±13.12	t=1.512	P=0.196
	Hospital discharge	78 ±19.45	68 ±12.88 *	t=2.064	p=0.046*
	Change	-0.52±1.67	-4.08±1.73*	t=7.10	p=0.000*
BMI (Kg/m <sup>2</sup> ) Mean Change	-0.38±0.85	-0.81±0.81	t=1.808	p=0.077	
Serum total Protein (g/dl)	Baseline	6.98±1.43	7.56±0.82		
	Hospital discharge	7.04±1.34	7.15±0.61		
	<b>Paired t test</b>	t=-0.72 P=0.47	t=2.126 P=0.04*		
	Change	0.06 ±0.375	-0.41 ±0.91*		
Serum Albumin (g/dl)	Baseline	3.57±0.68	3.57±0.48	t=2.251	p=0.029*
	Hospital discharge	3.45±0.65	3±0.537		
	<b>Paired t test</b>	t=1.472 P=0.155	t=5.033 P=0.000*		
	Change	-0.12 ±0.397	-0.58 ±0.551*	t=3.225	p=0.002*

Data show mean ± SD

\*P < 0.05 versus Gln group

The majority of Gln group (82.6%) and nearly half of control group (47.8 %) did not experience any complication other than FN. However, their occurrence differed significantly between both groups. The Gln group had no hypokalemia or hemorrhage. Nevertheless, one case (4.3%) had fistula. In the control group, three cases (13%) had hypokalemia and one case (4.3%) had both hemorrhage and fistula (Table 4).

**Correlations:** A positive correlation was found between days of neutropenia and LOS. This correlation was found weak ( $r = +0.351$ ) among the Gln group and moderate ( $r = +0.621$ ) among the control group, with a statistical significance difference between both groups. Likewise, SAG correlated positively with ANC on date of sampling, A moderate positive correlation was found in in Gln group ( $r = +0.551$ ) comparing to a weak positive one ( $r = +0.124$ ) in the control group. The length of NF increased with longer LOS. This positive

correlation was found weak ( $r = +0.127$ ) in Gln group and moderate ( $r = +0.493$ ) in control group with a statistically significance difference between both groups. Furthermore, days of neutropenia favored the occurrence of complications other than neutropenic fever. The correlation was again very weak ( $r = +0.078$ ) in the intervention group and moderate ( $r = +0.292$ ) in the control group (Figure 1, 2, 3).

Based on the findings of univariate analysis, all variables were included for the multiple regressions where intervention was found to be the most relevant factor affecting the weight difference. This means that glutamine supplementation has a highly significant effect on weight difference. Other factors affected the weight difference were as gender, protein adequacy, SAG, LOS, serum total protein difference, serum albumin difference, and complications other than neutropenic fever (Table 5).

**Table (3): Comparison of laboratory results in acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls**

Laboratory results	Group					
	Glutamine (n=23)			Control (n=23)		
	On admission Mean±SD	Before discharge Mean±SD	Paired t-test P	On admission Mean±SD	Before discharge Mean±SD	Paired t-test P
Hemoglobin Level (g/dl)	10.84±2.15	9.3±1.32	t=2.886 P=0.009*	10.57±1.76	9.14±1.22	t=3.32 P=0.003*
Red Blood Cells (cells/L)	3.66±0.77	3.19±0.44	t=2.67 P=0.014*	3.564±0.65	3.28±0.43	t=1.612 P=0.121
Urea Level (mg/dl)	24.91±9.05	23.91±11.06	t=0.406 P=0.689	26.17±8.78	21.09±8.62	t=1.818 P=0.083
Creatinine (mg/dl)	0.743±0.178	0.752±0.22	t=-0.24 P=0.812	0.787±0.28	0.71±0.21	t=2.313 P=0.03*
Uric Acid (mg/dl)	4.71±1.252	3.23±1.23	t=5.32 P=0.000*	5.04±1.61	3.26±1.32	t=1.609 P=0.000*
SGOT (U/L)	27.43±13.97	19.26±8.61	t=2.657 P=0.014*	29.78±12.4	25.39±19.62	t=1.191 P=0.246
SGPT (U/L)	46.04±21.73	36.83±14.80	t=2.434 P=0.024*	44.43±15.2	41.04±31.03	t=6.347 P=0.000*

Data show mean ± SD. \*P < 0.05

**Table (4): Comparison of clinical end points in acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls**

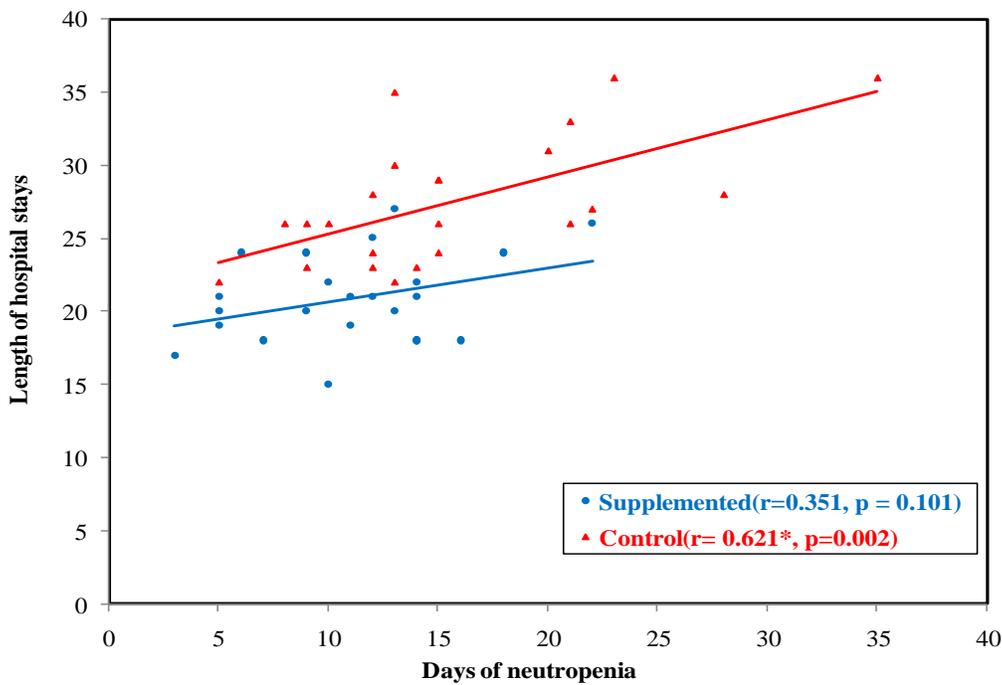
Parameters	Group		Test of Significance	P
	Glutamine (n=23)	Control (n=23)		
Length of hospital stay (in days)~	21 ±3.05*	28 ±4.326	t= -6.027	0.0001*
Days of neutropenia~	11±4.592*	15.65±6.92	t= 20.193	0.01*
Superoxide anion generation (ng/L)~	50±19.424	43.04±12.036	t= 1.460	0.151
Incidence of febrile neutropenia #	9 (39%)	13 (56.5%)	$\chi^2 = 0.797$	0.372
Length of neutropenic fever (in days)~	2.11±1.167	5.15±3.105	t= -3.220	0.005*
Complications other than neutropenic fever #	4 (17.4%)	12 (52.2%)	$\chi^2 = 6.133$	0.013*

~ Data show mean ± SD \* statistically significant difference ( $P < 0.05$ ).  
# Data show number and percent t= Independent student t-test  $\chi^2 =$  Pearson Chi square test

**Table (5): The multiple logistic regression analysis of variables related to weight difference**

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Group	-2.578	0.789	-0.535	-3.267	0.001*
Patient age	-0.013	0.027	-0.076	-0.477	0.645
Patient Sex	-3.297	0.785	-0.537	-4.198	0.002*
Energy adequacy	-0.005	0.019	-0.058	-0.290	0.779
Protein adequacy	0.022	0.008	0.355	2.762	0.022*
Days of Neutropenia	-0.013	0.072	-0.033	-0.180	0.861
Superoxide anion generation	0.054	0.019	0.345	2.922	0.017*
Length of hospital stay	-0.294	0.086	-0.656	-3.434	.007*
Frequency of neutropenic fever	0.125	0.112	0.149	1.119	0.292
Serum total protein differences	0.974	0.464	0.393	2.100	0.065
Serum albumin differences	-2.210	0.883	-0.479	-2.504	0.034*
Complications other than febrile neutropenia	-0.497-	0.224	-0.272	-2.216	0.054

Dependent Variable: Weight Difference R Square (coefficient of determination) = 0.928  
 Multiple linear regression equation:  $Y = a + b_1x_1 + b_2x_2 + \dots$   
 Y: Weight difference a: Constant b: Unstandardized Coefficients x: Variable



**Figure (1): Correlation between days of neutropenia and length of hospital stays among acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls**

r: Spearman correlation coefficient

**Interpretation of r:** r value was scaled as weak (0.1-0.24), intermediate (0.25-0.74) and strong (0.75-0.99).

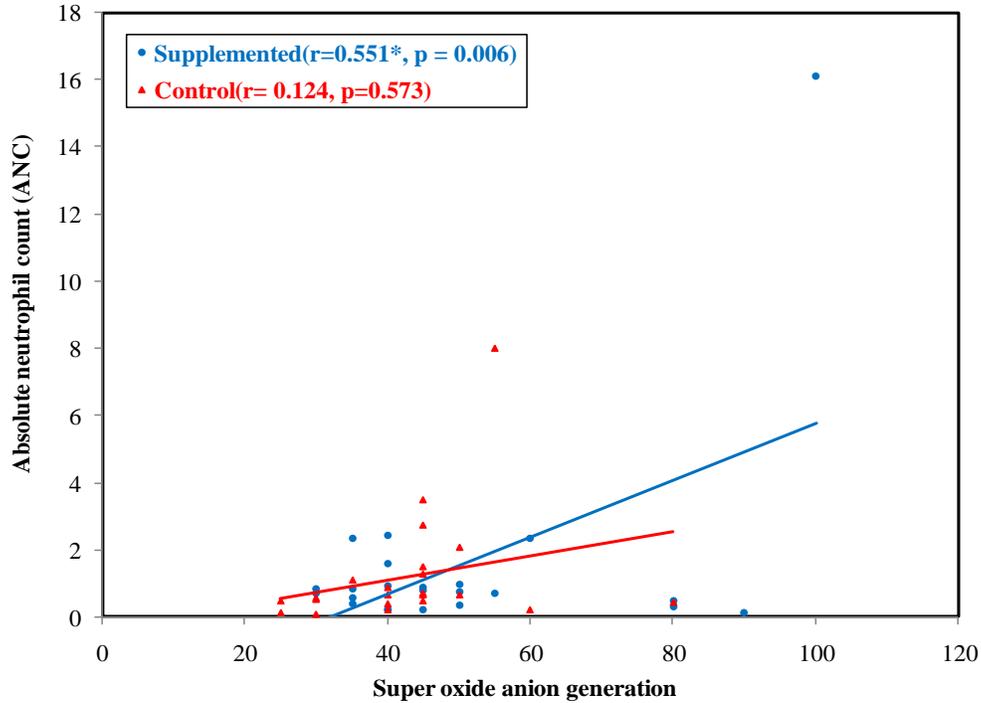


Figure (2): Correlation between superoxide anion generation and ANC among acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls

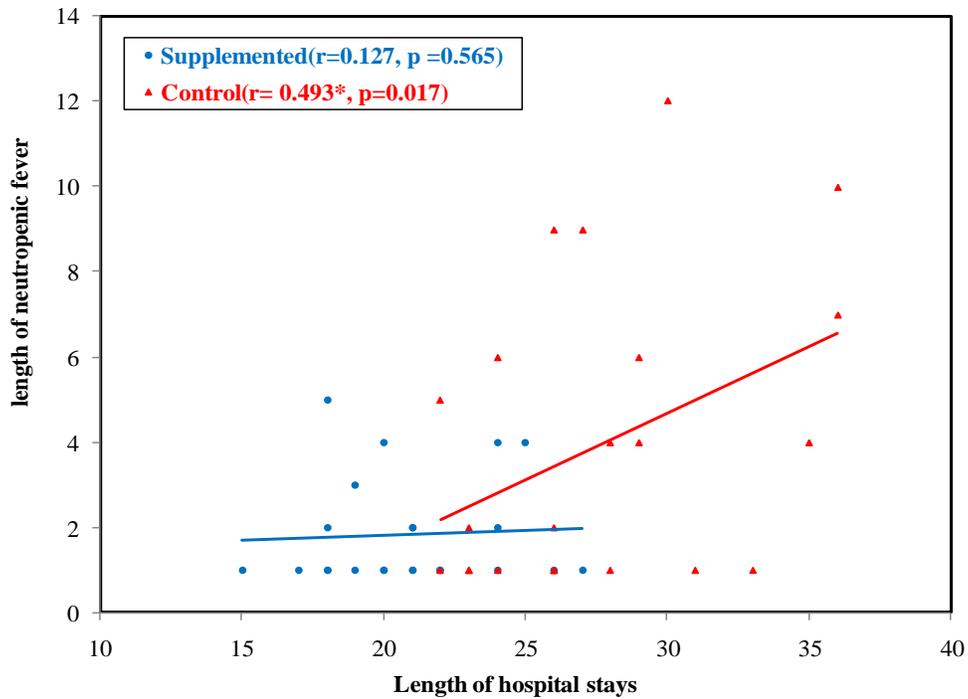


Figure (3): Correlation between length of hospital stays and length of neutropenic fever among acute myeloid leukaemia patients grouped into cases receiving Glutamine and controls

## DISCUSSION

Glutamine is a non-essential amino acid that may be conditionally essential for patients in hyper catabolic states. It helps maintaining the integrity of the intestinal mucosa by reducing intestinal atrophy and can improve weakened immune function in onco-haematological patients.<sup>(19)</sup> Glutamine is depleted in the bone marrow of patients after receiving intensive myelo-suppressive chemotherapy which delay cellular recovery. This effect is translated into days of neutropenia. Berget *et al.*,<sup>(20)</sup> showed that enteral glutamine administration is of beneficial effects. Nevertheless, there is always an uncertainty whether or not the patient actually has received the prescribed dose. Moreover, the complete absorption of glutamine in the upper part of the intestine leaves very little extra glutamine to other tissues as almost nothing passes through the liver into the general circulation. These arguments favor the administration of glutamine by parenteral route.<sup>(21)</sup> In the present study, the proper dosage of glutamine supplementation has not been completely studied. However, it is presently not recommended to give less than 20 grams to critically ill patients, which is in full concordance with the present study.<sup>(22)</sup> Glutamine plays an important role in nitrogen transport and as a precursor for nucleotide synthesis. ASPEN<sup>(9)</sup> has published an exhaustive review of the use of glutamine in parenteral nutrition. It warns that the potential beneficial effect of glutamine supplementation remain unclear since there is only a reduced length of hospital stay in studies combining autologous and allogenic transplants. Accordingly, glutamine supplementation should be further investigated in the areas of timing, dosing, and cost benefit analysis.<sup>(9)</sup> The mean length of hospital stay in the Gln group was significantly lower than the control group. This reduction in length of hospital stay matched reports from Sornsuvit *et al.*<sup>(7)</sup>, Ziegler *et al.*,<sup>(23)</sup> Herrera-Martínez *et al.*,<sup>(24)</sup> and Scheid *et al.*,<sup>(25)</sup>. Days of neutropenia are also affected by the use of G-CSF's in the appropriate dose. The observed effect of glutamine dipeptide on neutrophil recovery was not influenced by the use of G-CSF's in the present study. Ziegler *et al.*,<sup>(23)</sup> concluded that supplemental dietary glutamine does not appear to enhance neutrophil recovery after chemotherapy. Other studies [Scheid *et al.*<sup>(25)</sup> and Sornsuvit *et al.*,<sup>(7)</sup>] showed a non-significant trend toward shorter duration of neutropenia in cycles with glutamine when compared with cycles without glutamine, perhaps due to the low number of patients in those studies. This was not in agreement with the present study since the mean days of neutropenia for patients supplemented with glutamine was significantly lower than that for control group. The

present study showed that early supplementation of glutamine dipeptide in patients with AML, improved the function of neutrophils as indicated by the elevation of the level of SAG. This proved to have a positive effect on the reduction of days of neutropenic fever. The results of a study conducted by Sornsuvit *et al.*,<sup>(7)</sup> supported this view, while that of Scheid *et al.*,<sup>(25)</sup> did not. Incidence of neutropenic fever was reduced by intervention in the present study which did not agree with Scheid *et al.*<sup>(25)</sup>

All patients included in the study were weighted on admission and before discharge to monitor weight changes regardless the use for chemotherapy dose calculations. Weight loss is an important prognostic factor in cancer. The higher the extent of weight loss the shorter the survival time. Weight loss in cancer patients is due to depletion of both adipose tissue and skeletal muscle mass, while the non-muscle protein compartment is relatively preserved.<sup>(26)</sup> Each gram of nitrogen lost during stress can be translated into the breakdown of approximately 30 g of hydrated lean tissue, a loss that consists mainly of alanine and glutamine.<sup>(26,27)</sup> Patients receiving glutamine in the present study showed a significantly lower weight loss, hence less BMI reduction comparing to the control group. It is conceivable that glutamine supplementation increases protein synthesis and decreases protein degradation, improves the ability of the patient to eat, and improves the acid-base balance.<sup>(28)</sup> The present study demonstrated that supplementation with glutamine helped to reduce the loss of body weight and this was in agreement with finding of Sornsuvit *et al.*<sup>(7)</sup>

The length of hospital stay for both group ranged between 21-28 days indicating that the half-life of serum albumin (20 days) can be used as a reference for nutritional status.<sup>(26,29)</sup> Monitoring of laboratory data indicating nutritional status as serum albumin and serum total protein are reliable indicators of visceral protein status. These parameters showed statistically significance differences between Gln and control groups in the present study which contradicted findings in Herrera-Martínez *et al.*,<sup>(24)</sup> and Sornsuvit *et al.*<sup>(7)</sup>. This may be due to the small sample size collected particularly in the later. Adequacy of nutrient intake showed that the mean percent of protein adequacy in relation to calculated nutrient need was more than 100%. In Gln group, the percent of protein adequacy was lower than that of control group, although there was a highly statistically significant difference between both groups regarding the weight difference which may be due to glutamine supplementation.

Multiple regression analysis demonstrated that glutamine dipeptide supplementation was the most

relevant factor affecting weight reduction. Also, weight difference between both groups was found to be significantly affected by gender, length of hospital stay, serum albumin difference, serum total protein difference, complications other than neutropenic fever, length of neutropenic fever, superoxide anion generation levels and protein adequacy. In agreement with the present results, YehSL *et al.*,<sup>(30)</sup> showed for the first time that oral glutamine supplementation for 10 days before sepsis was induced in patients with abdominal surgery, in whom preventive use of a glutamine-supplemented enteral diet may be recommended rather than glutamine in TPN after sepsis. for the early preventive use of glutamine dipeptide. Furthermore, Cerchietti *et al.*,<sup>(27)</sup> study showed that 0.4g/Kg/day glutamine supplementation was separate and independent from the application of nutritional support which was equally applied across the two groups for patients with head and neck cancer receiving chemo-radiotherapy with a high yield of oral mucositis. Intravenous glutamine dipeptide may be an effective preventive measure to decrease the severity of damage. The present study supported the role of Gln supplementation in preventing weight loss and minimizing side effects of chemotherapy. In agreement with the present results, Topkan *et al.*,<sup>(31)</sup> study showed that supplementation with glutamine dipeptide in a dose of 10g/8hr orally in water or fruit juice, started 1 week before treatment and continuing for 2 weeks after completion of radiotherapy, during concurrent chemo-radiotherapy. Gln supplementation had no detectable negative impact on tumor control and survival outcomes in patients with Stage IIIB non-small cell lung carcinoma. Glutamine appeared to have a beneficial effect with respect to prevention of weight loss and unplanned treatment delays, and reduced the severity and incidence of both acute and late radiation-induced esophagitis..

Pytlík *et al.*,<sup>(32)</sup> showed that patients undergoing Hematopoietic stem cell transplantation received 30g of alanyl-glutamine dipeptide intravenously from day 1 to day 14 or to discharge, for oral mucosa protection. It may be more advantageous to start glutamine together with the conditioning regimen rather than after conditioning. The present also provided an evidence for the importance of early glutamine supplementation. The routine use of parenteral glutamine dipeptide supplementation is effective, if given early and in doses up to 0.7g/Kg/day intravenously. The effect of timing, dose, route and duration of glutamine dipeptide supplementation especially for hematologic patients require further investigations.

**Problems Encountered:** This study faced some problems during implementation. Firstly, refusal of

the patient to give blood sample despite signing informed consent. Secondly, patient discharge before recovery of neutrophil count to 500/ $\mu$ L in the peripheral blood. Finally, all patients refused to take peripheral parenteral nutrition bag, in spite of inadequate oral intake.

## CONCLUSIONS & RECOMMENDATIONS

The present study presented a preliminary clinical evidence that early parenteral glutamine dipeptide supplementation for AML patients receiving high doses of chemotherapy may minimize weight loss, reduce days of neutropenia, neutropenic fever and length of hospital stay, induce neutrophil recovery, improve serum total protein and serum albumin levels which all have an impact on treatment outcomes. Finally, the supplementation of glutamine dipeptide in a dose of up to 0.7 gm/kg/day (40 gm glutamine dipeptide) for patients with normal renal and hepatic function does not have any drawbacks..

Nutritional screening on patient's admission and routine weighing of patients is of utmost importance not only for chemotherapy dose calculations but for evaluation of nutritional status. Early supplementation with glutamine dipeptide is recommended for all AML patients in a dose up to 40 gm/day glutamine dipeptide for 5 days from starting of chemotherapy cycle after checking renal and liver functions. Further researches are warranted for better understanding of the relationship between the early effect of glutamine supplementation for all other oncohematological patient and to reproduce the present results.

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