ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 09, pp.7297-7305, September, 2019

DOI: https://doi.org/10.24941/ijcr.36485.09.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

IMPACT OF PARENTERAL GLUTAMINE DIPEPTIDE ON NUTRITIONAL AND OXIDATIVE STATE OF CRITICALLY ILL PATIENTS ON ENTERAL FEEDING

[1,*]EA Hassan, MD, [2]AssemAbdelarazek, MD, [2]Tamer A Helmy, MD and [2]Aglan, A. MD

[1]Critical Care Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[2]Critical Care Department, Faculty of Medicine, Alexandria University, Egypt

ARTICLE INFO

Article History:
Received 14th June, 2019
Received in revised form
18th July, 2019
Accepted 25th August, 2019
Published online 30st September, 2019

Key Words:

Parenteral Glutamine Dipeptide,
Oxidative state, Critical ill Patients.

ABSTRACT

Background and aims: The aim of this work was to study the effect of intravenous glutamine dipeptide on the oxidative state and outcome in enterally nourished critically ill patients as regards the improvement of nitrogen balance, improvement of Body Mass Index (BMI), changes in the level of total antioxidants (especially glutathione), serum albumin, WCBCs and C-reactive protein**,** duration of stay in ICU and prognosis and incidence and frequency of complications. **Patients and Methods:** This prospective study was carried on 60 critically ill patients who were admitted to ICU and they received their nutritional requirements from protein, fat and carbohydrates according to food composition table via enteral route for 7-10 days. Patients were divided into 2 groups (A and B) with 30 patients for each group. The patients of group (A) had received their daily caloric requirements via the enteral route with parenteral GD for 10 days. Whereas the patients in group B had received their daily caloric requirements via the enteral route of nutrition without GD supplementation for 10 days. All critically ill patients were fully examined and assessed by the standard methods of critical care assessment. Also, other measures were taken including complete history, physical examination, anthropometric measures and investigations. **Results:** Parenteral GD proved that it improves nitrogen balance, serum total protein, serum albumin, glycemic control and serum total antioxidant (as glutathione). There was less GIT complications with the patients received glutamine dipeptide. **Conclusion:** GD improved patient's nutritional status as regard serum albumin, total protein, nitrogen balance, and improved the patient's outcome as regard (oxidative state: serum total antioxidants),also it improved the patient's immunological reaction (total leukocytic count, C-reactive protein), and glycemic control. This was in addition to less frequency of GIT complications among those patients who received parenteral GD through the days of study. While the body weight, Body Mass Index, mortality rate, length of hospital stays, and the APACHE II score didn't be affected by parenteral GD.

Citation: EA Hassan, MD, AssemAbdelarazek, MD, Tamer A Helmy, MD and Aglan, A. MD. **2019.** "Impact of parenteral glutamine dipeptide on nutritional and oxidative state of critically ill patients on enteral feeding", *International Journal of Current Research*, 11, (09) , 7297-7305.

INTRODUCTION

Critically ill patients are at risk to develop protein-energy malnutrition as well as micronutrient deficiencies. Adequate nutritional support must be provided to these patients in order to improve survival and decrease the period of hospital stay (Parsons, 1992). The prevalence of malnutrition in hospitalized patients is high and the nutritional status worsens during hospitalization in multiple patient populations (Hill, 1997; Pinchcofsky, 1995; Weinsier, 1995). A nutritional assessment should be performed once a critically ill patient is admitted to the critical care unit. The nutritional status can be assessed by several means:

24 hours chart of food frequency cross check is the technique most commonly used in critical care departments to collect diet information.

****Corresponding author:*** **EA Hassan, MD,**
Critical Care Department, Faculty of Medicine, Cairo University, Cairo, Egypt.

Physical Examination: the findings must be integrated with other nutritional indices to make a proper diagnosis (Weinsier, 1992). A Body weight with its changes either loss or gain simple measures with important prognostic value and it can be measured using Chair-type Ward scales or Bed-type scales (Dorice, 1992). BMI accounts for differences in body composition by defining the level of adiposity according to the relationship between weight and height (Dorice, 1992). BMI = (weight in kg) / (Height in m)^{2,} Where BMI less than 20: health problems for some people, BMI 20 – 27: good weight for most people, BMI more than 27: increases risk of developing health problems. A body mass index (kg/m2) of less than or equal to 15 is associated with increased morbidity, and a weight loss of greater than 10% in 6 months indicates a worse clinical outcome (Almond *et al.,* 1990; DeWys, 1988).

Nitrogen balance is a measure of the extent of protein utilization by comparing the amount of nitrogen intake in the form of food protein with the amount lost in the excreta.

An individual in positive nitrogen balance is retaining more nitrogen than is being excreted. This occurs when the patient is in state of anabolism with synthesis of body tissue protein exceeding breakdown of tissue protein. Negative nitrogen balance often involves destructive catabolic processes such as those accompanying the trauma, bums, or surgery, which cause more protein to be lost than is retained (Vincent, 2008).

- ***Assessment of Visceral Protein:*** Serum Albumin with value of less than 3.0 g/dl correlates with an increased incidence of complications and mortality in general (Apelgren, 1988; Jeejeebhoy, 1998).
- ***Assessment of immunological status****:* Malnutrition is associated with depressed immune competence manifested by decreased lymphocyte count and delayed cutaneous hypersensitivity (Dorice, 1992).
- ***Assessment of physiological function:*** Handgrip strength using a dynamometer is a measure of skeletal muscle function that can be used to assess the effects of starvation or predict postoperative complications by measuring the extent of protein catabolism (Paige, 1988).
- ***Assessment of metabolic stress:*** measurement of resting metabolic expenditure (RME) by indirect calorimetry is the best way of quantifying the intensity of metabolic stress. Another method for measurement of metabolic stress is to measure the catabolic Index (CI).
- ***Assessment of nutritional status and its requirements*** including Subjective global assessment (SGA). Energy requirements can be measured by indirect calorimetry (McClave, 1992) after determining the BMR through Harris-Benedict equations (Aspen, 2002). Also, it can be measured through rough estimation, but it is less accurate and sometimes pragmatic determination of energy requirements is an estimate that men should receive 25 to 30 nonprotein kcal/kg/d and women should receive 20 to 25 kcal/kg/d. If the patient is physically active, the energy requirements are estimated to be approximately 1.15 to 1.20 times the calculated BMR. Adjustments for BMR based on stress factors and hypermetabolism should be performed. For critically ill patients, energy goals generally are met by administering 1.0 to 1.15 times the BMR (McClave, 1992). Protein requirements usually are met by giving healthy individuals 0.8 g/kg/d, hospitalized patients 1.2 to 1.5 g/kg/d, and critically ill patients 1.5 to 2.0 g/kg/d (Jolliet, 1998; Skipper, 1998). Micronutrients play critical roles in many various enzyme-catalyzed reactions (Shenkin, 1997). Glutamine-containing dipeptides are an integral part of routine clinical practice (Furst, 2000; Furst, 2004). Where it modifies the endogenous inflammatory responses. It stimulates growth hormone elaboration (Wilmore, 2000), and this hormone can up-regulate the immune system. Critically ill patients have reduced plasma and intracellular levels of antioxidants and free electron scavengers or cofactors, and decreased activity of the enzymatic system that is involved in ROS detoxification (Thérond *et al.,* 2000). Parenteral GD is the most reliable method of achieving a prolonged constant elevation of the body's free glutamine pool. GD should be provided immediately following catabolic insult in order to initially support the attenuated tissues with glutamine. In general glutamine dipeptides-containing solutions should be administered via a central vein and might be well tolerated when administered into a peripheral vein if a strict protocol is used (slow rate of infusion, daily change of the infusion site, removal of the cannula after the infusion).

Aim of the work: Was to study the effect of intravenous GD on the oxidative state and outcome in enterally nourished critically ill patients as regards improvement of nitrogen balance, improvement of BMI, changes in the level of total antioxidants (especially glutathione), serum albumin, WCBCs and C-reactive protein, duration of stay in ICU and prognosis and incidence and frequency of complications.

Patients: This prospective study was carried on 60 critically ill patients of both sex who were admitted to the critical care department. Patients in this study received their nutritional requirements from protein, fat and carbohydrates according to food composition table via enteral route for 7-10 days .The caloric requirement were calculated according to Harris Benedict equation (Harris, 1998; Dark, 1993) then these estimates were modified according to the degree of the patient's metabolic stress.

Patient's Exclusion Criteria included those who have contraindications for enteral feeding and Patients with advanced liver disease, and end stage renal disease.

MATERIALS AND METHODS

Patients were divided into 2 groups (A and B) with 30 patients for each group. Group (A) had received their daily caloric requirements via the enteral route with parenteral GD for 10 days. Whereas, group B had received their daily caloric requirements via the enteral route of nutrition without GD supplementation for 10 days. **Randomization:** patients were randomized to either to (Group A, n=30) or (Group B, n=30) using double blinded study. All patients were assessed by the standard methods of critical care assessment. In addition, the following measurements were done: *Complete history* from patients and their relatives. *Physical examination* on admission and daily basis including the use of APACHE II Score (on admission; day3,7,10). Other measurements including vital signs and routine Cardiac and chest examination. *Investigations* on admission, day 3, day 7 and day 10 which include Complete blood count, Serum Urea and creatinine. (mg/dl)**,** SGOT, SGPT. (IU/L), serum ammonia, Total protein, serum albumin, C-reactive protein, Serum antioxidants (glutathione). Random blood sugar(mg/dl)was done daily from day 1 to day 10 of the study.Urinary urea, urinary Na, serum K, Arterial blood gases, and Chest X-ray whenever it was indicated.

Anthropometric measures including Height, Weight changes and BMI were recorded on admission, day 3, day 7 and day 10. Patient's height was measured only on admission. *Electrolyte, Vitamins and trace elements* (Shenkin, 1997) Were given according to patient's daily requirements and his critical status. *Other investigations* according to the patient's need. *Statistical methods:* Using SPSS methods. End points of the study is after 10 days of starting enteral feeding or if there was a contraindication for enteral feeding.

RESULTS

Regarding the biochemical measurements, the following parameters showed significant changes as shown in Table (1), other parameters didn't show significant changes.

Table 1. Biochemical parameters in day 1, 3, 7 and 10

	GROUP	Day 1		Day3		Day7		Day 10		End of study
		Mean ± SD	t (p)	Mean ± SD	t (p)	Mean ± SD	t (p)	Mean ± SD	t (p)	t 1(p)
N.ba	A	4.97±1.35	0.096	10.69±2.20	0.069	18.83±3.33	< 0.001*	14.20±2.59	0.001 *	< 0.001*
	B	4.45±0.99		9.78±1.58		9.80±1.58		12.02±1.89		< 0.001*
S. urea	A	40±25.74	0.002 *	37.37±20.58	0.083	40.50 ±21.47	0.031*	45.56±28.60	0.0152*	0.221
	B	23.30±9.48		28.87±16.52		28.50±20.44		34.07±28.32		0.104
U.urea	A	202.53±115.79	0.153	191.68±110.97	0.063	201.35 ± 128.59	0.041 *	147.18±113.32	0.019 *	0.005 *
	B	251.26±143.23		246.65±117.51		270.71±127.91		231.16±134.05		0.448
S. Cr	A	1.19±0.47	0.010 *	1.14±0.36	0.226	1.60±2.18	0.338	1.24±0.41	0.946	0.557
	B	0.9±0.33		1.02±0.42		1.20±0.48		1.25±0.43		<0.001 *
SGPT	A	76.47±70.11	0.043 *	53.67±31.92	0.653	45.30±24.83	0.675	41.32±29.71	0.755	0.009 *
	B	48.00±20.65		50.70±16.59		47.47±13.26		39.30±12.62		0.084
SGOT	A	77±58.84	0.102	53.63±17.09	0.524	45.03±14.22	0.109	38.28±22.70	0.513	0.002 *
	B	56.53±32.93		57.03±23.50		51.30±15.61		42.11±19.16		0.008 *
S. Am	A	71.90±19.97	0.001 *	82.46±93.56	0.073	65.56±48.71	0.96	63.50±27.29	0.07	0.146
	B	50.23±24.49		50.27±24.06		66.13±38.86		51.50±19.03		0.961
T. protein	A	5.3±0.6	0.015 *	5.41±0.51	0.447	5.60±0.53	0.684	5.69±0.58	0.612	0.001 *
	B	5.66±0.53		5.50±0.43		5.55±0.41		5.62±0.39		0.847
S. alb	A	2.69±0.49	0.235	2.75±0.41	0.016 *	2.83±0.37	0.569	3.04±0.27	0.001 *	0.001 *
	B	2.54±0.46		2.51±0.34		2.52±0.68		2.51±0.43		1
WBCs	A	12.22±7.78	0.003 *	11.45±5.85	0.004 *	10.78±4.85	0.027 *	9.70±3.74	0.18	0.129
	B	7.19±3.77		7.61±3.83		8.23±3.78		8.33±3.55		0.204
N.count	A	7.700±4.900	<0.001 *	8.020±4.090	< 0.001 *	8.080 ± 3.640	0.006 *	8.05±3.10	0.028 *	0.437
	B	3.600±1.890		4.560±2.300		5.760±2.640		6.25±2.66		<0.001 *
L.count	A	2.44±1.56	0.964	2.42±1.23	0.665	2.37±1.07	0.2440.	1.990±1.070	0.057	0.106
	B	2.43±1.28		2.29±1.15		2.06±0.95		1.500±0.840		< 0.001 *
CRP	A	98±85.17	0.040 *	73.51±61.47	0.948	52.44±43.90	0.013 *	36.22±32.48	0.001 *	< 0.001 *
	B	61.27±41.86		74.4±42.58		80.50±40.38		73.3±39.95		0.251
RBG	A	198.37±97.41	0.051	133.4±29.80	0.988	109.4±24.23	0.001 *	107.88±17.53	0.004 *	< 0.001 *
	B	150.40±89.14		133.53±38.99		137.17±36.59		133.78±39.94		0.305
S. Na	A	139.50±9.08	0.039 *	133.45±4.75	0.006 *	134.17± 4.03	0.028 *	132. ±19.64	0.051	0.06
	B	135.23±6.28		138.17±7.56		139.67±9.97		140.22±8.07		0.017 *
T.oxid	A	338.30±112.42	0.146	335.12±112.6	0.397	418.87±117.19	0.119	447.17±104.05	0.013 *	0.002 *
	B	299.97±87.48		312.14±95.40		350.73±204.43		352.05±154.58		0.133

N.balance: nitrogen balance, S. urea: serum urea, U. urea: urinary urea, S.cr: serum creatinine, S.Am: serum ammonia, T. protein: total protein, S.alb: serum albumin, WBCs: white blood count, N.count: neutrophils count, L.count : lymphocytes count , CRP: c reactive protein , RBG : random blood glucose , S.Na : serum sodium , T.oxid: total antioxidants t: Student t-test between the two groups t_1: Paired t-test between day 1 and day 10 p: Statistically significant at $p \leq 0.05$

Table 2. Correlation between Serum urea / Urinary urea and BMI /APACHE II at day 3, day 10

		Day3			Day 10		
		Group A	Group B	All samples	Group A	Group B	All samples
Serum urea / Urinary urea	r	0.062	0.036	-0.069	0.460	-.039	0.102
	p	0.747	0.849	0.600	0.021	0.848	0.473
BMI / APACHE II	r	0.213	0.240	0.176	0.009	0.138	0.055
	p	0.256	0.201	0.179	0.967	0.493	0.699

r: Pearson coefficient
p: Statistically significant at $p \leq 0.05$

Table 3. Agreement of nitrogen balance, antioxidant, lymph, CRP and BMI after 10 days in group A with APACHE II at specific normal ranges

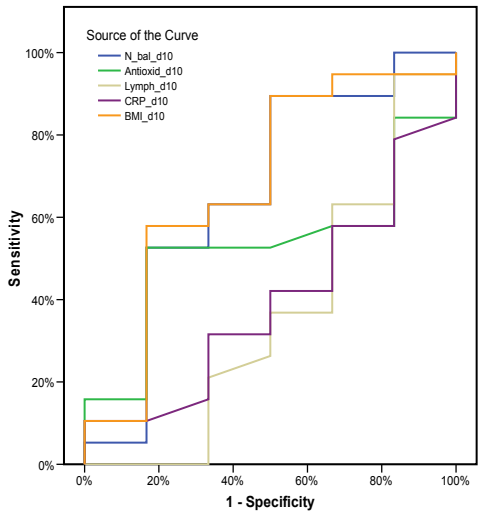
Nitrogen balance (>0)	Sensitivity	0.00	PPV	-	Accuracy	76.00
	Specificity	100.00	NPV	76.00	LR	-
Antioxidant (355.2±102.7)	Sensitivity	33.33	PPV	16.67	Accuracy	44.00
	Specificity	47.37	NPV	69.23	LR	0.63
Lymp ($1.5 - 3 \times 10^{3}$)	Sensitivity	66.67	PPV	66.67	Accuracy	78.57
	Specificity	84.21	NPV	84.21	LR	4.22
CRP (<10)	Sensitivity	83.33	PPV	27.78	Accuracy	44.00
	Specificity	31.58	NPV	85.71	LR	1.22
BMI (20-27)	Sensitivity	16.67	PPV	16.67	Accuracy	60.00
	Specificity	73.68	NPV	73.68	LR	0.63

Lymph: Lymphocytes, PPV: Positive predictive value, CRP: C- reactive protein NPV: Negative predictive value, BMI: Body Mass Index, LR: Likelihood ratio

Table 4. Patient's outcome in two groups (A, B):

Outcome	Group A		Group B		Test of sig.
	No. (%)		No. (%)		
Died	11	36.7	12	40.0	χ^2=0.071
Survived	19	63.3	18	60.0	(p) = (0.791)

χ^2: Chi square test



Diagnostic performance
Nitrogen balance= 0.667
Total Antioxidants = 0.531
Lymphocytes count = 0.364
C-reactive protein = 0.395
BMI = 0.684

Figure 1. ROC curve for some markers as regards APACHE II in group A

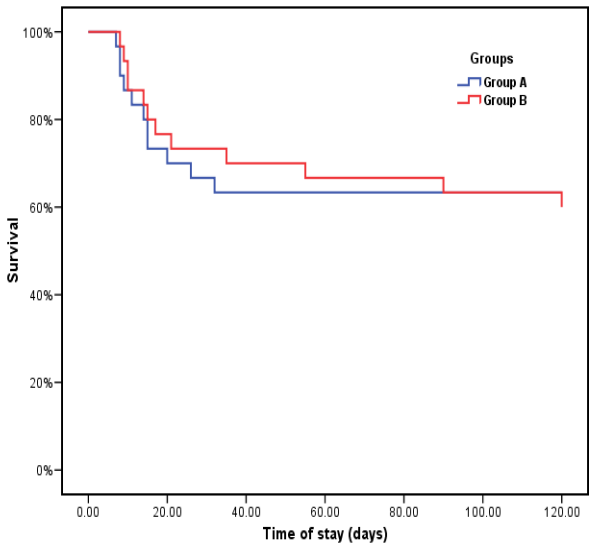


Figure 2. Kaplan and Meier Survival curve for Group A and B

In day 1: Significant difference was found between two groups regarding the Serum urea (mg/dl) (p= 0.002), Serum creatinine (mg/dl). (p= 0.010), Serum SGPT(U/L). (p= 0.043), Serum Ammonia (microgram/ mol. (p= 0.001), Serum total protein (gm/ dl). (p= 0.015), White count blood cells (cells/m^3). (p= 0.003), Neutrophils count (cells/$m^{3)}$. (p< 0.001), C -reactive protein (mg/L). (p= 0.040) and Serum Na (mEq/L). (p= 0.039), as shown in Table (1).

In day 3, significant difference was found between two groups regarding the Serum Na (mEq/L). (p= 0.006), Serum albumin (gm/ dl). (p= 0.016), White count blood cells (cells/m^3). (p= 0.004), Neutrophils count (cells/m^3). (p< 0.001) and Serum Na (mEq/L). (p= 0.006), as shown in Table (1). In day 7, significant difference was found between two groups regarding theNitrogen balance (grams/day). (p <0.001), Serum urea (mg/dl). (p= 0.031), Urinary urea (mg/L),(p= 0.041), Serum

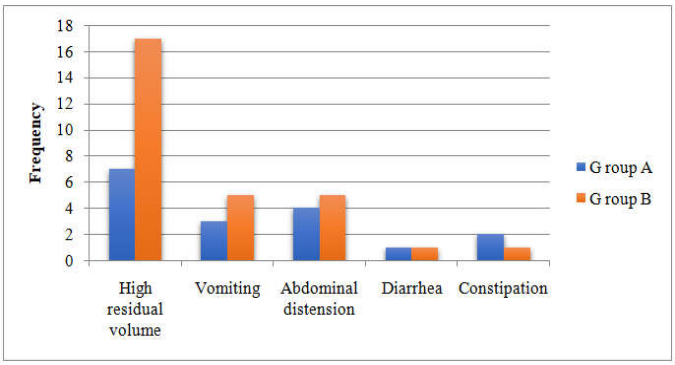


Figure 3. Complications in Group A and B

Na (mEq/L. (p= 0.028), WBCs (cells/m^3). (p= 0.027), Neutrophils count (cells/m^3). (p= 0.006), C -reactive protein (mg/L). (p= 0.013) and Random blood glucose (mg/dl). (p= 0.001), as shown in Table (1). In day 10, significant difference was found between two groups regarding the Nitrogen balance (grams/day).(p= 0.001), Serum urea (mg/dl).(p= 0.0152), Urinary urea (mg/L). (p= 0.019),). Serum albumin (gm/ dl) (p= 0.001), Neutrophils (cells/m^3 (p= 0.028), C -reactive protein (mg/L). (p= 0.001), Random blood glucose (mg/dl). (p= 0.004), and Serum total antioxidants (micromole/L). (p= 0.013). Significant change was found at the end of the study in comparison to the start of the study regarding the nitrogen balance in group A (p <0.001) and in group B (p < 0.001), Urinary urea (mg/L) in group A (p=0.005), Serum creatinine (mg/dl). (p< 0.001) in group B, Serum SGOT(U/L). In group A (p=0.002) and in group B (p= 0.008), Serum SGPT (U/L) in group A (p=0.009).Neutrophils (cells/m^3) in group B (p < 0.001), lymphocytes count (cells/m^3)in group B (p < 0.001).C -reactive protein (mg/L) in group A (p <0.001), Random blood glucose (mg/dl)in group A(p <0.001), Serum total protein (gm/ dl)in group A, (p=0.001), Serum albumin (gm/ dl) in group A(p=0.001), Serum Na (mEq/L) in group B (p= 0.017) and Serum total antioxidants (micromole/L) in group A (p=0.002), as shown in Table (1)

Correlation between serum and urinary urea: In day 3, there was a weak correlation between urinary and serum urea in group A and B without significant difference. There was an inversed relation between serum and urinary urea in the All sample as (r= -0.069 without significant difference as p= 0.600).In day 10, there was a weak correlation between urinary and serum urea in group A (r =0.460 with a significant difference, p =0.021) whereas in group B there was inversed relationship between the two parameters as (r=-0.039 without significant difference, p =0.848).There was a weak correlation in the All sample between serum and urinary urea (r= 0.102 without significant difference as p= 0.473) as shown in Table (2)

Body Mass Index kg/m2 and APACHE II score: Regarding BMI in day 7, significant difference was found between two groups (p= 0.028) and in day 10, there was significant difference between the start and the end of the study in group A (p <0.001. Regarding APACHE II score, significant decrease was found at the end of the study in comparison to the start of the study in group A (p=0.001) and in group B (p=0.001). By correlating the BMI to APACHE II, there was a weak correlation between BMI and APACHE II in group A and B without significant difference in day 3 and day 10.Also,there was a weak correlation between the BMI and APACHE II in the all sample as shown in the Table (2).

Diagnostic performance: The ROC curve which in Figure (1) gives an idea about the diagnostic performance of (nitrogen balance, total antioxidants, lymphocytes number, C-reactive protein and Body Mass Index) regarding the patient's APACHEII score.

The Agreement of nitrogen balance, antioxidant, lymph, CRP and BMI after 10 days in group A with APACHE II score at specific normal ranges, shown as following: (Table 3). Regarding the *Nitrogen balance*, when the normal value was taken as (>0), the value of diagnostic performance was 0.667 with a sensitivity of 0.00% and accuracy of 76 %, whereas the specificity of nitrogen balance (>0), was 100% with negative predictive value of 76.00. For the *Total antioxidants*, when the normal value was taken as (355.2±102.7), the sensitivity was 33.33 %, with PPV of 16.67 and accuracy of 44.00 whereas the specificity was 47.37% with NPV of 69.23 and LR 0.63. When the normal range of *Lymphocytes* was taken as (1.5 and 2x10^3), the sensitivity was 55.66.67% with PPV of 66.67 and accuracy of 78.57, whereas the specificity was 84.21% with NPV of 84.21 and LR of 4.22. When the normal value of *C-reactive protein* was taken as (<10), the sensitivity was 83.33% with PPV of 27.78 and accuracy of 44.00, whereas the specificity was 31.58 % with NPV of 85.71 and LR of 1.22.When the normal range of *Body Mass Index* was taken as (20 and 27), the sensitivity was 16.67 % with PPV of 16.67 and accuracy of 60.00, whereas the specificity was 73.68 % with NPV of 73.68 and LR of 0.63, as shown in Table (3).

Patient's outcome in two groups (A, B): Patients were classified to survived group and non-survived group and the survived group was sub classified into three categories: to patients who discharged to home, patients who referred to outside the ICU to another unit in the hospital and patients who discharged on their responsibilities. No significant difference found between both groups (A and B) as regard patient's outcome as (p=o.791), as shown in table (4).

Complications during the length of study in both groups: In group A, the number of patients developed complications was (no=13 as43.3%) and the number of patients didn't developed complications was (no=17 as 56.7%), whereas in group B, the number of patients developed complications was (no=20 as 66.7%) and the number of patients didn't developed complications was (no=10 as 33.3%), as shown in Figure (3).

DISCUSSION

Nutrition is one of the keystones of treatment that is, unfortunately, over passed during the management of critically ill patients. The fundamental goal of nutritional support was just to provide patients with their daily nutritional requirements but increasing research in the field of nutrition presently is directed toward nutrition providing more than simply the needed nutrients, but using nutrition to provide pharmacotherapy that may improve the health of the patient and the gastrointestinal tract (Patrick, 2000). Enteral tube feeding may also attenuate the acute phase and cytokine response to injury (Charash, 1994). Overall, septic morbidity and even mortality may be decreased compared with total parenteral nutrition (Moore, 1991; Kudsk, 1992; Kilmberg, 1990; Mertes, 2002). This has led to an aggressive application of enteral tube feeding in the intensive care setting. Recent knowledge about efficient utilization of intravenously supplied dipeptides has made it possible to substitute available amino

acid solutions with stable, highly soluble, glutamine-containing dipeptides. This novel approach has opened a new dimension: for glutamine-containing dipeptides are an integral part of routine clinical practice (Wilmore, 1998; Thérond, 2000). Glutamine deficiency is associated with gut atrophy during stress. Maintaining the integrity of the gastrointestinal tract is a major goal in the treatment of critically ill patients because translocation of bacteria and toxins via the gastrointestinal tract is thought to be a cause of multiple organ failure. Large doses of glutamine have been shown to prevent gut atrophy, maintain bowel integrity, and prevent bacterial translocation after various insults, which include methotrexate toxicity and radiation injury (Szijártó, 2007). In the present work, there was no effect for GD on the level of serum urea as comparing the mean at the end of the study with that of the start of the study, in the glutamine group or the group (B) as (p= 0.221,0.104 respectively). As regard the urinary urea, the effect of glutamine dipeptide parentally increased the retention of urinary urea in the group (A) and there was a significant difference between the start and the end of the study as regard the mean value of urinary urea (p=0.005) in comparison by group (B) whereas there was no significant difference between the start and the end of the study as (p=0.448). In the present work, there was an increase in the nitrogen balance among the patients of group A and there was significant difference between the start and the end of the study as regard the value of nitrogen balance as (p <0.001).There was an increase also in the nitrogen balance among the patients of group B, but the difference between the mean of the start and the mean of the end in group A was higher than that of the group B. This can be explained by the fact that glutamine dipeptide supplementation improves the patient's outcome as regard nitrogen balance.

Also, a better significant mean nitrogen balance was observed on the 7^{th} day and 10^{th} (p=<0.001, 0.001 respectively) and there was no significant difference between the two groups in the 3^{rd} day. This agreed with Schulzki et al. (2002) conducted a study to assess the effect of GD postoperative patients and he that supplemental alanyl-glutamine improved the overall mean nitrogen balance -3.5±-1.6 v -5.5±-1.4gas (p= <0.05) compared with is onitrogenous isoenergetic standard regimen. In the present work, there was a significant decrease in the level of (SGOT and SGPT) at the end of the study in comparison to the start of the study in group (A), whereas in group (B) there was no significant difference between the start of the study and the end of study. This can be explained as the glutamine dipeptide didn't increase the level of serum SGOT, SGPT when given to the patients of group A. As regard the serum ammonia, there was no significant difference between the start and the end of the study in group A or B. This can be explained as the glutamine dipeptide didn't increase the level of serum ammonia when given to the patients of group A. In a study (Szijártó, 2007) to determine the effect of alanyl-glutamine dipeptide on hepatic microcirculation, the levels of SGOT and SGPT were significantly lower in the group of glutamine rather than in the group without glutamine dipeptide, so glutamine pretreatment is beneficial in supporting hepatic microcirculation and can prevent hepatocellular necrosis in liver reperfusion injury. In the present study, in group A, the serum protein level, significantly increased at the end of the study compared to the start (p=0.001) while, there was no statistical difference in group B (p=0.847).This can prove that glutamine dipeptide improved the patient's outcome as regard the level of total protein among the patients of group A, who received it during the period of the study. These results agree with Barua *et al.* (1992) who concluded that the supplementation of alanyl glutamine results in significant increase in the rate of the protein synthesis in post-operative patients. In the present study, the serum albumin, in group A there was a significant increase at the end of the study in comparison to the start of the study. Whereas in group B, there was no significant difference between the end and the start of the study. This can prove that glutamine dipeptide improved the patient's outcome as regard the level of serum albumin among the patients of group A, who received it during the period of the study. In contrast, Bargo and Gianotti, (1996) had used the albumin in the assessment of nutritional status of 40 patients receiving early enteral nutrition after major abdominal operations. The serum albumin did not change notably. This is due to long half-life of serum albumin (16-21 days), it is commonly used to assess the nutritional status in critically ill patients and the drop in its value could be attributed to the physiologic stress itself as well as the malnutrition. Thus, a low value of albumin doesn't define malnutrition, but often points towards an increased risk of malnutrition due to stress.

In the present study there was a significant difference in comparison between two groups A and B as regard the count of neutrophils in the 1^{st}, 3^{rd} ,7^{th} and 10^{th} day (p = (<0.001), (<0.001), (0.006) and (0.028) respectively). These results can be explained by the higher incidence rate of infection in the glutamine group compared to the control group,this may be due to several causes as: First the patients in group A who diagnosed on admission to ICU as having sepsis were 8 patients representing 21% of the patients of group A, whereas in group B, the patients with Sepsis presented by 4 patients accounting 13% of the patient of group B. Second it can be attributed to the fact that the duration between the start and the end of the study was longer in group A, allowing a more time for the change in these values. Third, parenteral glutamine dipeptide didn't improve patient's outcome as regard incidence of infection in group A. Whereas, in a study (Grigorakos *et al.,* 2009) to assess the effect of glutamine dipeptide on the outcome of the COPD patients on mechanical ventilation conducted on two groups of the patients (study and control group), there was no significant difference in the study group from the start to the end of the study.

In contrast to the control group who showed a significant increase in both the total white blood count and the neutrophils count at the end of the study. In the present study, the number of lymphocytes decreased significantly (p= <0.001) from 2.43 cells/m^3 to 1.5 cells/m^3 in group B in comparison to group A whereas the lymphocyte count decreased non significantly (p=0.106) from 2.44 cells/$m^3$to 1.99 cells/m^3. In contrast to the present work, in Frobes study (Frobes, 2000) the mean lymphocytic count in group A increased significantly at the end of the study while in group B no significant difference in the mean value of lymphocytes between the start and the end of the study. In the present study the effect of glutamine dipeptide on C-reactive protein. There was a significant difference between the measurement of C-reactive protein at the start of the study and at the end of the study in group (A) as (p <0.001). whereas in group B, There was no significant difference between the start and the end of the study as (p= 0.251).This meant that administration of glutamine dipeptide parenterally affected the level of C-reactive protein by decreasing it at the end of the study among patients of glutamine group and improved patient's outcome as regard to inflammatory response represented by C-reactive protein. In

contrast, Pierre *et al.* (2006) studied the effect of L-alanyl-L-glutamine dipeptide- supplemented total parenteral nutrition on infectious complications and glucose intolerance in critically ill patients on two groups and he found that the value of C-reactive protein did not change significantly between the start and the end of the study in the Ala- Glutamine group and the control group. In the present study reported the effect of glutamine dipeptide on glycemic control among the patients in both groups A and B. There was a significant decline in the mean of random blood glucose (RBG) at the end of the study in comparison to the start of the study in the glutamine group. Whereas in group B, there was no significant difference between the start and the end of the study as regard RBG. This can be explained by the effect of parenteral glutamine dipeptide on patient's outcome as regard glycemic control in patients of group A in comparison with group B who didn't receive glutamine dipeptide with their nutritional requirements. This was in agreement with Pierre D et al. (2006) who studied the effect of parenteral glutamine dipeptide on glucose intolerance in critically ill patients, hyperglycemia was less frequent (20 vs. 30 patients; $p<0.05$) and there were fewer insulin-requiring patients (14 vs. 22; $p <0.05$) in the Ala-Glutamine group.

In the present study the patients included in the two groups of the study were classified into 3 categories according to their body weight changes as patients with weight gain, patients with weight loss≤ 10% and patients with weight loss >10% .There was no significant difference between the two groups of the study(A and B) in the three categories of the patients between the start and the end of the study. This can explain that parenteral glutamine dipeptide didn't affect the patient's outcome as regard body weight changes in the group of glutamine dipeptide during the period of the study. This agreed with a study [(33)] conducted on A COPD patient to assess the effect of the glutamine on the patients' outcome as regard the body weight changes. There was no significant difference in the body weight between the start and the end of the study. Whereas in the control group, there was a significant decline in the body weight at the end of the study compared to the weight at the start ($p= 0.006$).

In the present work, the mean of BMI decreased significantly ($p <0.001$) at the end of the study in comparison to the start in group A. as whereas in group B, there was no significant difference between the start and the end of the study. This can be explained by two reasons, *first:* Although the body weight is one of the most useful parameters of the assessment of nutritional status, yet its use in critically ill patients with short period of illness is controversial. Rapid weight changes in critically ill patients are almost exclusively due to alteration in body fluids i.e. over or dehydration (Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients, 1993).

Second: there was no significant difference between the two groups as regard (BMI), so GD didn't affect the patient's body weight. The present study showed that parenteral GD had significant increase in the mean of serum total antioxidants at the end of the study in comparison to the start of the study in group A. While in group B, there was no significant difference between the start and the end of the study. This can explain the effect of parenteral GD on the patient's outcome as regard improving the oxidative state and serum total antioxidants. This was agreed with a study conducted by Fernandez-Estivariz et al the Depletion of plasma antioxidants in surgical intensive care unit patients requiring parenteral feeding: effects of parenteral nutrition with or without alanyl-glutamine dipeptide supplementation (Forest, 1990), the results showed, low plasma levels of key antioxidants were common in this group of patients in the SICU despite administration of PN containing conventional micronutrients. Compared with standard PN, Glutamine-supplemented PN improved plasma GSH levels in patients in the SICU after cardiac, vascular, or colonic operations. In contrast to the present work, Menghua Luo et al. (Garrel, 2003) conducted a study on forty-four medical and surgical ICU patients received identical Gln-free tube feedings 24 h/day for nine days and were randomized to either isonitrogenous control (n=15), Enteral Alanyl-Glutamine (n=15) or Parenteral Alanyl-Glutamine (n=14) groups (AG). There were no differences in concentrations of plasma GSH, vitamin C or MDA (an index of lipid peroxidation) over time.

In the present study, there was no significant difference between two groups (A and B) as regards length of hospital stay as ($p= 0.200$).This can explain that parenteral GD didn't improve the patient's outcome as to decrease the length of hospital stay in the group of GD during the period of the study. In contrast to the present work, Furst et al. (Galbán, 2000) found that the supplementation of parenteral L-alanyl L-glutamine following elective operation leads to a significant reduction in the hospital stay. As regard mortality rate, in the present work, there was no significant difference between two groups (A and B). This can be explained by less mortality rate in patients with glutamine group (A) and GD intravenously didn't affect the patient's outcome as regard mortality rate. This can be explained as the duration of study was too short to evaluate such mortality well. In contrast, Garrel and Patendaude (Galbán, 2000) conducted a study on 45 adult patients with severe burn to assess the effect of GD supplementation in decreasing the ICU mortality. Mortality rate was significantly lower in glutamine than in control group. In the present study there was a significant decline in the value of the APACHE II score between the start and the end of the study in group A and B. This meant that parenteral GD didn't affect patient's severity of illness represented by APACHE II score. Juan Carlos et al. (2003) conducted a study on one hundred eighty-one septic patients presenting for enteral nutrition in an ICU and presented the mortality rate as a function of APACHE II score. There was a significant reduction in the mortality rate for the immune-nutrition group for patients with APACHE II scores of 10-15. In a similar manner, if all patients with APACHE II score 10-25 are grouped together, there remains a significant reduction in mortality rate for the treatment group. In the present work, there was a weak correlation between BMI and APACHE II in group A ($r =0.213$ without significant difference, $p =0.256$) or group B ($r =0.240$ without significant difference, $p =0.201$). There was a weak correlation between the BMI and APACHE II in the All sample as ($r= 0.176$ without significant difference as $p= 0.179$). In correlating the BMI and APACHE II at the 10^{th} day of the study between two groups, there was a weak correlation between BMI and APACHE II in group A ($r =0.009$ without significant difference, $p =0.967$) or group B ($r =0.138$ without significant difference, $p =0.493$).There was a weak correlation between the BMI and APACHE II in the All sample as ($r= 0.055$ without significant difference as $p= 0.699$). In the present study as regard the incidence of GIT complications (as diarrhea, abdominal pain,), administration of GD intravenously

was associated with less incidence of gastrointestinal tract complications like high residual volume, vomiting, abdominal distension, diarrhea and constipation. Glutamine group developed less incidence of complications 43.3% rather than group B (66.7%). The highest rate of incidence of complications was for high gastric residual volume either in group A or B, and the least common complication in the two groups was the diarrhea. This agreed with Heyland et al. (1995) and Sherman et al. (1990) who found that high gastric residual was the most frequent gastrointestinal complication in the study. However, Montejo et al. (2001) found that in 400 consecutive patients with prolonged critical illness on EN were studied prospectively and GI complications correlated with length of stay and mortality. The incidence of overall complications was 62.8% with high gastric residuals seen in 39%, constipation in 15.7%, diarrhea in 14.7%, abdominal distention in 13.2%, vomiting in 12.2%, and regurgitation in 5.5%.

Limitations of this study: Limitations of the current study were mostly due to cost and resources availability, specially limited number of studied patients, and combined other co morbidities.

Conclusion

Glutamine dipeptide improved patient's nutritional status as regard serum albumin, total protein, nitrogen balance, and improved the patient's outcome as regard (oxidative state: serum total antioxidants),also it improved the patient's immunological reaction (total leukocytic count, C-reactive protein), and glycemic control. This was in addition to less frequency of GIT complications among those patients who received parenteral glutamine dipeptide through the days of study. While the body weight, Body Mass Index, mortality rate, length of hospital stays, and the APACHE II score didn't be affected by parenteral glutamine dipeptide.

Financial Support Issue: There was no organization body claimed to offer special funds or sponsorship for our study.

Conflicts of Interest: Nobody from the sharing authors have any conflict of interest.

REFERENCES

Almond DJ, King RFGJ, Burkinshaw L. 1990. Potassium depletion in surgical patients. Intracellular cation deficiency is independent of loss of body protein. *Clin Nutr.,* 6:45-50.

Apelgren KN, Rombeau JL, Twomey PL. 1988. Comparison of nutritional indices and outcome in critically ill patients. *Crit Care Med.,* 10:305-7.

ASPEN Board of Directors and the Clinical Guidelines Task Force.Guidelines for the use of parenteral and enteral nutrition in adult andpediatric patients. JPEN J Parenter Enteral Nutr 2002;26(1 Suppl):1SA-138SA.

Bargo ME, Gianothi LN. Immune and nutritional effects of early enteral nutrition after major abdominal operation.Eur J Surg 1996;162:105-12.

Barua E.Maintenance of muscle protein synthesis in postoperative patients.Proc Nutr Soc 1992;51:104A.

Charash WE, Kearney PA, Annis KA. Early enteral feeding is associated with an attenuation of the acute phase/cytokine response following multiple traumas. J Trauma 1994;37:1015.

Dark DS, Pingleton SK. Nutrition and Nutritional support in critically ill patients.J Intensive Care Med 1993;8:16-33.

Déchelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coëffier M, Hecketsweiler B, et al. L-alanyl-L-glutamine dipeptide- supplemented total parenteral nutrition on infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multi-center study.Crit Care Med 2006;34:598-604.

DeWys WD, Bogg C, Lavin PT. 1988. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am J Med.,* 69:491.

Dorice M. Czajka N. 1992. The assessment of nutritional status. In: Mohan LK, Arlin MT. Krause's Food, Nutrition, and Diet Therapy. 8th ed. Philadelphia: W.B. Saunders company. 293-313.

Forest HP. Prolonged tube feeding in long term care: Nutritional status and clinical outcome.Crit Care Med 1990;4:121-25.

Frobes A. Parenteral nutrition: New advances and observations current opinion. Gastroenterology 2004;20:114-8.

Furst P. 2000. A thirty-year odyssey in nitrogen metabolism: from ammonium to dipeptides. JPEN; 24:197-209.

Furst P., Stehle P. 2004. Glutamine and glutamine-containing dipeptides.InMetabolic and therapeutic aspects of amino acids in clinical nutrition. 2nd ed. Cynober, Boca Raton, Crc Press. p613-31.

Galbán C, Montejo JC, Mesejo A, Marco P, Celaya S, Sánchez-Segura JM, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med., 2000;28:643-8.

Garrel D, Patenaude J.Decreased mortality and morbidity in adult burn patients given glutamine supplements.Crit Care Med 2003;31:2444-9.

Grigorakos L, Sotiriou E, Markou N, Stratouli S, Boutzouka E, Philntisis G, et al. Combined nutritional support in patients with chronic obstructive pulmonary disease (COPD), under mechanical ventilation (MV). Hepatogastroenterology 2009;56:1612-4.

Guidelines for the use of parenteral and enteral nutrition in adult and paediatric patients. JPEN 1993; 17:1SA.

Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington: Carnegie Instit; 1919. Quoted from:Paul LM. Nutrition and Metabolism. In: The ICU Book.2nded. Philadelphia: Lea and Farbiger;1998. p723.

Heyland D, Cook DJ, Winder B. Enteral nutrition in the critically ill patient. Crit Care Med 1995;23:1055-60.

Hill GL, Pickford I, Young GA. 1997. Malnutrition in surgical patients. An unrecognized problem. Lancet 689-92.

Jeejeebhoy KN. 1998. Nutritional assessment. *Gastroenterol Clin North Am.,* 27:347-369.

Jolliet P, Pichard C, Biolo G. 1998. Enteral nutrition in intensive care patients. *Intensive Care Med.,* 24:848-59.

Kilmberg VA, Souba WW, Dolson DJ. 1990. Prophylactic glutamine protects the intestinal mucosa from radiation injury. *Cancer.,* 66:62-8.

Kudsk KA, Croce MA, Fabian TC. 1992. Enteral versus parenteral feeding. Effects on septic morbidity after blunting and penetrating abdominal trauma. *Am Surg.,* 215:503-11.

Luo M, Fernandez-Estivariz C, Jones DP. Depletion of plasma antioxidants in surgical intensive care unit patients requiring parenteral feeding: effects of parenteral nutrition

with or without alanyl-glutamine dipeptide supplementation.Nutrition. 2008;24:37-44.

Luo M, Bazargan N, Griffith DP, Estívariz CF, Leader LM, Easley KA, et al. Metabolic effects of enteral versus parenteral alanyl-glutamine dipeptide administration in critically ill patients receiving enteral feeding: a pilot study. Clin Nutr 2008;27: 297-306.

McClave SA, Snider HL. 1992. Use of indirect calorimetry in clinical nutrition. *Nutr Clin Pract.,* 7:297.

Mertes N, Schulzki C, Goeters C, Winde G, Benzing S, Kuhn KS, et al.Cost containment through L-alanyl-L glutamine supplemented total parenteral nutrition after abdominal surgery: a prospective randomised double-blind controlled study.Clin Nutr2002;19:395-401.

Montejo J.C. Enteral nutrition–related gastrointestinal complicationsin critically ill patients. Crit Care Med 2001;27:1447-53.

Moore EE, Moore FA. Immediate enteral nutrition following multisystem trauma. J Am Coll Nutr 1991;10:633-48.

Paige D. 1988. Clinical Nutrition. 2nded. Estados Unidos: Mosby p342-71.

Patrick R. Pfau, John L. Rombeau. Advances in gastroenterology. Departments of Medicine, University of Pennsylvania, 2000.

Pinchcofsky GD., Kalminski MV. 1995. Increasing malnutrition during hospitalization. Documentation by a nutritional screening program. *Am J Clin Nutr*., 4:471-9.

Parsons PE, Jeanine PW. 1992. Critical Care Secrets. Philadelphia: Hanley &Belftis INC. 27-33.

Shenkin A. Micronutrients. In: Rombeau J, Rolandelli R.Clinical Nutrition. Enteral and Tube Feeding. Philadelphia: WB Saunders. p96-111.

Sherman BW, Hamilton C, Panacek EA. Adequacy of early nutrition by the enteral route in patients with acute respiratory failure. Chest 1990;98:104S.

Skipper A. 1997. Dietitians handbook of parenteral and enteral nutrition. 2nd ed. Gaithersburg : Aspen Publishers; 1998.

Szijártó A, Hahn O, Batmunkh E. Short-term alanyl-glutamine dipeptide pretreatment in liver ischemia-reperfusion model: effects on microcirculation and antioxidant status in rats. Clin Nutr 2007;26:640-8.

Thérond P, Bonnefont-Rousselot D, Davit-Spraul A, Conti M, Legrand A. Biomarkers of oxidative stress: an analytical approach. Curr Opin Clin NutrMetab Care 2000;3:373-84.

Vincent JL. 2008. Intensive care medicine. New York : Springer.

Weinsier RL, Morgan SL, Perrin VG. 1992. Fundamentals of Clinical Nutrition. Baltimore: Mosby - Yearbook INC .p133-46.

Weinsier RL., Hunker EM., Krumdieck CL. 1995. A prospective evaluation of general medical patients during the course of hospitalization. *Am J Clin Nutr*., 32:418-26.

Wilmore D W, Shabret J K. Role of glutamine in immunologic responses. Nutrition 1998; 14:618-26.

****