Effect of Early Postoperative Intravenous Glutamine Supplementation on the Outcome after Colorectal Cancer Surgery

Dr. Mustafa Kamel Reyad, Dr. Mahmoud Hassan Mohamed Hassan, Dr. Rania Hassan Abd El-Hafiez and Tasneem Ameen Abd El-Sattar Kabeel

Anesthesia, Intensive Care & Pain Management Department, Faculty of Medicine, Ain Shams University, Egypt.
tasneemkabeel33@gmail.com

Abstract: Background: Glutamine is the most abundant amino acid in the body and constitutes 61% of the total pool of amino acids in the human muscle. It is the most important circulating "nitrogen shuttle" accounting for 30%-35% of all amino acid nitrogen transported in the blood and serves as important precursor for the de novo synthesis of nucleotides, nucleic acids, amino acids, proteins, and glutathione. **Objectives:** To evaluate the effect of intravenous glutamine supplementation on the postoperative complication rate and duration of hospital stay in colorectal cancer patients. **Patients and Methods:** Type of Study: Prospective analytic study, study Setting: Ain-Shams University Hospitals and Tanta Cancer Institute, Study Period: from May 2018 to December 2018, Study Population: Patients underwent colorectal cancer surgery. **Results:** In our study, the median C-reactive protein levels were significantly lower from day 7 in glutamine group in comparison with control group but still higher than normal range. At days 10 and 14, the CRP level reached the normal range. These suggests the positive effects of glutamine in relieving the stress response in colon cancer patients. The detected high C-reactive protein levels could result from the presence of some factors that affect the CRP levels like fever, leukocytosis, the surgical maneuver and the presence of inflammation. **Conclusion:** We found that early postoperative supplementation of parenteral glutamine in addition to standard nutritional support in patients that underwent colorectal cancer surgeries reduced the incidence of postoperative complications and improved the outcome in those patients.

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1. Introduction

Glutamine is the most abundant amino acid in the body and constitutes 61% of the total pool of amino acids in the human muscle. It is the most important circulating "nitrogen shuttle" accounting for 30%-35% of all amino acid nitrogen transported in the blood and serves as important precursor for the de novo synthesis of nucleotides, nucleic acids, amino sugars, proteins, and glutathione ***(Kraemer et al., 2009).*** It is mainly synthesized in muscles and the lungs through glutamine synthetase. It is a vital fuel source for the intestines and immune system that helps to keep defenses up against microbes. By nourishing these cells, it maintains the integrity of the gastro intestinal tract ***(Wernerman, 2008).***

There are studies reporting that muscle and plasma glutamine levels are reduced up to 50% in patients with critical illness, or following major surgery, stress, trauma, and muscular dystrophy suggesting that the body's demand for glutamine is increased in these situations ***(Tao et al., 2014).***

Cancer is a hyper inflammatory cytokine release pattern combined with an insufficient endogenous availability of glutamine due to increased consumption. Overall glutamine deprivation is associated with reduced protein synthesis, muscle loss and possibly physical as well as emotional fatigue. Consequently, glutamine is considered a "conditionally indispensable amino acid" in hyper metabolic and hyper catabolic situations ***(Kuhn et al., 2010).***

Malnutrition, pro-inflammatory reactions, and weight loss occur at prevalence of 38% in cancer diseases. In addition, the location of the tumor, the advancement and severity of the underlying disease, as well as the modalities and lines of treatment may influence these hyper catabolic reactions ***(Peter et al., 2014).***

Colorectal surgical procedures carry a high risk of postoperative complications due to altered host defense, homeostasis and inflammatory complications. Furthermore, surgical stress, full mechanical bowel preparation, increased metabolic rate, potential risk for the intraoperative bacterial contamination of peritoneal cavity and surgical wound are important factors enhancing the risk of

postoperative infectious complications ***(Singer et al., 2011).***

In addition, inadequate nutrition in these patients has an additive effect for these complications. Approximately one-third of patients with colorectal cancer have malnutrition at the time of admission. Nutritional depletion not only can adversely affect a surgical patient's clinical condition, but it may also increase his or her risk of a poor postoperative outcome, thereby increasing healthcare costs for both patients and health insurance companies ***(Gupta et al., 2005).***

In addition to the nutritional support, recent studies suggested that supplementation of specific nutrients such as glutamine enhances gut mucosal growth, repair and function, decreases gut related sepsis and improves intestinal atrophies, intestinal injuries and improves postoperative outcome ***(Kuhn et al., 2010).***

Aim of the Work

To evaluate the effect of intravenous glutamine supplementation on the postoperative complication rate and duration of hospital stay in colorectal cancer patients.

2. Patients and Methods

- **Type of Study:** Prospective analytic study.
- **Study Setting:** Ain-Shams University Hospitals and Tanta Cancer Institute.
- **Study Period:** from May 2018 to December 2018.
- **Study Population:** Patients underwent colorectal cancer surgery.

- Inclusion Criteria: Adult patients (more than 18 years old), both sexes**,** diagnosed by CT or MRI and underwent anterior resection either with end to end anastomosis or with colostomy.

- Exclusion Criteria: Patient refusal**,** patients received chemotherapy or radiotherapy, metastases, recurrence, palliative or abdomenoperineal surgeries, hepatic or renal patients.

- **Sampling Method:** Sample size was calculated using PASS version 11 program, setting the type-1 error α at 0.05 with a power of 80%. Results from a previous study ***(Oguz et al., 2006)*** reported that abdominal abscess and wound dehiscence were detected among 8% of control group compared to 0% among glutamine group. Calculation according to these values produced a minimal sample size of 55 participants per group.
- **Sample Size:**120 patients divided into two groups:
  - Control group didn't receive glutamine.
  - Glutamine group received IV glutamine for 14 days postoperatively.
- **Ethical Considerations:** All patients were consented after explaining the detailed study. Moreover, their privacy was maintained and no personal or medical data was disclosed to third party.
- **Study Tools:**

1) Measurement of serum pre-albumin, serum transferrin and blood culture post ICU admission, at day 0,2,7,10,14.

2) Routine laboratory investigations including ESR, CRP, CBC, liver enzymes, urea, creatinine and electrolytes at day 0,2,7,10,14.

3) Full clinical evaluation including medical history, heart rate, temperature, mean arterial blood pressure and urine output and wound healing for 10 days postoperative at day 0,2,7,10,14.

- **Study Procedures:** Serial blood samples of prealbumin and transferrin were analyzed by ELISA. Specimen collection of 1ml of venous blood of selected patients and were collected in anticoagulant tubes. No specimen preparation was required. Samples were stored at 2-8˚C if the assay was performed within 72hrs.
- **Study Interventions:** This study measures serum pre-albumin, serum transferrin and blood culture to evaluate the effect of intravenous glutamine supplementation postoperatively in colorectal cancer patients.
- **Statistical Analysis:** All data was collected and analyzed statistically.
- **Statistical Package:** Data was analyzed using Statistical Program for Social Science (SPSS) version 20.

3. Results

Table (1): Comparison between two studied groups regarding CRP

CRP		GROUPS		Mann-Whitney U test	
		Glutamine	Control	Z_{mw}	P value
D0 (on ICU admission)	Range	3.14-201.00	1.98-196.00	.978	.328
	Median	37.00	47.00		
D2	Range	6.00-211.00	4.00-204.00	.65	.52
	Median	52.00	50.00		
D7	Range	3.00-158.00	5.00-186.30	3.37	.001*
	Median	15.00	44.00		
D10	Range	3.00-127.90	3.00-87.80	2.62	.009*
	Median	5.90	20.00		
D14	Range	1.50-78.70	2.50-54.50	4.18	<.001*
	Median	3.80	8.30		

*significant at p<.05

At D0 and D2, there were no significant difference between the two groups (p>.05). However, the median CRP levels were significantly lower in glutamine than control group at D7 (15 and 44 respectively), at D10 (5.9 and 20 respectively), and at D14 (3.8 and 8.3 respectively).

Table (2): Comparison between two studied groups regarding ESR

ESR		GROUPS		Mann-Whitney U test	
		Glutamine	Control	Z_{mw}	P value
D0 (on ICU admission)	Range	4.0-106.0	5.0-99.0	1.96	0.050
	Median	28.0	36.0		
D2	Range	13.0-93.0	5.0-115.0	1.272	.203
	Median	34.0	39.0		
D7	Range	2.0-68.0	3.0-93.0	3.0	.003*
	Median	22.0	36.0		
D10	Range	.00-83.0	3.0-53.0	4.05	<.001*
	Median	7.0	22.0		
D14	Range	.00-50.0	.00-47.0	3.09	.002*
	Median	2.0	9.0		

*significant at p<.05

There were no significant differences between the two groups at D0 and D2. However, the median ESR levels were significantly lower in glutamine group than control group at D7 (22 and 36 respectively), at D10 (7 and 22 respectively), at D14 (2 and 9 respectively).

Table (3): Comparison between two studied groups regarding WBCs

WBCs		GROUPS		Mann-Whitney U test	
		Glutamine	Control	Z_{mw}	P value
D0 (on ICU admission)	Range	4.90-19.90	3.20-27.00	1.02	.308
	Median	12.70	13.20		
D2	Range	3.20-26.47	4.70-20.70	1.862	.062
	Median	13.40	15.50		
D7	Range	5.10-14.07	2.50-23.70	2.63	.008*
	Median	9.50	11.45		
D10	Range	6.20-23.90	3.30-18.50	.556	.578
	Median	8.50	8.20		
D14	Range	3.90-12.00	2.50-23.70	1.57	.116
	Median	6.90	5.20		

*significant at p<.05

The median WBCs levels were significantly lower in glutamine than control group at D7 (9.5 and 11.45 respectively). Otherwise, they were insignificant.

Table (4): Comparison between two studied groups regarding D0 (on ICU admission) and D10

Blood cultures			**GROUPS**		**Chi-Square test**	
			Glutamine	**Control**	**X^2**	**P value**
D0 (on ICU admission)	**No growth**	N	37	29	5.515	.063
		%	67.3%	52.7%		
	Growth	N	18	26		
		%	32.8%	47.3%		
	MRSA	N	15	15		
		%	27.3%	27.3%		
	Klebsiella	N	3	11		
		%	5.5%	20.0%		
D10	**No growth**	N	49	36	14.86	.002*
		%	89.1%	69.2%		
	Growth	N	6	16		
		%	11%	30.7%		
	MRSA	N	3	10		
		%	5.5%	19.2%		
	Klebsiella	N	0	6		
		%	0.0%	11.5%		
	Staphylococcus	N	3	0		
		%	5.5%	0.0%		

*significant at p<.05

At D0, there were no significant differences between the two groups.

At D10, significantly higher percent of patients in glutamine group showed no growth in blood culture compared to control group (89.1% and 69.2% respectively). Likewise, the growth of MRSA and Klebsiella was significantly higher in control group than in glutamine group (19.2% and 5.55 respectively) and (6% and 0% respectively). However, the growth of staphylococcus was detected only in glutamine group.

Table (5): Comparison between two studied groups regarding Prealbumin

Prealbumin		**GROUPS**		**Mann-Whitney U test**	
		Glutamine	**control**	**Z_{mw}**	**P value**
D0 (on ICU admission)	Range	8.10-27.10	8.70-27.00	.039	.96
	Median	16.00	15.80		
D2	Range	8.00-24.20	7.30-25.30	1.43	.15
	Median	13.00	15.10		
D7	Range	10.50-26.00	8.30-24.90	-3.66	<.001*
	Median	16.00	13.50		
D10	Range	13.70-28.00	6.00-25.30	-5.76	<.001*
	Median	21.00	13.00		
D14	Range	13.70-32.00	5.00-25.00	-6.53	<.001*
	Median	25.00	11.10		

*significant at p<.05

There were no significant differences at D0 and D 2 (p>.05). on the other hand, the median prealbumin levels were significantly higher in glutamine than control group at D7 (16.00 and 13.50 respectively), at D10 (21.00 and 13.00 respectively), and D 14 (25.00 and 11.10 respectively).

Table (6): Comparison between two studied groups regarding Serum Transferrin

Serum Transferrin		GROUPS		Mann-Whitney U test	
		Glutamine	Control	Z_{mw}	P value
D0 (on ICU admission)	Range	102.00-299.00	123.00-297.00	-1.74	.082
	Median	205.00	174.00		
D2	Range	108.00-271.00	105.00-288.00	-1.92	.055
	Median	191.00	177.00		
D7	Range	102.00-307.00	89.00-290.00	-4.37	<.001*
	Median	206.00	150.00		
D10	Range	119.00-313.00	84.00-273.00	-5.89	<.001*
	Median	225.00	164.00		
D14	Range	127.00-320.00	80.00-265.00	-6.54	<.001*
	Median	250.00	166.00		

*significant at p<.05

There were no significant differences at D0 and D 2 (p>.05). on the other hand, the median serum transferrin levels were significantly higher in glutamine than control group at D7 (206 and 150 respectively), at D10 (225 and 164 respectively), and D 14 (250 and 166 respectively).

4. Discussion

Enhanced recovery after surgical interventions may be a multidisciplinary approach to the care of the surgical patient. This needs a team consisting of surgeons, anesthetists, associate degree ERAS organizer (often a nurse or a physician assistant), and members from units that provide care for the surgical patient ***(Ljungqvist et al., 2017).*** Enhanced recovery protocols for perioperative care have been detected to be valuable in reducing complications that happen after surgery, enhancing the overall outcomes and shortening the length of hospital stay, and also saving resources ***(Adamina et al., 2011).***

Many patients going to have a colorectal surgery are at risk of nutritional depletion, due to inadequate nutrients intake, surgical stress and also the subsequent increasing metabolic rate. Moreover, surgical trauma induces alternation in protein metabolism and changes the pattern of plasma free amino acids ***(Dudrick et al., 2011).*** These alterations contribute to increasing complication rate, delayed recovery, and increasing length of hospital keep ***(Hübner et al., 2016).***

Glutamine is a non-essential amino acid, that becomes conditionally essential under certain catabolic states like trauma or critical illness. It exerts its protective effects via multiple mechanisms, including direct protection of cells and tissues from injury, attenuation of inflammation and preservation of metabolic function. Data supports glutamine as an ideal pharmacologic intervention to prevent or treat multiple organ dysfunction syndrome after sepsis or other injuries in the intensive care unit population. A large and growing body of clinical data shows that in well-defined critically ill patient groups glutamine can be a life-saving intervention ***(Bongers et al.,2007).***

Depletion of plasma-free amino acids, particularly glutamine stores, would possibly result in severe complications, like infection, poor wound healing, impaired immunity, increased intestinal permeability and end by multiple organ failure ***(Cruzat et al., 2018).***

The level of C-reactive protein is the indicator of the most necessary biological function within the body, the role of that is to detect and to stimulate the clearance of the cell remnants ***(*Sproston and Ashworth, *2018).*** In our study, the median C-reactive protein levels were significantly lower from day 7 in glutamine group in comparison with control group but still higher than normal range. At days 10 and 14, the CRP level reached the normal range. These suggests the positive effects of glutamine in relieving the stress response in colon cancer patients. The detected high C-reactive protein levels could result from the presence of some factors that affect the CRP levels like fever, leukocytosis, the surgical maneuver and the presence of inflammation ***(Landry et al., 2017).***

A previous study that investigated the impact of the standard parenteral nutrition and glutamine enriched parenteral nutrition on C-reactive protein levels were determined for the analysis of systemic inflammatory response, and C-reactive protein concentrations of the patients had diminished within the glutamine group, whereas C-reactive protein level within the control group had diminished at the first week then increased after that. Likewise, a recent study compared the results of oral and parenteral glutamine on biochemical parameters of critically ill patients. They terminated that administration of glutamine with a dose of 0.3 g/kg/d parenterally was more efficient than 20 g/d orally in decreasing the C-reactive protein parameters after the course of therapy ***(Singh et al., 2019).***

Shibuya and colleagues (2018) investigated the relationship between erythrocyte sedimentation rate (ESR) and postoperative survival of patients with colorectal cancer. They found that ESR >40 mm/h had poorer postoperative survival. This study supports the promising effects of glutamine treatment on ESR in our study. At all the studied time points after glutamine, ESR was significantly reduced. This might help in improving outcome of these patients.

Glutamine is, generally, accepted to some extent as an immune modulatory agent. In several animal and clinical studies, it has helpful effects on the cells of the immune system and their functions, resulting in reduction in inflammatory responses and rate of infection as observed ***(Wang et al., 2014).*** In addition, comparison between standard parenteral nutrition and glutamine-enforced parenteral nutrition support revealed a significant improvement in the immune response and reduction of stress response in patients underwent esophageal cancer operation ***(Bin-Dong et al., 2016)***. In agreement with these findings, in our study there was a noticeable significant reduction in WBCs at day 7.

In the current study, results of blood culture have promising findings. Patients received glutamine showed significant reduction in microorganisms' growth. Likewise, growth of both MRSA and klebsiella was significantly lower in these patients.

Wischmeyer and colleagues' (2001) study, the frequency of Gram-negative bacteremia was 43% in the control group vs. 8% in the glutamine group. This difference was statistically significant.

This favorable result of glutamine is explained by the well-known role of glutamine in immune response. Glutamine in combination with glucose represents the most quantitatively precious oxidative fuel supply for activated immune cells such as lymphocytes ***(Altman et al., 2016).***

Moreover, work on lymphocyte cultures has discovered that the proliferative response and the differentiation of those cells depends on glutamine. Actually, proliferating lymphocytes could have 10-fold larger glutamine utilization compared with resting cells ***(Wasinski et al., 2014).***

Another earlier study in severely burnt patients revealed that glutamine administration has reduced gram negative bacteremia ***(Wischmeyer et al., 2001).*** Moreover, ICU patients admitted after complicated surgery, multiple trauma, and pancreatitis showed satisfactory responses to total parenteral nutrition supplemented with glutamine ***(Déchelotte et al., 2006).***

However, there is an abundant discrepancy as regard comparing single randomized controlled trials on glutamine supplementation's effects on clinical endpoints like infection rates, length of hospital stay and mortality ***(Mundi et al., 2016).***

This discrepancy may be a result of variations in study design, selected patient populations, severity of the disease, patient's nutritional status and/or the variations in glutamine supplementation which has different forms (free or dipeptide form), doses and administration method ***(McRae, 2017).***

Nienaber (2015) within the intensive care unit (ICU) has evolved from meeting nutritional needs to manipulating patient outcome. The most abundant amino acid within the body, glutamine, is additionally the most-researched pharmaconutrient. It is independently a predictor of mortality in ICU patients, at both deficient or really high levels.

Recent enhancements in perioperative care about to modulate the overwhelming surgical stress responses are well-tried to be effective. Moreover, glutamine supplementation is suggested within the social unit setting for its well-tried outcome edges ***(Mortensen et al., 2014).*** Therefore, the aim of this study was to assess the role of early postoperative intravenous glutamine supplementation on the outcome after colorectal cancer surgery.

Prealbumin is a misnomer, its correct name is transthyretin. It is a tryptophan-rich protein and similar to albumin, it is synthesized in hepatocytes of the liver. As it has a short half-life (2 days) and relatively small pool, it is a better indicator to assess nutritional status than the widely used albumin serum level ***(*Buxbaum and Natàlia, *2009).***

In agreement with our finding, ***Salem and colleagues (2017)*** recorded that early use of intravenous glutamine in severely burned patients was accompanied by a significant elevation in both serum prealbumin and serum transferrin by day 7. They attributed the increase in serum nutritional markers that have a relatively short half-life (transferrin and prealbumin) to the improvement in the absorptive function of the gut mucosal tissue layer that limits catabolic effects.

Meta-analysis of surgical patients with gastrointestinal tract cancers that received glutamine enriched nutrition found that serum prealbumin, transferrin and albumin were significantly elevated ***(Kang et al., 2015).***

The optimal dose of glutamine is a matter of debate; human studies suggest that glutamine supplementation up to 0.5 g/kg/day is safe ***(Wernerman, 2008).***

Novak and colleagues (2002) analyzed fourteen randomized trials comparing glutamine supplementation in surgical and critically ill patients. From subgroup analyses, they concluded that a trend could be identified favoring the prescription of glutamine parenterally at a dose more than 0.2

g/kg/day. Novak's data suggested that a dose higher than 0.2 g/kg/day has greater effect than a lower dose. Also he stated that seriously ill patients with gastrointestinal failure receiving parenteral nutrition should probably receive glutamine supplementation for at least 6 days to derive the maximum benefit ***(*Kim and Hyeyoung, *2017).***

5. Conclusion

In conclusion, we found that early postoperative supplementation of parenteral glutamine in addition to standard nutritional support in patients that underwent colorectal cancer surgeries reduced the incidence of postoperative complications and improved the outcome in those patients.

Corresponding author:

Dr. Tasneem Ameen Abd El-Sattar Kabeel,

Anesthesia, Intensive Care & Pain Management Department, Faculty of Medicine, Ain Shams University, Egypt.

E-mail**:** tasneemkabeel33@gmail.com

References

1. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ and Delaney CP."Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery." surgery, 2011; 149(6): 830-840.
2. Altman BJ, Stine ZE and Dang CV."From Krebs to clinic: glutamine metabolism to cancer therapy." Nature Reviews Cancer, 2016; 16(10): 619.
3. Bin-Dong X, Guo-Zhong H and Hao C. "Positive effect of glutamine-enforced parenteral nutrition on immune function and stress response of patients after esophageal cancer operation." Turk Gogus Kalp Damar Cerrahisi Dergisi-Turkish Journal of Thoracic and Cardiovascular Surgery, 2016; 24(3), 507-513.
4. Bongers T, Richard DG, and Anne M. "Exogenous Glutamine: The Clinical Evidence." Critical Care Medicine 2007; 35: S545–52.
5. Buxbaum JN and Natàlia R. "Transthyretin: The Servant of Many Masters." Cellular and Molecular Life Sciences: CMLS 2009; 66 (19): 3095–3101.
6. Cruzat VF, Maurício K and Philip N. "Amino Acid Supplementation and Impact on Immune Function in the Context of Exercise." Journal of the International Society of Sports Nutrition 2014; 11 (1): 61.
7. Déchelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coëffier M, Hecketsweiler L and Petit J. "L-alanyl-L-glutamine dipeptide–supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study." Critical care medicine, 2006; 34(3): 598-604.
8. Dudrick SJ and Pimiento JM. "Parenteral nutrition and nutritional support of surgical patients: Reflections, controversies, and challenges." Surgical Clinics, 2011; 91(3): 675-692.
9. Gupta D, Lammersfeld CA, Vashi PG, Burrows J, Lis CG, Grutsch JF."Prognostic significance of subjective global assessment (SGA) in advanced colorectal cancer." Eur J Clin Nutr 2005; 59: 35–40.
10. Hübner M, Mantziari S, Demartines N, Pralong F, Coti-Bertrand P and Schäfer M."Postoperative albumin drop is a marker for surgical stress and a predictor for clinical outcome: a pilot study." Gastroenterology research and practice, 2016.
11. Kang K, Shu XL, Zhang YS, Liu XL and Zhao J. "Effect of glutamine enriched nutrition support on surgical patients with gastrointestinal tumor: A meta-analysis of randomized controlled trials." Chinese Medical Journal, 2015; 128(2), 245.
12. Kim MH and Hyeyoung K. "The Roles of Glutamine in the Intestine and Its Implication in Intestinal Diseases." International Journal of Molecular Sciences 2017; 18 (5): 1051.
13. Kraemer WJ, Hatfield DL, Volek JS, Fragala MS, Vingren JL, Anderson JM, Spiering BA, Thomas GA, Ho JY, Quann EE, Izquierdo M, Häkkinen K, Maresh CM. "Effects of amino acids supplement on physiological adaptations to resistance training." Med Sci Sports Exerc 2009.
14. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P."Glutamine as indispensable nutrient in oncology: experimental and clinical evidence." Eur J Nutr 2010; 4: 197e210.
15. Landry A, Docherty P, Ouellette S and Cartier LJ. "Causes and outcomes of markedly elevated C-reactive protein levels." Canadian family physician Medecin de famille canadien, 2017; 63(6): e316-e323.
16. Ljungqvist O, Scott M and Fearon KC. "Enhanced recovery after surgery: a review." JAMA surgery, 2017; 152(3): 292-298.
17. McRae MP."Therapeutic benefits of glutamine: An umbrella review of meta-analyses." Biomedical reports, 2017; 6(5), 576-584.
18. Mortensen K, Nilsson M, Slim K, Schäfer M, Mariette C, Braga M and Enhanced Recovery After Surgery (ERAS®) Group. "Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery after Surgery

(ERAS®) Society recommendations." British Journal of Surgery, 2014; 101(10): 1209-1229.
19. Mundi MS, Shah M and Hurt RT. "When is it appropriate to use glutamine in critical illness?." Nutrition in Clinical Practice, 2016; 31(4): 445-450.
20. Nienaber A. "Plasma glutamine levels in critically ill intensive care patients." (Doctoral dissertation) 2015.
21. Peters ME, Goedendorp MM, Verhagen CA, van der Graaf WT, Bleijenberg G. "Severe fatigue during palliative treatment phase of cancer: an exploratory study." Cancer Nurs 2014; 37:139e45.
22. Salem YA, Labib HA and Algendy MA. "Intravenous glutamine supplementation improves gut mucosal function in burn patients: a randomized controlled trial." Ain-Shams Journal of Anaesthesiology, 2017; 10(1), 60.
23. Shibuya N, Ishizuka M, Takagi K, Iwasaki Y, Hachiya H, Aoki T and Kubota K."Relationship Between Preoperative Erythrocyte Sedimentation Rate and Survival After Surgery in Patients with Colorectal Cancer." Anticancer research, 2018; 38(12), 6783-6788.
24. Singer S, Kuhnt S, Zwerenz R, Eckert K, Hofmeister D, Dietz A, et al. "Age- and sex-standardised prevalence rates of fatigue in a large hospital-based sample of cancer patients." Br J Cancer 2011; 195:445e51.
25. Singh D, Saxena S, Bogra JS, Chaudhary AK, Chandra G and Bhushan S. "A comparative study of the effect of parentral and oral glutamine on biochemical parameters and on the duration of ICU stay in critically ill patients." Anaesthesia, Pain & Intensive Care, 2019; 123-127.
26. Sproston NR and Ashworth JJ."Role of C-Reactive Protein at Sites of Inflammation and Infection." Frontiers in immunology, 2018; 9: 754.
27. Tao K, Li X, Yang L, Yu W, Lu Z, Sun Y, Wu F. "Glutamine supplementation for critically ill adults." Cochrane Database of Systematic Reviews 2014; 9: CD010050.
28. Wang X, Pierre JF, Heneghan AF, Busch RA, Kudsk KA. "Glutamine Improves Innate Immunity and Prevents Bacterial Enteroinvasion During Parenteral Nutrition" JPEN. Journal of Parenteral and Enteral Nutrition 2014; 39(6): 688-97.
29. Wasinski F, Gregnani MF, Ornellas FH, Bacurau AV, Câmara NO, Araujo RC and Bacurau RF. "Lymphocyte glucose and glutamine metabolism as targets of the anti-inflammatory and immunomodulatory effects of exercise." Mediators of inflammation, 2014.
30. Wernerman J. "Clinical Use of Glutamine Supplementation." The Journal of Nutrition 2008; 138 (10): 2040S–2044S.
31. Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L and Kahana M. "Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control." Critical care medicine, 2001; 29(11): 2075-2080.

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