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Effects of Preoperative Glutamine Administration on Nutritional and Immunological Improvements and Reduction of Length of Stay in Colorectal Cancer Patients with Malnutrition

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ABSTRACT

Background: The progression of colorectal cancer includes metabolic and nutritional complications. In cancer cells, glutamine plays important roles in bioenergy, macromolecular synthesis, and oxidation-reduction homeostasis to promote cell proliferation and survival. ***Objectives:*** To investigate the effects of preoperative glutamine administration on nutritional and immunological improvement and reduction of length of stay (LOS) in malnourished colorectal cancer patients. ***Method:*** Prospective cohorts by bivariate analytic analysis, unpaired T-test, and Mann-Whitney test with the help of the Windows Statistical Package for the Social Sciences (SPSS) version 24.0. ***Results:*** Of the 40 study subjects, which were divided into 20 control patients and 20 treatment patients, results were obtained where glutamine had significant effects on reducing the patient's LOS ($p< 0.030$) and the patient's weight difference ($p< 0.000$). In addition, glutamine also had significant effects on the difference in BMI ($p< 0.000$), the difference in albumin ($p< 0.000$), the difference in SGOT ($p< 0.000$), the difference in SGPT ($p< 0.000$), and the difference in WBC ($p< 0.000$) between 2 groups. ***Conclusion:*** Preoperative administration of glutamine has significant effects in maintaining and increasing body weight, reducing the risk of infection, and reducing the length of stay in colorectal cancer patients with malnutrition.

Keywords: glutamine; nutrition; immunology; length of stay; colorectal cancer; malnutrition

INTRODUCTION

Colorectal cancer progression includes metabolic and nutritional complications associated with decreased response to treatment [1]. Although early-stage colorectal cancer patients can be treated successfully with surgery, major surgery will likely cause homeostatic dysfunction and altering the immune system against the inflammatory response, then will potentially leads to the increased of postoperative complications and prolonged the hospital stay[2].

Decreased levels of glutamine in the body, especially in the glutamine pool, can lead to various postoperative complications, such as impaired wound healing resulting in surgical site infection (SSI), impaired immunity which can cause multiple organ failure, resulting in extending the length of stay (LOS) in the hospital even in more severe conditions can result in mortality[3].

Most studies have focused on the diagnostic value of glutamine in colorectal cancer, and a limited number of studies have investigated the association between the prognostic value and the predictive value of glutamine [4]. In addition, some studies report an association between patients with low initial glutamine levels and a higher mortality rate of patients treated in the Intensive Care Unit (ICU), but this association is not significant [5].

An assessment of the *Modified Glasgow Prognostic Score (mGPS)*, which is an inflammation-based cancer prognostic marker consisting of an increase in serum C-Reactive Protein (CRP) and a decrease in albumin concentration, is a very well-known prognostic marker for cancer patients and reflected as body responses through systemic inflammation.

Since it is known that cancer patients show a decline in nutritional status which can be measured by nutritional screening tool like *Subjective Global Assessment (SGA)*, nutritional support interventions are essential to treatment therapy. This nutritional support aims to ensure the nutritional needs of cancer patients, reduce micronutrient deficiencies, maintain muscle mass, and increase food intake and quality of life. In surgical patients, nutritional support therapy is vital in preventing and treating malnutrition and catabolic processes. This support can be enhanced if supplemented with an immunomodulatory nutrient such as glutamine [6]. Therefore, the authors are interested in conducting research and knowing the effectiveness of preoperative glutamine administration on mGPS and SGA, as well as the clinical outcomes represented in the form of LOS in colorectal cancer patients with malnutrition.

METHODS

This research was an analytic observational study with a prospective cohort design. This study was divided into 2 groups: the control and case groups. Measurement of the dependent variable was carried out 2 times, so this research was also called a pre and post-test control group design study. The research location was conducted at Prof. Dr. IGNG Ngoerah Central General Hospital Denpasar, from October 2021 to December 2021. The inclusion criterias were colorectal cancer pre-surgery patients with malnutrition status. The exclusion criterias were: (1) Patients with incomplete medical records. (2) Patients with history of immunosuppressant medications, such as corticosteroids. (3) Patients who were suffering from septic shock or severe sepsis while being treated. (4) Patients forced home from the treatment of their own will.

Samples were taken consecutively (consecutive sampling), i.e. all patients who have been diagnosed with colorectal cancer histopathologically from Anatomical Pathology (PA) laboratory and will be prepared for surgeries, were screened for malnutrition status using the SGA, namely the nutritional screening method using the following parameters: current weight, weight before illness and changes in body weight in the history of the previous six months and the last 15 days, nutritional history (appetite, food intake, gastrointestinal symptoms), presence of digestive disorders on the gastrointestinal tract (diarrhea, vomiting, nausea), functional physical capacity, and physical assessment (fat loss, oedema, muscle wasting, and ascites). In addition, an assessment of the mGPS were carried out, which is an inflammation-based cancer prognostic marker consisting of an increase in serum CRP and a decrease in albumin concentration. Samples were taken consecutively and analyzed statistically descriptive bivariate analytic analysis, unpaired T-test, and Mann-Whitney test with the help of the Windows Statistical Package for the Social Sciences (SPSS) version 24.0

RESULT

A total of 40 research subjects were involved in this study. The characteristics of the research data are presented in Table 1. The average age in the control group was 60.35 (±10.922) years, while in the treatment group, the average age was 60.85 (±10.333) years. The proportion of sex was also found to be balanced in the two groups, with the proportion of males being higher, compared to females in both study groups.

The other variables, such as body weight, height, BMI, albumin, CRP, SGOT, SGPT, WBC, SGA and mGPS, which were measured before treatment, did not differ significantly in the two groups.

TABLE 1: Basic Characteristics of Research Subjects.

Variable	Group		p-value
	Treatment (N: 20)	Control (N:20)	
Age	60.85±10.333	60.35±10.922	0.883
Gender			
Man	12 (30.0%)	11 (27.5%)	0.749
Woman	8 (20.0%)	9 (22.5%)	
Weight	48.05±4.536	47.55±3.187	0.602
Height	166.20±8.076	165.80±5.187	0.758
BMI	17.36±0.765	17.30±0.922	0.758
Albumin	3.44±0.526	3.48±0.543	0.678
CRP	8.88±7.673	11.64±8.270	0.565
SGOT	33.3500±8.70738	32.3500±9.48281	0.314
SGPT	45.9000±10.31555	44.0000±11.03106	0.577
WBC	10648.5000±3351.99434	8938,5000±2375,52271	0.07
SGA			
B	17 (42.5%)	13 (32.5%)	0.465
C	3 (7.5%)	7 (17.5%)	
mGPS			
0	12 (30.0%)	9 (22.5%)	0.490
1	3 (7.5%)	6 (15.0%)	
2	5 (12.5%)	5 (12.5%)	

The results of the bivariate analysis showed that the administration of glutamine was significantly associated with several variables, namely LOS, the difference in BMI, the difference in albumin, the difference in body weight, the difference in SGOT, the difference in SGPT, and the difference in WBC found in Table 2.

Glutamine administration significantly reduced LOS, as the data shows that the average LOS of patients receiving glutamine was 10.15 (±1.089) days compared to control patients, which was 11.00 (±1.170) days. Glutamine administration also significantly increased albumin levels, BMI, and body weight compared to the data obtained before the treatment. However, SGOT and SGPT levels in the treatment group also decreased compared to the control group. In addition, there was also a decrease in WBC levels in the treatment group compared to the control group.

Table 2: Bivariate Analysis of the Effects of Treatment on the Dependent Variable.

Variable	Group		p-value
	Treatment	Control	
Weight	48.55±4.608	47.03±3.283	0.602
Height	166.20±8.076	165.80±5.187	0.758
BMI	17.55±0.773	17.12±0.987	0.758
Albumin	3.59±0.495	3.41±0.513	0.678
CRP	15.53±32.357	12.20±8.415	0.565
SGOT	27.2000±7.76361	39.7000±11.59900	0.314
SGPT	38.5000±9.06410	52.7500±12.04760	0.577
WBC	8912.0000±2450.30310	10083.0000±2820.30625	0.07
LOS	10.15±1.089	11.00±1.170	**0.030***
SGA			
B	17 (42.5%)	13 (32.5%)	0.465
C	3 (7.5%)	7 (17.5%)	
mGPS			
0	12 (30.0%)	9 (22.5%)	0.490
1	3 (7.5%)	6 (15.0%)	
2	5 (12.5%)	5 (12.5%)	
ILO			0.311
No	20 (50.0%)	19 (47.5%)	
Yes	1(2.5%)	0 (0%)	
Difference in BMI	0.1950±.15720	-0.1850±.16631	**0.000***
Albumin difference	0.1550±.08721	-0.0705± .07950	**0.000***
CRP difference	6.6550±26.77472	0.5610±3.18597	0.072
Weight difference	0.5000±.36274	-0.5250±.47226	**0.000***
SGOT difference	6.1500±3.29713	-7.3500±3.01357	**0.000***
SGPT difference	7.4000±4.78374	-8.7500±2.88143	**0.000***
WBC difference	1736.5000± 1300.90768	-1144.5000±1014.32620	**0.000***

DISCUSSION

Although many other studies have shown that patients with stage IV colorectal cancer showed a highly significant negative correlation between mGPS and glutamine (p< 0.001) by Sirniö et al., (2019), but this study shows there was a significant decrease in mGPS in colorectal cancer patients with malnutrition through preoperative glutamine administration [7]. This was also seen in other studies, where approximately 38.9% of colorectal cancer patients with low serum glutamine levels showed mGPS = 2, which means pre-operatively those patients were in systemic inflammation status [8].

Meanwhile, the most significant correlation between mGPS and glutamine can be caused by the anti-inflammatory activity of glutamine. Indirectly, it is reported that glutamine can reduce the body's inflammatory response by reducing CRP, which then will reduce the mGPS value. As one of the mGPS calculations, CRP is a protein affected by the body's inflammatory status. CRP synthesis is also influenced by pro-inflammatory cytokines, especially IL-6, which increases in the acute phase [9].

In addition, there is a role for IL-6 and IL-8 in CRP production as an inflammatory marker [10], and also the role of TNF-α in CRP production in a study by Zhang et al. (2017) [11]. However, despite the wide variety of pro-inflammatory cytokines and chemokines involved in CRP synthesis, IL-6 remains the mediator with the most critical role in CRP synthesis [12]. Based on the CRP synthesis pathway, it can be concluded that glutamine as an amino acid that can suppress pro-inflammatory cytokines and chemokines, such as IL-6, IL-8, IL-17, etc., can suppress CRP numbers which leads to a decrease in mGPS. However, this study found that the CRP difference was almost significant (p< 0.072) after being given glutamine in the treatment group.

Glutamine's anti-inflammatory ability generally also involves suppressing NF-kB expression, a transcription factor of various immune responses [13–15]. NF-kB has a role in immune regulation and inflammatory response, one of which is through the production of pro-inflammatory chemokines and cytokines, such as TNF-α, IL-1β, IL-6, IL-12p40, and COX-2 [16–18].

Glutamine activity in suppressing NF-kB is also supported by in vitro and in vivo studies. NF-kB suppression by glutamine was also reported to correlate with an increase in HSF-1, such as HSP25 and HSP70 [19]. Based on this mechanism, it can be also concluded that glutamine can indirectly suppress pro-inflammatory cytokines and chemokines, decreasing the inflammatory response.

Apart from going through the NF-kB pathway, glutamine can suppress CRP through signal transducer and activator of transcription (STAT) inhibition. Until now, STAT has been reported as related to its activity in regulating the body's inflammatory response by inducing the expression of cytokines, such as IL-6 and IL-8. In vivo studies have shown the activity of glutamine in inhibiting STATs, such as STAT1 and STAT5. Other in vitro studies also found that glutamine deficiency increased STAT4 expression, while glutamine supplementation decreased STAT4 expression and IL-8 production [13]. Apart from IL-6 and IL-8, research by McGovern et al. (2012) also found STAT activity in binding to the IL-7 locus, which led to increased production of IL-17 [20]. Based on this mechanism, the decrease in STAT by glutamine also causes a decrease in the expression of IL-6, IL-8, and IL-17, proving glutamine's ability to suppress the inflammatory response [20].

In this study, it was found that there was an improvement in the nutritional condition (as seen from the difference in weight) in colorectal cancer patients with malnutrition after preoperative glutamine administration. However, this did not indicate an increase in SGA values. This could have happened because apart from the qualitative points in the form of weight being evaluated and the presence of other physical examinations such as edema, muscle wasting, and ascites differ in each patient. The nutritional screening method through SGA also contains many subjective points from the patient, for example, appetite patterns, food intake patterns, diseases or other disorders of the gastrointestinal tract, as well as the functional physical strength of patients that differ from one patient to another. Besides that, the preoperative condition that required fasting before and after surgery in these malnourished colorectal cancer patients should also be considered, which the first intake of meal after surgery differs and depends on patient's clinical condition.

These results are in line with study by Blass et al. (2012), who found that giving a placebo was better than glutamine for overcoming malnutrition, where only 20% of individuals were assessed as at risk of experiencing malnutrition based on SGA by giving a placebo meanwhile this number will increase to 50% if the patient was given glutamine [21].

Another inversely proportional result was found in a study by Vidal-Casariego et al. (2015) which compared patients' nutritional condition after the administration of glutamine and placebo. Based on SGA calculations, the study found no malnutrition among the sample group given glutamine. In contrast, in the placebo group, the sample was still malnourished [22]. Although not showing significant results, research by Al-Shebli also found a positive correlation between glutamine and SGA. In 93 patients, SGA was higher in the treatment group (a combination of glutamine and arginine) than in the control group, with a ratio of 44: 49 [23]. These results were supported by Shehata et al. (2020), which found that combining alanyl and glutamine could prevent malnutrition in an individual and increase the patient's SGA status [24].

SGA is used as a medium that can assess individual nutritional intake patterns, so it is often used to examine malnutrition [25].

Glutamine is an amino acid nutrient that helps metabolic processes, improves the function of the digestive tract barrier, and regulates cell proliferation. The correlation between glutamine and SGA can be related to the fundamental properties of glutamine as a nutrient [26]. Adequate nutritional intake is one of the components assessed in SGA, therefore, glutamine intake which is a nutrient also helps increase SGA because it fulfils one of its components. However, the findings regarding the decrease in SGA due to glutamine can also be based on the correlation between glutamine and nutrient intake itself. Glutamine has been found to improve the tight junction system in the small intestine and repair damaged intestinal barriers by increasing transepithelial electrical resistance (TER). The glutamine mechanism can go through its effect in reducing permeability, which results in decreased transport in the intestine [27]. Low intestinal permeability can make it difficult for nutrients to be absorbed in the small intestine. Based on this mechanism, it can be concluded that glutamine allows a decrease in nutrient absorption, which results in inadequate nutritional intake, so the SGA value in this study did not increase significantly.

Based on the results of data analysis, preoperative administration of glutamine significantly reduced LOS in hospitalized patients. These findings are similar to previous studies, which reported a reduction in postoperative infection rates of 42% in patients receiving standard isocaloric/isonitrogenous tube feeds to 28% in patients receiving interventions in the form of high arginine and glutamine nutrition orally before surgery [28]. A decrease in LOS in the hospital was also reported by 2.1 days in the treatment group compared to the control group, especially in gastroesophageal, pancreatic, and colorectal cancer patients[29]. Previous studies also reported that administration of glutamine before and after surgery reduced the infection rate with a ratio of infection rates of 47% in the standard group to 33% in the group with glutamine administration in a population of patients with pseudocyst infection after pancreatic necrosis surgery[30].

In addition, other studies have reported that nutritional formulations containing a combination of arginine or glutamine, omega-3 fatty acids, and nucleotides can improve the immune response, oxygenation, and micro perfusion of the gastrointestinal tract. Preoperative administration of glutamine or arginine was also known to reduce the postoperative infection rate by 12% in the group receiving glutamine-containing immune nutrition compared to 32% in the group receiving isoenergetic formula, whereas the LOS of patients with glutamine was shorten and reported for 9.5 days, compared to 12 days in the control group. These findings may be due to the effect of glutamine on increasing the number and function of immune cells, gut barrier function, and regulation of cytoprotective molecules similar to the endogenous antioxidant class (glutathione). In another study, it was reported that there were no significant changes in either the number of systemic T lymphocytes or CD-4 and CD-8 T cells [31].

In another study, patients who underwent colorectal cancer surgery and received parenteral pre- and postoperative glutamine therapy (1 g/kg/day) had significantly lower rates of wound infection, intra-abdominal abscess formation, wound dehiscence and duration of hospital stay compared to patients received enteral nutrition with standard isonitrogenous and isocaloric formula for 5 days post-intervention [32].

The effects of glutamine on reducing the duration of hospitalization and infection rates can be mediated through the capacity of glutamine to increase T-lymphocyte proliferation and normal immune function, as well as regulation of intracellular energy production. In addition, glutamine also acts as a nucleotide precursor needed for cell proliferation and protein synthesis. It can reduce the production of IL-2 cytokines, which acts as regulators of the immune system and activate NK cells [11,33]. Glutamine can also accelerate wound healing, thereby reducing infection risks by increasing fibroblast cell proliferations. In addition, the proline molecule, a product of glutamine metabolism, is also known to play an essential role in collagen production. What is more, glutamine can be metabolized to arginine, that functions as an accelerator of wound healing [3,34].

Parenteral nutrition formulations containing glutamine are generally used in the management of gut-associated lymphoid tissue (GALT) atrophy that occurs as a result of long-term parenteral nutrition, therefore it can also help to prevent digestive tract immune system dysfunction and enterocyte atrophy in patients with complete parenteral nutrition and prevent the risk of infection spontaneously. This study also found that preoperative glutamine gave significant results on albumin differences in colorectal cancer patients with malnutrition. This is in line with a study conducted by Jin-Ming Wu et al. (2020), which stated that parenteral glutamine increased albumin levels in post-gastrectomy gastric cancer patients. The mechanism by which glutamine can increase serum albumin levels is through its effect on the process of osmotic balance, which in turn also increases the number of hepatocytes. Improved liver function affects anabolic processes, such as the synthesis of glycogen, fat, and protein but also reduces proteolysis mediated by activation of the P38 mitogen protein kinase signal [35].

Based on the results of data analysis, preoperative administration of glutamine gave significant results on the difference between SGOT and SGPT in colorectal cancer patients with malnutrition. This can also be seen from the research conducted by Syahrizal et al. (2020), who proved that there was a positive correlation between the protective effect of glutamine on the transaminase enzyme, in which the research was conducted on rats given lead and the levels of the transaminase enzyme were measured after being given glutamine. This is because glutamine is a potent scavenger, that is able to block damage to the autocatalytic process of lipid peroxidation of cell membranes to maintain the integrity of the cell itself. Besides that, the administration of glutamine is also thought to improve the condition of the body's antioxidant system by increasing levels of reduced glutathione, where glutathione is an endogenous antioxidant that has protective function. A decrease in glutathione levels is the leading cause of hepatotoxicity in the liver [36].

CONCLUSION

The conclusions that can be drawn from this study are as follows:

(1) Preoperative administration of glutamine in colorectal cancer patients with malnutrition has no significant association with the Modified Glasgow Prognostic Score (mGPS) and Subjective Global Assessment (SGA).
(2) Preoperative administration of glutamine in colorectal cancer patients with malnutrition is significantly associated with reducing the length of stay (LOS), increasing patient's body weight, and increasing patient's BMI.
(3) Preoperative administration of glutamine in colorectal cancer patients with malnutrition is significantly associated with albumin difference, SGOT difference, SGPT difference, and WBC difference.

Author Contribution Statement

DN wrote the main manuscript text and reviewed the manuscript.

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Approval

The Udayana University approved ethical the study.

Ethical Declaration

Our data was extracted from Prof. Dr. IGNG Ngoerah Center General Hospital Denpasar.

Data Availability

Our data is enclosed within this manuscript.

Conflict of Interests

No conflicts of interest to disclose.

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