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ORIGINAL ARTICLE – OPEN ACCESS

The Effects of Arginine and Glutamine Used Before Laparoscopic Cholecystectomy on Postoperative Stress Hormones

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ABSTRACT

Objective: Enteral nutrition products containing amino acids of glutamine and arginine were administered to patients to be operated under general anesthesia and the response of stress hormones after surgery was evaluated after surgery. The aim of this study is to examine the effect of enteral nutrition, which is provided 3 days before the surgery and includes glutamine and arginine amino acids, on the stress hormones of the patients.

Materials and Methods: In this study, a total of 60 patients were included and randomly assigned to three different groups (n = 20): glutamine group, arginine group, and control group. The patients who were above 18, were classified as ASA 1–2, and were not pregnant were recruited in this study. All groups except the control group were administered with glutamine (3*2) and arginine (2*1) 3 days before the study was conducted. Cortisol, insulin, insulin resistance, and glucose levels were measured at the 3rd and 24th hour before and after the surgery. All of the participants underwent laparoscopic cholecystectomy in the general surgery clinic department.

Results: Although significant results were obtained regarding the insulin and insulin drain groups in the glutamine and arginine groups compared with the control group, no significant results were found between the glutamine and arginine groups. Among the three groups, significant results were obtained from the arginine group. When all groups were compared, the hospital stay of the patients in the arginine group was shorter than the others. Moreover, the insulin resistance and cortisol levels in the arginine group were slightly increased.

Conclusion: Overall, it was observed that arginine and glutamine amino acids administered before surgery can reduce the surgical stress levels of patients.

Keywords: Laparoscopic cholecystectomy, arginine, glutamine, stress hormones, surgical stress

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INTRODUCTION

Stress is a situation characterized by several factors and leads to imbalances in the metabolism, nervous system disorders, and psychic tension (1). Following an unpleasant event or situation, individuals mostly show physical, emotional, mental, and behavioral reactions. Even though they consider themselves as not being affected by the so-called situation, they may unintentionally demonstrate some reactions (2). Stress triggers (stressors) could include the following: cold, hot, X-rays, less oxygen source, surgical or medical treatments, infections, malnutrition, pain, obesity, old age, tuberculosis basil, extended muscular exercises, depression, and anxiety (3). In the present study, we investigated the effect of anabolic amino acids, arginine, and glutamine on stress hormones to reduce the anxiety and stress attributed to surgery. Based on the findings of this study, which are supported by the existing literature, we can conclude that providing patients with anabolic amino acids, arginine, and glutamine may reduce their surgical stress levels when compared to those who did not receive any support and thereby accelerate their recovery.

MATERIALS and METHODS

This study was conducted in the General Surgery Clinic of The Amasya University Sabuncuoğlu Şerefetin Training and Research Hospital. A total of 60 patients were included and randomly assigned to three groups: glutamine group, arginine group, and control group. The glutamine group was administered with enteral solution containing glutamine amino acids, whereas the arginine group was administered with enteral solution containing arginine amino acids. The control group, on the other hand, took regular diets. The patients in the experimental groups (glutamine and arginine groups) were advised to take regular diets as well.

Patients who were above 18, were classified as ASA 1–2 according to the American Society of Anesthesiologists (ASA) physical status classification system, and were not pregnant were recruited in this study. They were subjected to elective laparoscopic cholecystectomy. The exclusion criteria are as follows: under the age of 18 and over 70; pregnant; having a fasting blood glucose above 106 mg/dl and below 80 mg/dl; not diagnosed with

diabetes; presenting with metabolic disease, chronic heart disease, and chronic obstructive pulmonary disease (COPD). The length of hospital stay was also noted in all groups.

In the study, blood cortisol, insulin, blood glucose, and insulin resistance levels were recorded 3 days before surgery and at the 3rd and 24th hour after surgery in all groups.

In all groups, blood cortisol (6.02 mg/dl<normal<19.4 mg/dl), insulin (2.5 mg/dl<normal<24.9 mg/dl), glucose (80 mg/dl<normal<106 mg/dl), insulin resistance (HOMA-IR) (normal<2,5 mg/dl), and hormonal and biochemical samples were obtained from the patients 3 days before the planned day of surgery.

Clinical, Surgical, And Laboratory Investigations

The glutamine group was orally administered with two packets of Resource Glutamine® powder diluted into 200 ml of water three times a day for 3 days. The patients were asked not to take any food or drink as of the midnight (00:00) before the surgery. Blood cortisol, insulin, glucose, insulin drain, and albumin hormone and biochemical samples were obtained from the patient at the 3rd and 24th hour after the operation, and the samples were examined in the hospital laboratory.

The arginine group was orally administered with a packet of Abound® powder diluted into 200 ml of water two times a day for 3 days. The patients were asked not to take any food and drink as of the midnight (00:00) before the surgery. Blood cortisol, insulin, glucose, insulin drain, and albumin hormone and biochemical samples were taken from the patients at the 3rd and 24th hour after the operation, and the samples were examined in the hospital laboratory.

As opposed to the other groups, Resource Glutamine® powder and Abound® powder were not administered to those in the control group. Instead, the patients in the control group maintained their routine daily diets, but the same tests were conducted.

Resource Glutamine®: It is a nutritional preparation that contains glutamine amino acids, particularly in the form of powder used orally in wound healing, immune system regulation, and nutrition. It is added into 200 ml of water and taken orally. Its recommended regular dose is 3*2 posology according to the Ministry of Health. The product used in this study was donated to the hospital.

Abound®: It is a nutritional preparation which contains oral glucose, arginine, and hydroxymethylbutyrate, especially in the form of powder used in wound healing, immune system regulation, and nutrition. It is added into 200 ml of water and taken orally. Its recommended regular dose is 2*1 posology according to the Ministry of Health. The product used in this study was donated to the hospital.

Ethics Committee Approval

The Ethical Committee of the Ondokuz Mayıs University Faculty of Medicine, approved this study (KAEK 2019/42).

Statistical Analysis

The obtained data were analyzed using SPSS (Statistical Package for the Social Sciences) version 16.0 package program. At this point, it was found that the data did not show normal distribution as the significant values of the Shapiro-Wilk test were less than 0.05. Therefore, the data were analyzed using the Mann-Whitney U test, one of the non-parametric tests. During the statistical analyses, p-values less than 0.05 were considered statistically significant. In the power analysis performed using the G power program, a sample size of 20 subjects in each group, average of 1.56 unit difference between the groups, 0.8 unit standard deviation, 95% confidence interval, and at least 95% test power were calculated. Since the sample has more than one group, one-way ANOVA test and non-parametric Mann-Whitney U test were used to assess the groups among themselves.

RESULTS

In this study, a total of 60 patients were included and randomly assigned to three different groups (n=20): glutamine group, arginine group, and control group. The mean age of the patients was 50.2. 21.7% of the patients were male. 46.7% were operated with the risk of ASA 1, whereas 53.3% with the risk of ASA 2. BMI values were in the range of 20–25 in all patients. In the Shapiro-Wilk normality test, the groups were not normally distributed. When the three groups were compared to each other, a significant difference was observed in the postoperative insulin and insulin resistance values ($p<0.05$) (Table 1). On the other hand, when the groups were compared using the Mann-Whitney U test, a significant difference was observed between the control group and the glutamine group, between the control group and the arginine group, and between insulin and insulin resistance, but no significant difference was observed in the cortisol and glucose levels. However, unlike the glutamine and arginine groups, no significant results were found in the control group. When the groups were compared, significant results were found in the arginine group rather than the control and glutamine groups (Table 2). Additionally, no significant differences were found between the male and female participants according to the results of the chi-square test ($p>0.05$). When all groups were compared, the hospital stay of the patients in the arginine group was shorter than that in the other groups ($p<0.05$). Moreover, the insulin resistance and cortisol levels increased slightly in the arginine group.

DISCUSSION

Stress is an emotional state triggered by various factors, such as imbalance in body work, disorders in the nervous system, and psychic tension. Following an unpleasant event or situation, individuals mostly show physical, emotional, mental, and behavioral reactions. Response to stress and related complications constitute metabolic responses leading to trauma and tissue damage. An examination of the literature on the studies conducted with arginine and glutamine amino acid support has revealed that its effects on direct surgical stress were not examined, but positive effects were observed on blood glucose regulation (4) and the level of stress hormones, particularly in cancer patients (5) and those undergoing supportive therapy (6). Furthermore, it was found that necrotizing enterocolitis was less common in patients administered with arginine and glutamine supplementation, especially in newborns and patients recovered earlier (7). In studies that investigated the efficacy of arginine and glutamine amino acid support, it was found that its effects on direct surgical stress were

Table 1. Statistical analysis results between the arginine, glutamine, and control groups

Groups	Cortisol			Insulin			Glucose			Insulin resistance			Albumin		
	BS	3^{rd} h AS	24^{th} h AS	BS	3^{rd} h AS	24^{th} h AS	BS	3^{rd} h AS	24^{th} h AS	BS	3^{rd} h AS	24^{th} h AS	BS	3^{rd} h AS	24^{th} h AS
Glutamine															
Arginine	0.563	0.977	0.564	1.000	0.987	0.645	0.031	0.735	0.260	0.232	0.968	0.380	0.471	0.314	0.346
Control	0.494	0.985	0.508	0.024	0.030	0.047	0.059	0.486	0.537	0.016	0.099	0.082	0.998	0.658	0.758
Arginine															
Glutamine	0.563	0.977	0.564	1.000	0.987	0.645	0.031	0.735	0.260	0.232	0.968	0.380	0.471	0.314	0.346
Control	0.086	0.999	0.996	0.026	0.020	0.284	0.961	0.915	0.864	0.451	0.058	0.673	0.506	0.824	0.769
Control															
Glutamine	0.494	0.985	0.508	0.024	0.030	0.047	0.059	0.486	0.537	0.016	0.099	0.082	0.998	0.658	0.758
Arginine	0.086	0.999	0.996	0.026	0.020	0.284	0.961	0.915	0.864	0.451	0.058	0.673	0.506	0.824	0.769

BS: Before surgery; AS: After surgery; h: Hour

not significant. For this reason, in the present study, we investigated whether we could reduce the surgical stress after the operation. Particularly, in cancer patients (5) and patients undergoing supportive therapy in intensive care units (6), significant positive effects on blood sugar regulation (4) and stress hormones were observed. Additionally, it was determined that necrotizing enterocolitis was less common in patients given arginine and glutamine supplementation in newborns and patients recovered earlier (7). We also found similar findings in our study. We observed that our patients were mobilized earlier in the postoperative period and their mood was better compared with control group. Visser et al. (8) have developed strategies to suppress stress response which could prevent postoperative negative results. Similarly, in their study in 2018, Picard, Martin, et al. (9) found that the autonomic nervous system, hypothalamus-pituitary-adrenal axis, and cardiovascular, metabolic, and immune systems protect the body against internal and external stress during allostasis which has the ability to maintain the body's stability against stressors. Such changes as enlargement in the adrenal gland cortex, atrophy of the thymus and other lymphoid structures, bleeding ulcers in the stomach and duodenum, immune system deficiency, and wound healing problems in patients having undergone surgery are susceptible to the effect of stressors. This mostly leads to postoperative wound healing problems, mood disorders, and an increase in hospital admission days (10). In the present study, based on the evaluation of the patients by the psychiatry clinic, the emotional states of the patients were better and their hospital admission period was shorter, as was found in the study conducted by Hattori et al. (10) It was also found that the patients returned to their social life earlier. Selye et al. argued that in the alarm stage of the "general adaptation syndrome," which they determined in 1946, the central nervous system is activated, the body defense systems are mobilized, and the stressor pituitary gland and sympathetic nervous system are triggered. During the resistance or adaptation stage, cortisol, norepinephrine, and epinephrine are released from the adrenal gland at high levels. Finally, they mentioned that if the adaptation is successful in the stage of exhaustion and the stress is persistent, the compensatory mechanisms could be destroyed, the immune system could be suppressed, and heart and kidney problems and other diseases could occur (11, 12). In our research, we interfered with the increase of cortisol level, especially in the second phase of adaptation, and found that especially cortisol, insulin, and insulin resistance decreased significantly. Raghav et al. argued that by eliminating stress, inactivation will occur and cortisol and catecholamine secretions will return to their regular values. On the other hand, if inactivation is not sufficient, they mentioned that exposure to stress hormones could be excessively prolonged. This also indicated that exposure to stress hormones for weeks, months, and years could lead to allostatic load and physiopathological consequences (13, 14). This condition may lead to delayed bowel movements, especially delayed or even scarring surgical patients. In our research, we found that the patients who were administered with enteral solutions containing arginine and glutamine amino acids had lower stress hormone levels, performed their physiological functions earlier, and left the hospital earlier. Some evidence suggest that the main purpose of dealing with stress is to eliminate early stress exposure in the organism exposed to stress or to minimize the impact of the stressor. If the so-called stressor is surgical trau-

Table 2. Statistical analysis results of the arginine, glutamine, and control groups using Mann-Whitney U test

	N	Mean	SD	Min.	Max.	Mann-Whitney U (p value)		
						GA	AC	GC
Cortisol								
Before surgery	60	12.9612	4.92918	5.35	28.8	0.588	0.088	0.16
3rd hour after surgery	60	18.0965	8.22451	5.79	41.68	0.735	0.978	0.57
24th hours after surgery	60	8.7813	6.53491	0.69	50.57	0.685	0.978	0.685
Insulin								
Before surgery	60	10.2712	5.87208	1.86	31.9	0.871	0.007	0.002
3rd hour after surgery	60	18.4152	17.78311	1.29	85.3	0.776	0.006	0.001
24th hours after surgery	60	20.428	17.42146	1.4	84.3	0.552	0.025	0.009
Glucose								
Before surgery	60	109.72	23.501	85	201	0.018	0.551	0.021
3rd hour after surgery	60	141.58	42.977	85	245	0.402	0.882	0.291
24th hours after surgery	60	125.57	45.925	65	354	0.401	0.871	0.465
Albumin								
Before surgery	60	43.92	3.29601	35.7	50.6	0.304	0.33	0.968
3rd hour after surgery	60	39.0217	2.93316	33.1	47.1	0.185	0.507	0.525
24th hours after surgery	60	38.5617	3.20016	31.5	45.4	0.199	0.598	0.372
Insulin Resistance								
Before surgery	60	3.5112	3.97251	0.41	28.6	0.133	0.006	0.001
3rd hour after surgery	60	7.5905	9.56662	0.28	51.6	0.579	0.033	0.001
24th hours after surgery	60	7.2373	8.08774	0.36	44.7	0.457	0.083	0.015

SD: Standard deviation; Min.: Minimum; Max.: Maximum; GA: Glutamine-arginine; AC: Arginine-control; GC: Glutamine-control

ma, it should be intended to decrease the catecholamine levels triggered by the stressor. As stated in our study, arginine and glutamine amino acids administered before surgery may lessen the surgical stress. Although significant results were observed in reducing the surgical stress in both the glutamine group and arginine group compared to the control group, the effect was more significant in the arginine group. Even though arginine and glutamine both have similar amino acid structures, we assume that the more significant effect of arginine may be due to the fact that glutamine, hydroxymethylbutyrate, and arginine are present in Abound® powder.

Therefore, we suggest that further research on the effect of hydroxymethylbutyrate should be conducted and new studies should recruit more cases with similar types of diets administered days before surgery.

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Ethics Committee Approval: The Ondokuz Mayıs University Clinical Research Ethics Committee granted approval for this study (date: 17.01.2019, number: KAEK 2019/42).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept – YP, VT; Design – YP, VT; Supervision – YP, VT; Resource – YP, VT; Materials – YP, VT; Data Collection and/or Processing – YP, VT; Analysis and/or Interpretation – YP, VT; Literature Search – YP, VT; Writing – YP.

Conflict of Interest: The authors have no conflict of interest to declare.

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