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Glutamine Supplemented Parenteral Nutrition to Prevent Ventilator-Associated Pneumonia in the Intensive Care Unit

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ABSTRACT

Objective: Ventilator-associated pneumonia (VAP) is a form of nosocomial pneumonia that increases patient morbidity and mortality, length of hospital stay, and healthcare costs. Glutamine preserves the intestinal mucosal structure, increases immune function, and reduces harmful changes in gut permeability in patients receiving total parenteral nutrition (TPN). We hypothesized that TPN supplemented by glutamine might prevent the development of VAP in patients on mechanical ventilator support in the intensive care unit (ICU).

Material and Methods: With the approval of the ethics committee and informed consent from relatives, 60 patients who were followed in the ICU with mechanical ventilator support were included in our study. Patients were divided into three groups. The first group received enteral nutrition (n=20), and the second was prescribed TPN (n=20) while the third group was given glutamine-supplemented TPN (n=20). C-reactive protein (CRP), sedimentation rate, body temperature, development of purulent secretions, increase in the amount of secretions, changes in the characteristics of secretions and an increase in requirement of deep tracheal aspiration were monitored for seven days by daily examination and radiographs.

Results: No statistically significant difference was found among groups in terms of development of VAP (p=0.622).

Conclusion: Although VAP developed at a lower rate in the glutamine-supplemented TPN group, no statistically significant difference was found among any of the groups. Glutamine-supplemented TPN may have no superiority over unsupplemented enteral and TPN in preventing VAP.

Key Words: Nutritional support, glutamine, ventilator-associated pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is the most frequent infection seen among intensive care patients (1). Its prevalence varies depending on care conditions of the intensive care unit (ICU), number of beds, duration of ventilatory support, and underlying disease. The most important factor affecting the incidence of VAP is the duration of supportive treatment. As the length of supportive treatment is prolonged, VAP prevalence increases by 1-3% every day. This infection is significant because the risk of mortality is 2-10 fold higher in patients who develop VAP (2, 3). Glutamine is the most abundant free amino acid in plasma and body fluids. Although it is non essential in healthy people, glutamine may be essential in critically ill patients (4). It is the primary energy source for the enterocyte. This substance preserves intestinal mucosal structure, increases immune function and offsets harmful changes in gut permeability in patients receiving total parenteral nutrition (TPN) (5). Administration of glutamine to patients of multiple trauma reduces the incidence of bacteremia, pneumonia and sepsis. A decrease in glutamine plasma concentration impairs the structure of intestinal mucosa (6, 7). Although some studies have investigated the effect of TPN supplemented with glutamine on infectious complications, as far as we know, no study has yet analyzed its effect on the incidence of VAP.

In the present study, we investigated whether glutamine-supplemented TPN was superior to enteral and parenteral nutrition in preventing the development of VAP in patients with mechanical ventilatory support.

Material and Methods

After an ethics committee approval and informed consent from the relatives of the patients were obtained, 60 patients between the ages of 18-65 who had received mechanical support for at least seven days were included in this study. The study was planned as a prospective randomized study. Patients were randomized according to the sequence of admittance to the intensive care unit. Patients with brain death, lung infection, adult respiratory distress syndrome (ARDS), aspiration history and those who had a diagnosis of pneumonia at the time of admission to ICU were excluded from the study. Patients with diabetes mellitus, hypertension and chronic cardiac diseases were evaluated as chronic diseases. We performed routine catheterization of the internal jugular vein, radial artery, stomach and bladder in all patients. The participant's daily calorie need was calculated as

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25-30 kcal/kg a day (45% carbohydrate, 35% lipid and 20% protein). Group 1 received enteral nutrition solutions, while TPN was administered to the second group (Group 2). Group 3 was given TPN supplemented with 40 g glutamine; the patients received these nutritional regimens daily. According to the calculated daily needs, enteral solutions containing 1 kcal/mL were administered. The TPN solution was used at a concentration of 1 mL/kcal that contained 20-30% dextrose, 20% lipid and 5.4-10% amino acid. Insulin was used to buffer the TPN solution according to its dextrose content. Serum electrolytes were replaced depending on the serum electrolyte levels of the patients. Nutrition was started at one third of the daily calorie need, and a complete dose was reached on the third day. Leukocytes were investigated daily. Results over 10,000 mm^3 were regarded as leukocytosis, and those under 4,000 mm^3 were labelled leukopenia. C-reactive protein (CRP) was evaluated at 48, 96 and 144 hours following admission, while sedimentation rate was assessed at 48 and 144 hours. Fever was monitored daily. A body temperature over 38°C was considered to be a fever. When a patient's body temperature exceeded 39°C, blood cultures were taken. Lung radiographs were taken daily to check for infiltration. Newly developing purulent secretions, an increase in the amount of secretions, changes in the nature of secretions, or an increase in deep tracheal aspiration requirements were closely monitored. Arterial blood gases were measured four times per day. Lungs were examined daily for rales and rhonchi. At 24 and 120 hours after admission to the ICU, a deep tracheal aspirate (DTA) was obtained to evaluate leukocyte count and for gram staining and culture. Gram staining results were evaluated as follows:

- No or few leukocytes: 0
- Between 2-6 leukocytes: 1
- Many leukocytes: 2
- No microorganisms: 0
- Microorganisms present: 1

The sample sizes were calculated with the assumption of a possible difference in VAP development ratio of at least 35% between any two groups. Therefore, 20 patients were allocated into each group in order to obtain an alpha error of 5% and statistical power of 80%.

Statistical analysis

Statistical calculations were performed with the Number Cruncher Statistical System (NCSS) 2007 (Utah, US) statistical software program for Windows. Besides standard descriptive statistical calculations (mean, standard deviation, median, interquartile range (IQR), frequency), a one-way analysis of variance (ANOVA) was used in the comparison of groups for parametric variables. For non-parametric variables, the Kruskal Wallis test was used to compare groups; a post hoc Dunns multiple comparison test was used in the comparison of subgroups, while the Friedman test was employed in the assessment of treatment values. Chi square test was performed during the evaluation of our qualitative data, and McNemar's test was employed in the assessment of pre- and post-treatment values. Statistical significance level was established at $p<0.05$.

Results

No statistically significant differences were present among groups in terms of demographic characteristics, Glasgow coma score (GCS), Apache II score (Table 1), other chronic disease, steroid treatment, presence of chest tube, fever, secretion increase, ronchus, increase in the need for oxygen, or development of infiltration ($p>0.05$) (Table 2).

No statistically significant difference was observed between the 48-, 96- and 144-hour CRP values of the three groups ($p=0.957$, $p=0.123$ and $p=0.297$, respectively). We also found no statistically significant difference between the 48- and 144-hour sedimentation rate values of all groups ($p=0.617$ and $p=0.664$). Finally, we did not record a statistically significant difference between the 48- and 144-hour sedimentation rate values of each group ($p=0.131$, $p=0.184$ and $p=0.191$, respectively) (Table 3).

Table 2. The distribution of chronic disease, steroid treatment, the presence of chest tube, fever, secretion increase, ronchus, lung infiltration and increase in need for oxygen

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	p
Chronic disease	5 (25%)	10 (50%)	9 (45%)	0.233
Steroid treatment	15 (75%)	13 (65%)	15 (75%)	0.720
Chest tube	4 (20%)	1 (5%)	3 (15%)	0.364
Fever	8 (40%)	7 (35%)	6 (30%)	0.803
Increase in Secretion	10 (50%)	11 (55%)	9 (45%)	0.819
Rhonchus	6 (30%)	5 (25%)	4 (20%)	0.766
Lung infiltration	4 (20%)	5 (25%)	2 (10%)	0.459
Increase in need for oxygen	2 (10%)	4 (20%)	1 (5%)	0.322

Table 1. Demographic data of the groups, GCS and APACHE II scores

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	p
Age (year)	33.55±14.14	45±18.2	36.35±16.37	0.119
Sex (M/F)	11 (55%)/9 (45%)	10 (50%)/10 (50%)	9 (45%)/11 (55%)	0.819
GCS	8.40±1.98	7.30±2.23	7.40±2.74	0.247
APACHE II score	20.75±4.74	20.75±5.85	21.45±5.99	0.976

GCS: Glasgow Coma Scale
APACHE II: Acute Physiology and Chronic Health Evaluation Score

When groups were compared in terms of leukocyte numbers, no significant difference was found (p>0.05). No statistically significant difference was observed betweeen the leukocyte averages taken on days 1, 2, 3, 4, 5, 6, and 7 or between all individual measurement times for all groups (p>0.05) (Table 3). Leukopenia did not occur in any of the patients.

In samples obtained by DTA 24 and 120 hours after admisssion to the ICU, no statistically significant difference between the number of leukocytes as examined by gram staining was found among the groups (p=0.321 and p=0.115). No statistically significant difference was found in the groups (p=0.214, p=0.446 and p=0.261) (Table 4).

In gram staining done on samples obtained from DTAs at 24 and 120 hours following admisssion to the ICU, no statistically significant difference was found among groups in terms of the presence of microorganisms (p=0.054 and p=0.921). There was also no statistically significant change 24 and 120 hours after admission in the presence of microroganisms in gram stains in all groups (p=0.116, p=0.998 and p=0.998, respectively). We saw no statistically significant change at 24 and 120 hours after admission in proliferation in the DTA cultures in the groups (p=0.004, p=0.008 and p=0.031). There was no statistically significant change at 24 and 120 hours in the DTA culture proliferation among groups (p=0.851 and p=0.819). No statistically significant difference was found among groups in proliferation of blood cultures (p=0.349) and in terms of the development of VAP (p>0.05) (Table 5).

Discussion

Mechanical ventilation prolonged for more than 48 hours is the most important risk factor for VAP. Other independent risk factors include a patient age over 65 years, serum albumin levels lower than 2.2 gr/dL, ARDS, chronic obstructive pulmonary disease, coma and impairment of consciousness, burns, trauma, organ failure, severe critical disease, gastric aspiration at high volume, increase in gastric pH, gastric colonization, sinusitis, paralytic agents, continuous intravenous sedation, positive end expiratory pressure (PEEP), frequent changes of mechanical ventilator cycle, reintubation, nasogastric tube, supine head position, transport from ICU to outside, witholding of antibiotic treatment, or indequate treatment (8-15). In our study, of the aforementioned risk factors, mechanical ventilation application longer than 48 hours, head trauma, sedation,

Table 3. Comparison of measurement times CRP, sedimentation rate and leukocytes in the groups

		Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	p
CRP	48th hour	79.6±66.22	75.3±60.13	73±60.11	0.957
	96th hour	97.9±73.29	80.45±64.43	70.35±73.77	0.123
	144th hour	96.05±71.04	78.85±66.68	68.6±61.77	0.297
	p	0.397	0.404	0.109	
Sedimentation rate	48th hour	23.6±17.49	29.2±26.12	22.95±19.92	0.617
	144th hour	29.9±19.95	33.25±20.1	26.1±14.44	0.664
	p	0.131	0.184	0.191	
Leukocytes	1st day	11980±6229.52	12295±4765.61	11030±3752.91	0.978
	2nd day	10020±4888.94	16740±20136.28	10925±3859.76	0.116
	3rd day	10525±5963.92	13250±9437.41	9630±2715.09	0.818
	4th day	11425±6484.06	12714.5±6875.39	10032.5±3453.99	0.695
	5th day	11220±5059.81	13303±7950.28	12450±7298.34	0.715
	6th day	12275±4936	15030±6963.22	11945±7236.27	0.358
	7th day	12480±4992.58	13180±7699.87	10765±5756.58	0.113
	p	0.067	0.543	0.521	

Table 4. The distribution of patients according to number of leukocytes in gram staining

	Group 1 (n=20)			Group 2 (n=20)			Group 3 (n=20)			p
	none	between	over	none	between	over	none	between	over	
GS 24 Leukocyte	9 (45%)	8 (40%)	3 (15%)	9 (45%)	8 (40%)	3 (15%)	6 (30%)	6 (30%)	8 (40%)	0.321
GS 120 Leukocyte	7 (35%)	5 (25%)	8 (40%)	9 (45%)	7 (35%)	4 (20%)	3 (15%)	5 (25%)	12 (60%)	0.115
p		0.214			0.446			0.261		

GS 24 Leukocyte: Number of leukocytes in gram staining at 24th hour
GS 120 Leukocyte: Number of leukocytes in gram staining at 120th hour

Table 5. The distribution of the presence of microroganisms in gram staining, proliferation in cultures from deep tracheal aspirate (DTA) and blood cultures, patients according to the development of VAP in the groups

		Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	*p
		Presence	Presence	presence	
In gram staining	24th hour mic.	7 (35%)	14 (70%)	13 (65%)	0.054
	120th hour mic.	14 (70%)	15 (75%)	14 (70%)	0.921
	p	0.116	0.998	0.998	
DTA culture	24th hour mic. proliferation	2 (10%)	2 (10%)	3 (15%)	0.851
	120th hour mic. proliferation	10 (50%)	11 (55%)	9 (45%)	0.819
	p	0.004	0.008	0.031	
Proliferation of blood culture		2 (10%)	0 (0%)	1 (5%)	0.349
Development of VAP		9 (45%)	10 (50%)	7 (35%)	0.622

paralytic agent employment, PEEP application, and placement of a nasogastric tube were present. However, care was taken to change the mechanical ventilation cycle frequently and to keep the head at a 30-40 degree angle. In addition, we also studied patients under 65 years old, which may have affected our results. According to consensus criteria, the diagnosis of VAP requires at least two of the following criteria: fever over 38°C, leukocytosis or leukopenia, and increase in purulent respiratory secretions[2]. In some studies, it has been reported that new and persistant infiltrations on lung radiography, abundant purulent tracheobronchial secretions, fever of 38°C or higher, leukocytosis, and impaired gas exchange are required for a diagnosis of VAP (16). In the present study, however, we diagnosed VAP according to the consensus criteria. Various studies have reported that the presence of leukocytosis and purulent secretions is highly sensitive for the diagnosis of VAP, even if their specifity is weak. However, over prolonged periods, the development of purulent bronchitis may lead to false positive results by inducing leukocytosis. Moreover, the volume of tracheobronchial secretions and the degree of purulance may be evaluated subjectively (17).

Life-threatening bacteremia may develop as a result of insufficiency in the intestinal barrier and bacterial translocation in patients with burn injuries (18). Two important factors may lead to bacterial translocation in the gastrointestinal system: mesenteric hypoperfusion and long-term nonuse of the intestine. The risk of sepsis originating from the gastrointestinal system may be decreased by enteral nutrition, which abolishes these factors. Enteral nutrition products have positive effects on intestinal cell viability and functions of the mucosal barrier. The risk of sepsis derived from the gastrointestinal system may be decreased by enteral nutrition abolishing these factors. Enteral nutrition products have positive effects on intestinal cell viability and functions of the mucosal barrier (19). However, although early initiation of enteral nutrition is usually beneficial, it has disadvantages, such as gastric colonization, gastroesophageal reflux, aspiration, and increase in the incidence of pneumonia (20-22). It has been demonstrated that, in patients on TPN, as intestinal permeability and bacterial translocation increase, rapid alterations occur in secretory immunoglobulin A (IgA) levels, B cells and intestine-dependent lymphoid tissue T cells in the intestines. In the respiratory tract mucosal immunity, which is dependent upon IgA, is impaired, and neutrophil functions are disturbed; mucosal atrophy also develops in the gastrointestinal tract (23). Therefore, in animal studies, enteral and parenteral glutamine supplementation has dramatic effects on the maintenance of intestine-dependent lymphoid tissue T cells; glutamine-enriched TPN also markedly reduces mucosal hypoplasia, which occurs in patients on long-term TPN (24). In human models, it was proposed that glutamine supplementation has similar effects (25). In some controlled studies and cases with short intestine syndrome on long-term TPN, glutamine is useful for intestinal adaptation; other studies have stated that it leads to a decrease in the incidence of infections due to its role in immune function (26-28). According to Yeh et al. (29) TPN supplemented with glutamine apparently reduced postoperative inflammation and immunosuppression in patients undergoing gastrointestinal surgery. Nevertheless, a study investigating the effect of glutamine on the development of acquired infections reported that the administration of glutamine along with TPN did not prevent the development of acquired infections but did reduce the risk of death (28).

Wernermen et al. (30) stated that a shortage of glutamine is reflected as a decrease in plasma concentration, which is a poor prognostic sign for septic patients, because glutamine is a precursor for nucleotide synthesis. Grau et al. (31) studied the effect of alanine-glutamine dipeptide supplemented TPN on incidence of nosocomial infections and found that TPN supplemented with alanine-glutamine in ICU patients is associated with reduced occurence rate of infectious complications. Although glutamine seems to have an effect on the immune system, antioxidant status and glucose metabolism, the benefit of exogenous glutamine on morbidity and mortality is not universally accepted (32).

Of the patients who developed VAP in this study, there were differences amongst the three groups. In Group 1, six experienced fever, and leukocytosis was documented in eight patients, while all Group 1 patients had an increase in secretions. In Group 2, fever occurred in six patients, and leukocytosis and

an increase in secretions were seen in all of the patients. For Group 3, fever occurred in four patients, and secretion increases were seen in six patients; all had leukocytosis. In previous studies, the prevalence of VAP has been reported to vary between 6-52% (33), and the rate of pneumonia is typically 6-21% higher in intubated patients (2). In a different study, the incidence of the development of VAP was followed in a few different ICUs for a period of 15 months between 2006-2007. VAP developing in the first few days was diagnosed as early VAP, while that developing after five or more days was termed late VAP. The incidence of early VAP was 41.7%, and the incidence of late VAP was 58.3% (34). In the present study, VAP developed at the rates of 45%, 50% and 35% in Groups I, II and III, respectively, at the end of seven days. The main limitation of our study is the low patient numbers in the groups.

Conclusion

We initially expected a difference as high as 35% in VAP development ratios between groups, but the difference remained only at 15%. Further studies investigating larger number of patients are required to clarify the issue.

Conflict of Interest

No conflict of interest was declared by the authors.

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