The effects of oral liquid and intravenous glutamine on bowel adaptation in a rabbit short bowel syndrome model

Oral sıvı ve intravenöz glutaminin kısa barsak sendromu geliştirilmiş tavşanlarda barsak adaptasyonu üzerine etkileri

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Background/aims: *The aim of this study was to examine whether liquid glutamine given to rabbits after resection is as effective as intravenous (iv) glutamine and to study the positive effects of glutamine on mucosal atrophy that occurs after bowel resection.* ***Methods:*** *Thirty rabbits with an average weight of 2500 g were used. On the third day, 30 rabbits were divided into three groups as follows: Group I (controls): bowel resection + oral total parenteral nutrition, Group II (oral liquid L-glutamine): Bowel resection + oral total paranteral nutrition + oral liquid L-glutamine, and Group III (iv L-glutamine): bowel resection + oral total paranteral nutrition + iv L-glutamine. On the postoperative 7th day, all subjects were sacrificed to examine intestinal adaptation indicators.* ***Results:*** *There was an increase in average villus height and crypt depth in Group III compared to the other groups (p=0.0001). In Group II, the villus height and crypt depth increased more than in Group I, but the difference was less significant (p=0.038). There was no significant difference between groups in terms of average goblet cell proliferation.* ***Conclusions:*** *In our experimental study, it was observed that the orally given L-glutamine liquid in the rabbit intestinal adaptation model prevented mucosal atrophy after 50% bowel resection and even increased mucosa mass. However, iv glutamine led to similar and even better results. Neither route of glutamine administration was determined to have an effect on goblet cell proliferation.*

Key words: Liquid glutamine, iv glutamine, bowel resection, bowel adaptation

Amaç: *Tavşanlarda rezeksiyon sonrası intestinal adaptasyon için oral yolla verilen sıvı glutaminin intravenöz (iv) verilen glutamin kadar etkili olup olmadığı ve rezeksiyon sonrası oluşan mukozal atrofiye glutaminin olumlu etkisini araştırmaktır.* ***Yöntem:*** *Çalışmada ağırlıkları ortalama 2500 g olan 30 adet erkek tavşan kullanıldı. Üçüncü günde 30 tavşan 3 gruba ayrıldı. I. grup (kontrol grubu): Barsak rezeksiyonu + oral total parenteral nutrisyon, II. grup (oral sıvı glutamin grubu): Barsak rezeksiyonu + oral total parenteral nutrisyon + oral sıvı glutamin, III. grup (iv glutamin grubu): Barsak rezeksiyonu + oral total parenteral nutrisyon + iv L-glutamin. Postoperatif 7. günde intestinal adaptasyon göstergelerinin incelenmesi için bütün denekler sakrifiye edildi.* ***Bulgular:*** *Üçüncü grupta ortalama villus yüksekliği ve kript derinliği açısından diğer gruplara oranla anlamlı bir artış olduğu görüldü (p=0.0001). İkinci grupta villus yüksekliği ve kript derinliği birinci gruba göre artmıştı fakat üçüncü gruba göre daha az anlamlıydı (p=0,038). Ortalama goblet hücre proliferasyonu yönünden tüm gruplar arasında anlamlı bir fark yoktu.* ***Sonuç:*** *Tavşanlar üzerinde yapılan deneysel çalışmamızda %50 ince barsak rezeksiyonu sonrası intestinal adaptasyonda oral verilen sıvı L-glutaminin mukozal atrofiyi önlediği, hatta mukoza kitlesinde artmaya sebep olduğu ancak iv verilen glutaminin benzer etkileri daha iyi sağladığı, her ikisinin de goblet hücre proliferasyonuna etkisi olmadığı gözlenmiştir.*

Anahtar Kelimeler: Sıvı glutamin, iv glutamin, barsak rezeksiyonu, barsak adaptasyonu

INTRODUCTION

Besides the vital functions of the digestion and absorption of food materials, the small intestine also has endocrine and immunologic functions. Massive resections, which can disorder the small intestine, lead to "short bowel syndrome". The significant decrease in the absorption surface of the intestine leads to serious diarrhea, malabsorption and malnutrition. The decrease in the absorption surface of the intestine triggers its reserve potential, and the rest of the intestine develops adapti-

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ve changes. The adaptation comes into being as a result of hyperplasia of the remaining enterocytes and an increase in the absorption surface. The intestinal villi elongate without increasing in number and the renewing speed increases. In intestinal adaptation, luminal food and endogenous and hormonal factors are effective (1). Recently, L-glutamine has also been used as a luminal food factor. In this study, using oral and intravenous (iv) L-glutamine, we aimed to examine the intestinal adaptation developed after small intestine resection in rabbits.

If a part of the small intestine is removed and the absorption surface decreases, the rest of the intestine develops an adaptation against the resection. Parameters such as increase in the intestinal mucosa, increase in the intestinal mucosal length, increase in glucose absorption, increase in intestinal mucosa mass, and enterocyte proliferation are used in the assessment of intestinal adaptation. The histopathologic indicators of these parameters are crypt depth, villus length and goblet cell number (1). The severity of the adaptation reaction is directly proportional with the length of the resected intestine. The ileum's adaptation reaction is higher than that of the jejunum. While adaptation in the immediate distal anastomosis line is stronger, adaptation decreases in conjunction with distance from the anastomosis. Intestinal adaptation begins 48 hours after the operation and can last for months. With the hyperplasia of the remaining enterocytes, the absorption surface increases, and this forms the basis of the adaptation mechanism. The intestinal villi lengthen without increasing in number. The number of the cells increases and cell renewal speeds up. The length and volume of the intestine thus increase. In this adaptation process, the most important factors that increase cellular growth are luminal factors and hormones (2, 3). After resection, the relation between food and endogenous growth factors is important in understanding the essential mechanisms behind the mucosal growth during intestinal adaptation (4, 5). In elderly patients, the intestinal adaptation is impaired and not as efficient.

The small intestine can absorb 6 to 9 liters of fluid daily. In the development of intestinal adaptation, pancreatic and bile ejections are important. The stomach, duodenum and salivary glands also have hyperplasia-producing effects. The enteroglucagons ejected from the terminal ileum and colon, epidermal growth factor (EGF), transforming growth factor-a, peptide YY, insulin-like growth factor (IGF) I-II, prostaglandins, corticosteroids, cholecystokinin, secretin, and similar factors play roles in intestinal growth and in the adaptation of the functions after intestinal resection (6-9, 10, 30). They are thought to have a stimulant effect on the adaptation by increasing endogenous ejections of foods (4, 5). It is also known that foods taken orally cause hyperplasia and hyper-function in the intestinal mucosa. The structures of the food are also important. Disaccharides, monosaccharides and long-chain triglycerides cause more simulation than medium chains. The fibrous foods, which do not have a nutritive value, have trophic effects. Glutamine is an important food source for enterocytes in the development of adaptation after small intestine resection (11, 12).

L-Glutamine

Glutamine is the most commonly used amino acid to maintain the brain's functions. Arginine, ornithine and proline are derivatives of glutamic acid synthesized from amino acids. It is abundantly found in tissues and specifically functions as an amino acid depository. Glutamine is also found in animal proteins. It regulates mental vigilance, thought and spirituality. Glutamic acid is a precursor of gamma amino butyric acid (GABA). GABA is an important neuro-transmitter in the central nervous system. Glutamic acid is a stimulator neurotransmitter that helps the potassium passage in the spinal fluid. Glutamic acid cannot pass the blood-brain barrier. However, glutamine, which is metabolism's intermediate product, can pass this barrier. Glutamine metabolite is used by cells for energy just like glucose and it is a nitrogen provider for cells. Glutamine is the most abundant free amino acid in the muscle tissue of the body, and L-glutamine protein metabolism is very important in cell growth and in preventing catabolism. Thus, it helps in the prevention of muscle collapse (13). In the stress period, glutamine gains in importance (14). It was determined that L-glutamine is an important "fuel" for intestinal mucosal cells and regulates the nitrogen level. L-glutamine is taken and used by intestinal cells both vascularly and from the lumen and it prevents mucosal atrophy (15).

MATERIALS AND METHODS

This study was carried out with the cooperation of Selcuk University Meram Faculty of Medicine, General Surgery and Pathology Departments

(2003/21). In this study, 30 male rabbits with an average weight of 2500 g were used. The rabbits were housed and cared for in special cages. In order to prepare the subjects for a 21°C liquid diet before surgery, they were orally given a total parenteral nutrition (TPN) solution (Amino-sterile L-400 1.5 g nitrogen/kg/day + 30% hypertonic glucose 100 kcal/kg/day) for 48 hours as defined in the literature (16), and each subject was given 200 cc drinking water in separate bottles.

Before the surgical process, all subjects in all groups were anesthetized with 80 mg/kg intramuscular (im) ketamine HCl and 10 mg/kg acepromazine combination (17). In all groups, the stomachs of the rabbits were opened with a 5 cm midline incision. From the Treitz ligament beginning from 5 cm distal, 40 cm intestine meso was tied with 6/0 silk and cut, and then 50% proximal small intestine resection was performed. Later, 6/0 separated single layer polypropylene sutures were used for intestinal anastomosis. For each anastomosis, totally 6-7 sutures were used at intervals of approximately 2 mm. Care was taken to prevent ischemia and any iatrogenic mechanical lumen obstruction along the anastomosis line. On the third postoperative day, the 30 rabbits were divided into three groups and the nutrition of the subjects was designed as follows:

Group I (controls): Intestinal resection + oral TPN

Group II (oral liquid glutamine): Intestinal resection + oral TPN + oral liquid glutamine

Group III (parenteral iv glutamine): Intestinal resection + oral TPN + iv glutamine

In the postoperative period, the subjects were fed with 100 ml/day isolate M solution for one day in intervals. On the second day, rabbits were fed with TPN solutions and this was continued until the 7th day. Group II was given L-glutamine as oral gavage (Dipeptiven) in addition, at a dosage of 0.4 mg/kg/day twice a day for 7 days. Group III was given L-glutamine (Dipeptiven) from the ear vein at a dosage of 0.4 mg/kg/day twice a day for 7 days (18). After intestinal resection, on the postoperative 7th day (when intestinal adaptation indicators are the highest), the rabbits were sacrificed to obtain their tissue samples (7). After relaparotomy, a small intestine segment was taken so that all anastomosis lines were in the middle. The lumen of the intestine from which tissue samples were taken was washed in a 0.9 NaCl solution. For histopathological examination, samples were fixed in 10% formalin.

Histopathologic Examination

Histopathologic examination of the tissues was made by a pathologist included in the study and blinded to all information about the groups from the start. Tissue specimens were fixed in a 10% formaldehyde solution with a phosphate tampon. The materials were fixed in 10% buffered paraformaldehyde, prepared with autotechnicon, and then embedded in paraffin. At least two sections of 5 μ thickness were taken from each block and were stained with hematoxylin and eosin (HE). The stained materials were examined under Olympus CH2 light microscope. The data were recorded as units by accepting 100 units 1 mm with 10x10 magnification. In assessment, three criteria were evaluated:

1. Crypt Depth: The crypt depths were measured with ocular micrometer. Crypt depth was determined by dividing total data obtained in one cross-section by the measured crypt number.

2. Villus Length: In the cross-sections, the lengths of all the villi having a complete villus structure were measured with ocular micrometer. Degenerated villi were not included in the measurement. Villus length was determined by dividing total data obtained in one cross-section by the villus number.

3. Goblet cell number: In the cross-section, total goblet cells on the villi with complete villus structure were counted. The goblet cells on degenerated villi were not counted. The goblet cells on one villus in one section were divided by the total villus number, and the average goblet cell number was determined.

RESULTS

During the study, all subjects lost 10% body weight. In Group I, one rabbit died on the 3rd postoperative day, and two rabbits each in Groups II and III died on the 2nd and 3rd postoperative days. According to autopsy, the reasons for their deaths were intestinal blockage and anastomosis leakage and intestinal rotation. In the macroscopic assessment after relaparotomy, minimal mucosal atrophy was observed in Group II and more mucosal atrophy in Group III. These findings were also microscopically determined. The goblet cell numbers, crypt depth and villus length measurement results according to groups are given in Tables 1-3. In Group I, a decrease in villus length of the mucosa distal to the anastomosis and in the height of

Table 1. The microscopic measurement values of the control group

Subject	Goblet cell number (mm^3)	Crypt depth (unit)	Villus length (unit)
1	15	38	41
2	18	48	72
3	13	54	63
4	18	36	41
5	15	44	54
6	14	42	58
7	17	40	44
8	13	54	63
9	18	48	72
Average	15.6	44.8	56.4

Table 2. The microscopic measurement values of the oral liquid glutamine group

Subject	Goblet cell number(mm^3)	Crypt depth (unit)	Villus length (unit)
1	15	56	95
2	19	72	76
3	10	57	58
4	8	58	62
5	21	43	64
6	8	62	71
7	16	56	60
8	8	58	62
Average	13.1	57.6	68.5

Table 3. The microscopic measurement values of the intravenous glutamine group

Subject	Goblet cell number (mm^3)	Crypt depth (unit)	Villus length (unit)
1	19	83	96
2	17	86	104
3	18	74	110
4	21	77	88
5	24	78	101
6	13	72	98
7	16	76	108
8	16	83	79
Average	18	78.2	98

prismatic epithelial cells was observed (Figure 1). In Group II, an increase in the villus length and prismatic epithelial cells and enterocyte hyperplasia and thickening in the muscle layer and submucosa were observed. In Group III, it was seen that these values increased even more (Figure 2). When Groups I and II were compared in terms of villus length, the increase in length was significant in Group II (p=0.0001). The difference in increase in villus length between Group III and the other groups was found to be significant. It was observed that in Group II, the increase in crypt depth was higher compared to that seen in Group 1 (Figure 3), and the difference was statistically significant (p~0.0001). In Group III, increase in crypt depth was higher than in the other two groups (Figure 4), and this increase was found to be significant (p=0.0001). When the groups were compared in terms of goblet cell number, it was seen that there was an increase in Groups II and III; however, there was no statistically significant difference (p=0.081). In the statistical assessment, Kruskal-Wallis variance analysis was used, and Mann-Whitney test was performed as a correction test (Tables 4-6). When the villus lengths and crypt depths of all the subjects were compared, it was observed that there were positive relations between them (p=0.0001). In the present study, no statistically important differences were determined between the groups in terms of goblet cell number (p=0.081).

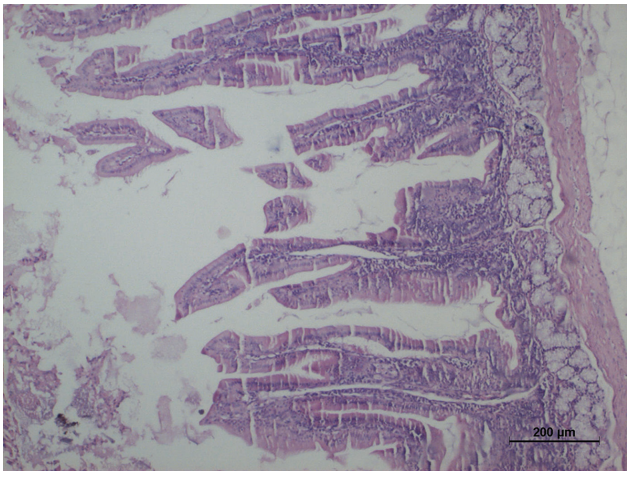

Figure 1. Decrease in the length of villus in Group I (H&E x 4)

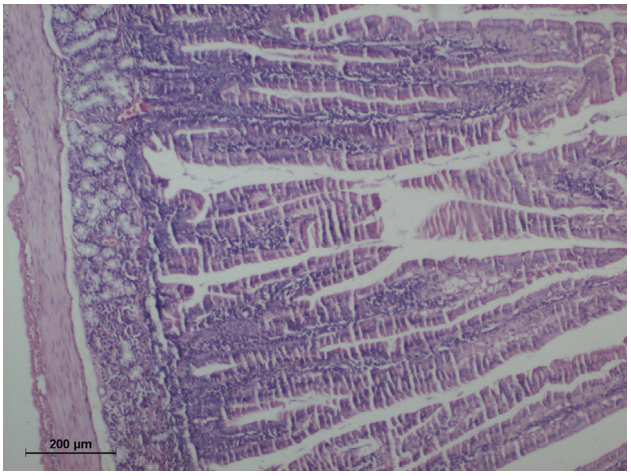

Figure 2. Increase in the length of villus in Group III (H&E x 4).

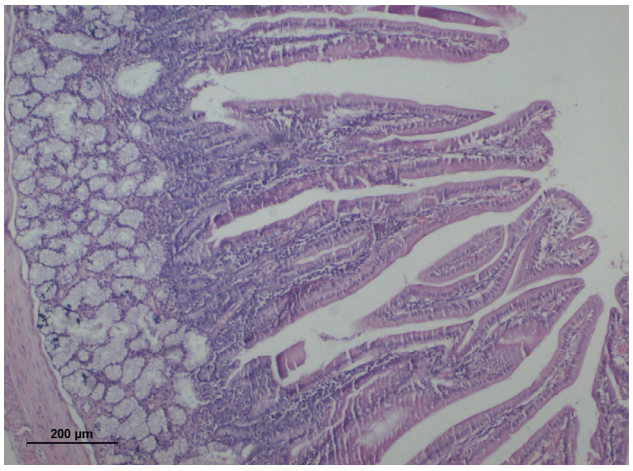

Figure 3. The increase in the crypt depth in Group II was higher compared to Group I (H&E x 4)

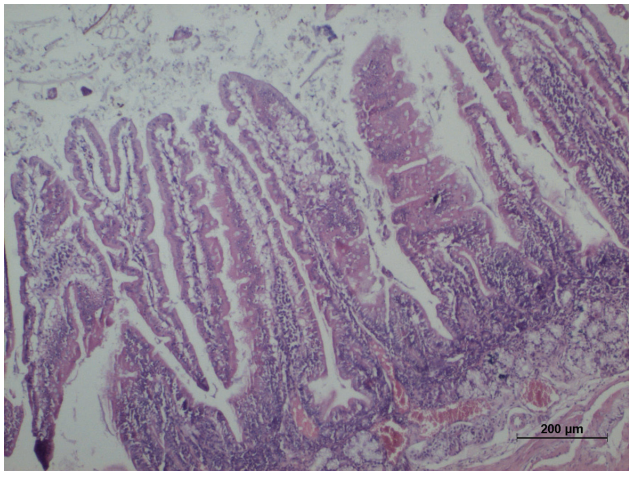

Figure 4. In Group III, increase in crypt depth was higher than in the other two groups (H&E x 4)

DISCUSSION

Massive small intestine resection, which leads to short bowel syndrome, has a high level of mortality and is one of the challenging surgeries for surgeons (19). The most important factor that increases mortality is that the remaining intestine cannot adequately fulfill gastrointestinal functions required for the patient's survival. To prevent this complication, attempts to achieve early intestinal adaptation are crucially important (20). In order for the remaining intestine to fulfill feeding function, adaptation is achieved by increasing some features of the intestinal mucosa. The absorption surface, glucose absorption (21), small intestine mucosa mass (22), and enterocyte proliferation need to be increased (23). Therefore, various substances have been used to support intestinal adaptation. Among these substances, the most widely known is glutamine, which the intestine uses directly as food.

In our study subjects, massive small intestine resection was established by applying 50 cm resection to their intestines, and glutamine, which has been widely emphasized in recent studies, was used to increase intestinal adaptation. The effects of glutamine given enterally are seen to be greater than when given by proximal GIS route (24). Therefore, glutamine has greater effects on the ileum, which has moved more proximally after the resection, than on the jejunum (25). After massive intestinal resection, the distal intestines are brought to a more proximal position and thus the increase in intestinal adaptation capacity becomes clearer as they encounter glutamine earlier (26, 27). The resection was deliberately applied in the region of the proximal jejunum, where the small intestine proximal passage is fast and absorption is low. Thus, in the rabbit model of small intestine syndrome, the adaptation mechanism could be observed by bringing the distal ileum segments, where the passage was slower and absorption was higher, closer to proximal.

L-glutamine is an important food and "fuel" for the small intestine (28, 29). Glutamine can be used orally or parentally by enterocytes (30, 31). In larger small intestine resection, adequate nutrition is possible with the effect of food taken from the lumen on mucosal tissue and portal circulation. Oral administration of L-glutamine increases mucosal

Table 4. Villus lengths of the groups

Groups	Subject Number	Maximum Value	Minimum Value	Average Value	Median Value
Group I	9	72	41	54.1	54
Group II	8	95	58	72.6	71
Group III	8	118	81	98.1	96

Table 5. Crypt depth of groups

Groups Number	Subject Value	Maximum Value	Minimum Value	Average Value	Median Value
Group I	9	54	36	45.1	47
Group II	8	72	56	57.6	57
Group III	8	86	68	78.5	77

Table 6. Goblet cell numbers of the groups

Groups	Subject Number	Maximum Value	Minimum Value	Average Value	Median Value
Group I	9	13	18	15.7	15
Group II	8	21	8	13.3	15
Group III	8	24	13	17.8	18

MDA synthesis (32). In previous studies, it was determined that glutamine yielded EGF increase in portal plasma and ileum mucosa in the early period after intestinal resection. In this way, during total parenteral feeding, the application of glutamine stimulates intestinal mucosa proliferation. In in vivo and in vitro studies, it was determined that L-glutamine protected nitrogen balance in catabolic cases, and prevented mucosal atrophy in the intestines (33-36). In spite of all these studies in the literature, the number of studies on whether parenteral or enteral administration of glutamine is better in terms of bio-benefit is still insufficient. In our study, the effects of glutamine, given by both enteral and parenteral routes, on intestinal adaptation were compared. We thus tried to contribute to the literature on this issue. After intestinal resection, glutamine application dramatically increased plasma peptide YY (PYY). It was demonstrated that this increase also leads to increase in tissue PYY content, and thus transit passage time in the intestine shortens and food absorption in the shortened intestines increases (37). It was also shown that PPY functionally damps the discharge of the stomach and extends intestinal passage time after colorectal surgery (38-42). After intestinal resection, with glutamine administration, the portal plasma entero-glucagon levels increase and effects similar to those in PPY increase are observed (39, 43, 44). Glutamine also increases mucosal IGF-II content, and in turn, IGF-II works as a means for the effect growth hormone (45-47). In the post-resection period, glutamine plays a stimulating role on mucosal adaptation and also increases the production and the release of gastrointestinal regulator peptide. This effect of glutamine depends on energy, and its being effective on enterocyte protein synthesis or on nucleotides. In a previous study carried out in our clinic, it was reported that glutamine also has positive effects on dysfunctional small intestine segments and prevented atrophy. This effect is dependent on glutamine being used by the intestines after being taken both from the lumen and parenterally. Glutamine can be taken from the parenteral circulation of the dysfunctional segment that does not encounter glutamine, and mucosal atrophy can be prevented (16).

Based on the results of our study, it was determined that L-glutamine given in oral gavage was effective on intestinal adaptation, prevented mucosal atrophy and increased enterocyte proliferation (p=0.0001). It was seen that there was an increase in villus length and crypt depth in the group receiving oral liquid glutamine. A microscopic increase in mucosal thickness was determined, and all were regarded as mucosal hyperplasia. However, it was similarly seen that after massive intestinal resection, the administration of parenteral glutamine led to a much greater increase in villus length and crypt depth when compared to the oral liquid glutamine group, and there was an increase in mucosal thickness, which was annotated to be intensive intestinal mucosa hyperplasia (p=0.0001). When compared with the control group, mucosal atrophy was prevented in the group administered oral liquid glutamine, and there was an increase in villus length and crypt depth; however, in the parenterally fed group, these positive effects were greater. It was also determined that administering both oral and parenteral glutamine not only prevents mucosal atrophy but also provides an evident enterocyte proliferation. In our study, there was differences between groups in terms of goblet cell number, but they were not significant (p=0.081).

Recently, many clinical and experimental studies have shown that parenteral administration of L-glutamine to some patients who underwent massive small intestine resection can be effective. According to the data obtained in our experimental study, we also observed positive effects on intestinal adaptation with parenteral glutamine application. Furthermore, we determined that these positive effects can also be achieved with oral glutamine, though they are less than observed with parenteral application. Oral glutamine application can be considered as an alternative to parenteral administration in some patients or both routes can be used. We believe that morbidity can be reduced and intestinal adaptation can be achieved earlier after surgery with glutamine administration.

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