Original Article

Clinical evidence of growth hormone, glutamine and a modified diet for short bowel syndrome: meta-analysis of clinical trials

Yong Zhou MD[1], Xiao-Ting Wu MD[1], Gang Yang MD[1], Wen Zhuang MD[1] and Mao-ling Wei PhD[2]

[1]*Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China*
[2]*Chinese Evidence-Based Medicine/Cochrane Center, Chengdu, China*

This study assessed the safety and efficacy of growth hormone (GH) and glutamine (GLN) combined with a modified (high-carbohydrate-low-fat, HCLF) diet in patients with short bowel syndrome. A meta-analysis of all the relevant clinical trials was performed. Clinical trials were identified from the following electronic databases: MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Chinese Bio-medicine Database. The search was undertaken in May 2004. Language was restricted to Chinese and English. Literature references were checked at the same time. Clinical trials were extracted and evaluated by two reviewers independently of each other. The statistical analysis was performed by RevMan4.2 software which was provided by the Cochrane Collaboration. A *P* value of <0.05 was considered statistically significant. Thirteen trials involving 258 patients were included. The combined results showed that GH, GLN and HCLF diet had positive treatment effect on body weight (weighted mean difference [WMD] = 2.44, 95%CI [1.62, 3.27], *P*<0.00001), stool output (WMD = -376.49, 95%CI [-600.35, -152.63], *P*=0.001), lean body mass (WMD = 2.16, 95%CI [0.91, 3.41], *P*=0.0007), absorption of carbohydrates (WMD = 6.21, 95%CI [5.27, 7.15], *P*<0.00001), absorption of nitrogen (WMD = 10.83, 95%CI [5.22, 16.44], *P*=0.0002), absorption of D-xylose (WMD = 0.37, 95%CI [0.29, 0.44], *P*<0.00001), and off TPN (total parenteral nutrition) (odds ratios [OR] = 64.63, 95%CI [15.51, 269.22], *P*<0.00001). But there were no improvements in fat mass (WMD = -1.50, 95%CI [-3.48, 0.48], *P*=0.14), absorption of energy (WMD = 7.48, 95%CI [-7.22, 22.17], *P*=0.32), and absorption of fat (WMD = 7.16, 95%CI [-2.95, 17.28], *P*=0.17). Most patients had side effects that are known to occur during treatment with high doses (0.14 mg/kg/day) of GH. No serious adverse effects occurred during active treatment with low doses (≤0.1 mg/kg/day) of GH. Treatment with a combination of low-dose GH, GLN and HCLF diet is effective without any major adverse effects in patients with short bowel syndrome. Further trials are required, especially in children, with sufficient size and rigorous design.

Key Words: short bowel syndrome, growth hormone, glutamine, high carbohydrate low fat diet, meta-analysis

Introduction

Short-bowel syndrome (SBS) is a result of loss of two-thirds or more of the small bowel. Removal of large segments of the small bowel with or without a portion of the colon is necessary because of thrombosis of mesenteric vessels, severe inflammatory bowel disease, abdominal trauma, congenital abnormalities, and volvulus. This intestinal loss results in malabsorption of fluid, electrolytes, and other essential nutrients; severe diarrhea; dehydration; and progressive malnutrition.

Patients with SBS often require parenteral nutrition for survival. But the use of life-long parenteral nutrition is expensive and associated with certain complications. However, small bowel transplantation is a treatment only for patients with very short segments of jejuno-ileum and no colon experiencing large fluid and electrolyte losses. Depending on the length of the residual bowel, the patient may become independent of parenteral nutritional support. This process may be enhanced with an appropriate diet and optimal therapy. Growth hormone (GH), glutamine (GLN) and a high-carbohydrate-low-fat (HCLF) diet, has been reported to increase the macronutrient and fluid absorption in patients with SBS.[1-17]

Meta-analysis has been gradually applied in medicine to improve statistical efficiency, to evaluate the disadvantages of established studies, to reach reliable conclusions from the mixed assortment of potentially relevant studies, and to determine the most promising directions for future research.[18] The aim of this meta-analysis was to assess the

Correspondence address:. Prof Xiao-Ting Wu, Department of General Surgery, West China Hospital, Sichuan University, 37 Guo Xue Rd., Chengdu 610041, Sichuan Province, China.
Tel: +86-28-85422480; Fax: +86-28-85422411
Email: nutritioner@163.com
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safety and efficacy of GH, GLN and HCLF diet in combination in patients with short bowel syndrome.

Materials and methods

Clinical trials of patients with SBS were included in this meta-analysis. Language was restricted to Chinese and English.

Search strategy

Search was applied to the following electronic databases: the Cochrane Library (2004.1), MEDLINE (1966-2004.5), EMBASE (1980-2004.5) and Chinese Biomedicine Database (1979-2004.5). Literature reference proceedings were handsearched at the same time. The searching words were short bowel syndrome.

Data collection and analysis

Data were extracted independently by two reviewers. The following data were extracted: the number of patients by the end of the follow-up; the different agents and doses of GH, GLN and HCLF diet; the baseline of trials; body weight, stool output, lean body mass, fat mass, absorption of energy, absorption of carbohydrates, absorption of fat, absorption of nitrogen, absorption of D-xylose, and the number of patients off TPN (total parenteral nutrition); the adverse events; the statistical consideration. The statistical analysis was performed by RevMan4.2 software, which was provided by the Cochrane Collaboration. A P value of <0.05 was considered statistically significant. Meta-analysis was done with random effects model or fixed effects model. Heterogeneity was checked by chi-square test. If the results of the trials had heterogeneity, random effects model was used for meta-analysis. The result was expressed with odds ratio (OR) for the categorical variable and weighted mean difference (WMD) for the continuous variable, and with 95% confidence intervals (CI).

Results

There were 2006 papers relevant to the searching words. Through the steps of screening the title, reading the abstract and the entire article, only thirteen clinical trials involving 258 patients were included. Characteristics of studies included in meta-analysis of GH, GLN and a modified diet on short bowel syndrome is presented in Table 1.

The combined results showed that GH, GLN and HCLF diet had positive treatment effect on body weight (weighted mean difference [WMD] = 2.44, 95%CI [1.62, 3.27], P<0.00001), stool output (WMD = -376.49, 95%CI [-600.35, -152.63], P = 0.001), lean body mass (WMD = 2.16, 95%CI [0.91, 3.41], P=0.0007), absorption of carbohydrates (WMD = 6.21, 95%CI [5.27, 7.15], P<0.00001), absorption of nitrogen (WMD = 10.83, 95%CI [5.22, 16.44], P=0.0002), absorption of D-xylose (WMD = 0.37, 95%CI [0.29, 0.44], P<0.00001), and off TPN (odds ratios [OR] = 64.63, 95%CI [15.51, 269.22], P<0.00001). But there were no improvements in fat mass (WMD = -1.50, 95%CI [-3.48, 0.48], P=0.14), absorption of energy (WMD = 7.48, 95%CI [-7.22, 22.17], P = 0.32), and absorption of fat (WMD = 7.16, 95%CI [-2.95, 17.28], P = 0.17). The results are presented in Table 2.

Table 1. Characteristics of studies included in meta-analysis of growth hormone, glutamine and a modified diet for short bowel syndrome

Author	Year	Study design	Age (year)	Growth hormone (mg/kg/day)	Glutamine (g/kg/day)	HCLF Diet
Byrne[9]	1995	Clinical trial	Range, 28~68 Mean, 43	0.14	OR: 0.63 PE: 0.42	YES
Byrne[8]	1995	Clinical trial	Range, 24~68 Mean, 44	0.14	OR/PE: 0.6	YES
Li N[10]	1997	Clinical trial	Range, 55~67 Mean, 60	0.0532	PE: 0.6	YES
Ellegard[7]	1997	Double-blind RCT	Range, 30~72 Mean, 49	0.024	None	YES
Scolapio[6]	1997	Double-blind RCT	Range, 39~69 Mean, 48.4	0.14	OR: 0.63	YES
Scolapio[5]	1999	Double-blind RCT	Range, 39~69 Mean, 48.4	0.14	OR: 0.63	YES
Szkudlarek[4]	2000	Double-blind RCT	Range, 32~74 Mean, 47	0.12	OR/PE: 0.56	NO
Jeppesen[3]	2001	Double-blind RCT	Range, 32~74 Mean, 47	0.12	OR/PE: 0.56	NO
Scolapio[2]	2001	Double-blind RCT	Range, 42~73 Mean, 65.5	None	OR: 0.45	YES
Zhu W[11]	2002	Clinical trial	Range, 9~67 Mean, 38.5	0.0532	OR: 0.6 PE: 0.3	YES
Seguy[1]	2003	Double-blind RCT	Range, 19~51 Mean, 35	0.05	None	NO
Wu GH[12]	2003	Clinical trial	Range, 7~68 Mean, 38	0.14	PE: 0.3	YES
Wilmore[13]	2003	Double-blind RCT	Range, 18~75 Mean, 50	0.1	OR: 0.49	YES

Abbreviations: RCT, randomized controlled trial; OR, oral; PE, parenteral; HCLF, High carbohydrate low fat.

Table 2. Results from meta-analysis of growth hormone, glutamine and a modified diet for short bowel syndrome

Outcome	Studies	Participants	Statistical method	Effect size (95% CI)	*P*
Body weight	6[1,3,7,8,10,11]	105	WMD (fixed)	2.44 [1.62, 3.27]	<0.00001
Stool output	2[1,8]	39	WMD (fixed)	-376.49 [-600.35, -152.63]	0.001
Lean body mass	3[1,3,7]	60	WMD (fixed)	2.16 [0.91, 3.41]	0.0007
Fat mass	3[1,3,7]	60	WMD (random)	-1.50 [-3.48, 0.48]	0.14
Absorption of energy	2[1,4]	40	WMD (random)	7.48 [-7.22, 22.17]	0.32
Absorption of carbohydrates	3[1,4,13]	60	WMD (fixed)	6.21 [5.27, 7.15]	<0.00001
Absorption of fat	2[1,4]	40	WMD (random)	7.16 [-2.95, 17.28]	0.17
Absorption of nitrogen	2[1,4]	40	WMD (fixed)	10.83 [5.22, 16.44]	0.0002
Absorption of D-xylose	4[1,10-12]	92	WMD (fixed)	0.37 [0.29, 0.44]	<0.00001
Off TPN	4[8,11-13]	121	OR (fixed)	64.63 [15.51, 269.22]	<0.00001

Abbreviations: TPN, total parenteral nutrition.

There were six trials[1,4-8] which detailed the side-effects of GH. Most patients had side effects that are known to occur during treatment with high doses (0.14 mg/kg/day) of GH. The major side effect of the treatment was fluid retention, manifested by peripheral oedema and arthralgia. Two patients developed signs and symptoms of carpal tunnel syndrome. Two patients noted sleep disturbances. Two patients had mild headaches. One patient developed nausea, vomiting, and a low-grade fever. Despite the occurrence of reversible side effects that resolved several days after active treatment was completed, all patients completed the study. No serious adverse effects occurred during active treatment with low doses (≤0.1mg/kg/day) of GH.[1,7,10,11,13] One patient reported arthralgia and myalgia at the beginning of treatment with GH. This discomfort seemed to be minor and did not justify any particular treatment. There was no oedema or glycosuria during active treatment.

Discussion

Somatotropin is a species-specific anabolic protein that promotes somatic growth, stimulates protein synthesis, and regulates carbohydrate and lipid metabolism. Both animal and human studies have demonstrated that GH stimulates intestinal growth and enhances transport of nutrients across the small bowel.[19] GH has been shown to increase small bowel growth after resection.[20] GH mediates its trophic effects primarily through insulin-like growth factor-1 (IGF-1). IGF-1 has been reported to increase mucosal DNA and protein levels in the jejunal mucosa of rats to reverse TPN-induced mucosal atrophy.[21]

Fluid retention is the major side effect of GH administration, which varied depending on growth hormone dose. This problem was attenuated by limiting fluid intake, reducing the growth hormone dose, or administering diuretics.[8] The sodium and fluid retaining impact of growth hormone (GH) was demonstrated in humans almost 50 years ago by Ikkos *et al.*[22] Underlying mechanisms of GH-induced fluid retention include: (1) GH can increase glomerular filtration rate mediated by IGF-1[23-25] (2) GH can stimulate the renin-angiotensin-aldosterone system (RAAS)[26-30] (3) GH can reduce atrial natriuretic factor (ANF).[31-34] (4) Prostaglandins could play a role in GH-induced fluid retention.[35] No serious adverse effects occurred during active treatment with low doses (≤ 0.1 mg/kg/day) of GH.[1,7,10,11,13] A low-dose GH should be considered.

GH synergistically promotes carcinogen-induced hepatocarcinogenesis in both sexes of GH-transgenic mice by stimulating tumor cell proliferation.[36] GH raises serum concentrations of IGF-1, which is mitogenic and antiapoptotic. Results from in-vitro and animal studies suggest that GH may raise the risk of hyperplasia and malignancy.[37] Only one RCT conducted an analysis of a multicentre study with 104 patients undergoing major gastrointestinal surgery to assess the risk of long-term tumor recurrence after short-term (5 days) postoperative GH treatment. The results of this study demonstrate that short-term treatment with GH for 5 days after major gastrointestinal surgery for adenocarcinoma does not increase the risk of tumor recurrence.[38] In reality, the role of growth hormone in carcinogenesis is unclear.

GLN is the most abundant free amino acid in the body. It is avidly consumed by rapidly dividing cells, such as those lining the gut, because its 5-carbon skeleton can provide energy whilst the nitrogen molecules support the synthesis of nucleic acids. Patients who are maintained using conventional solutions of parenteral nutrients become depleted in GLN, which has led to the reclassification of GLN as a conditionally essential nutrient.[39] GLN has been shown to be trophic to the intestinal mucosa and to enhance nutrient absorption.[40,41] The combination of GLN and GH was shown in two studies in rats to synergistically increase plasma IGF-1 levels, intestinal DNA, and villus growth of the resected small bowel.[42] Furthermore, the combination of GLN and GH may synergistically reduce bacterial translocation over time in sepsis.[43] However, the potential of exogenous GLN to stimulate intestinal adaptation remains debatable.[44]

A modified diet may be useful for clinically defining functional SBS. For example, one recommendation is to maintain patients with SBS with residual colon on a HCLF diet, which provides about 60% of calories as complex carbohydrates, 20% as protein, and the remainder as fat.[8,9,13] Such a diet results in greater caloric absorption than a high-fat, low-carbohydrate diet because malabsorbed carbohydrates are salvaged in the colon whereas malabsorbed fatty acids are not. In addition, fat restriction enhances mineral absorption and decreases oxalate hyper-

absorption. The goal of this approach is to control dietary intake and thereby prevent or control diarrhoea. Patients with a portion of colon in continuity should receive a HCLF diet, while those with small bowel ostomies may consume a diet containing more fat.[13]

Age is an important factor affecting patient outcome: the older the patient, the poorer the outcome. Children with intact ileocecal valve (ICV) even with <15 cm of small bowel length (SBL) and children with SBL >15 cm without intact ICV have a chance of intestinal adaptation.[45] But in adults, the minimal SBL is >60 cm.[13] In Zhu's trial, five patients were beyond 55 years, and four of them could not be weaned from TPN.[11] The results of Scolapio's study showed that 8 weeks of treatment with oral GLN and a HCLF diet did not significantly improve intestinalmorphology, gastrointestinal transit, D-xylose absorption and stool losses in patients with SBS. The reasons probably include the absence of GH and old age - all patients were beyond 63 years, except one aged 42 years.[2] The mean ages of patients included in this meta-analysis were greater than 35 years. Only two clinical trials in China enrolled paediatric patients.[11,12] Therefore, further trials are required in children with SBS.

Depending on the length of the residual bowel, the patient may become independent of parenteral nutritional support. This process is enhanced in selective individuals with a modified diet and the administration of GH and GLN. However, some patients experienced minimal to no change in parenteral nutritional requirements. These patients should be considered for either intestinal transplantation or other therapeutic approaches.

In conclusion, treatment with a combination of low-dose GH, GLN and HCLF diet is effective without any major adverse effects in patients with SBS. Nevertheless, this conclusion should be supported by high quality randomized, double-blind, controlled trials. Further trials are required, especially in children, with sufficient size and rigorous design.

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References

1. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. Gastroenterology 2003; 124: 293-302.
2. Scolapio JS, McGreevy K, Tennyson GS, Burnett OL. Effect of glutamine in short-bowel syndrome. Clin Nutr 2001; 20: 319-323.
3. Jeppesen PB, Szkudlarek J, Hoy CE, Mortensen PB. Effect of high-dose growth hormone and glutamine on body composition, urine creatinine excretion, fatty acid absorption, and essential fatty acids status in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. Scand J Gastroenterol 2001; 36: 48-54.
4. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut 2000; 47: 199-205.
5. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN 1999; 23: 309-313.
6. Scolapio JS, Camilleri M, Fleming CR, Oenning LV, Burton DD, Sebo TJ, Batts KP, Kelly DG. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. Gastroenterology 1997; 113: 1074-1081.
7. Ellegard L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. Ann Surg 1997; 225: 88-96.
8. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. Ann Surg 1995; 222: 243-255.
9. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN 1995; 19: 296-302.
10. Li N, Li J, Li Y. [Nutritional rehabilitation for patients with extreme short bowel] Zhonghua Wai Ke Za Zhi 1997; 35: 707-709.
11. Zhu W, Li N, Ren J, Gu J, Jiang J, Li J. Rehabilitation therapy for short bowel syndrome. Chin Med J 2002; 115: 776-778.
12. Wu GH, Wu ZH, Wu ZG. Effects of bowel rehabilitation and combined trophic therapy on intestinal adaptation in short bowel patients. World J Gastroenterol 2003; 9: 2601-2604.
13. Wilmore DW. Indications for specific therapy in the rehabilitation of patients with the short-bowel syndrome. Best Pract Res Clin Gastroenterol 2003; 17: 895-906.
14. Scolapio JS, Pasha T, Stoner G, Tarossa V. Growth hormone and glutamine increases lean body mass in patients with short bowel syndrome (SBS). JPEN 1999; 23: S2.
15. Dias MC, Faintuch J, Waltzberg DL, Cukler C, Santoro S, Maculevicius J, Gana-Rodrigues JJ, Pirotti HW. Oral diet and glutamine in patients with short bowel syndrome. JPEN 1999; 23: S157.
16. Hankard R, Goulet O, Ricour C, Rongier M, Colomb V, Darmaun D. Glutamine metabolism in children with short-bowel syndrome: a stable isotope study. Pediatr Res 1994; 36: 202-206.
17. Beaugerie L, Carbonnel F, Hecketsweiler B, Dechelotte P, Gendre JP, Cosnes J. Effects of an isotonic oral rehydration solution, enriched with glutamine, on fluid and sodium absorption in patients with a short-bowel. Aliment Pharmacol Ther 1997; 11: 741-746.
18. Sheldon TA. Systematic reviews and meta-analyses: the value for surgery. Br J Surg 1999; 86: 977-978.
19. Inoue Y, Copeland EM, Souba WW. Growth hormone enhances amino acid uptake by the human small intestine. Ann Surg 1994; 219: 715-724.
20. Lund PK. Molecular basis of intestinal adaptation: the role of the insulin-like growth factor system. Ann N Y Acad Sci 1998; 859: 18-36.
21. Peterson CA, Carey HV, Hinton PL, Lo HC, Ney DM. GH elevates serum IGF-I levels but does not alter mucosal atrophy in parenterally fed rats. Am J Physiol 1997; 272: G1100-1108.
22. Ikkos D, Luft R, Sjogren B. Body water and sodium in patients with acromegaly. J Clin Invest 1954; 33: 989-994.

23. Guler HP, Schmid C, Zapf J, Froesch ER. Effects of recombinant insulin-like growth factor I on insulin secretion and renal function in normal human subjects. Proc Natl Acad Sci 1989; 86: 2868-2872.
24. Hirschberg R, Kopple JD. Evidence that insulin-like growth factor I increases renal plasma flow and glomerular filtration rate in fasted rats. J Clin Invest 1989; 83:326-330.
25. Hirschberg R, Brunori G, Kopple JD, Guler HP. Effects of insulin-like growth factor I on renal function in normal men. Kidney Int 1993; 43: 387-397.
26. Venning Eh, Lucis OJ. Effect of growth hormone on the biosynthesis of aldosterone in the rat. Endocrinology 1962; 70: 486-491.
27. Ho KY, Weissberger AJ. The antinatriuretic action of biosynthetic human growth hormone in man involves activation of the renin-angiotensin system. Metabolism 1990; 39: 133-137.
28. Cuneo RC, Salomon F, Wilmshurst P, Byrne C, Wiles CM, Hesp R, Sonksen PH. Cardiovascular effects of growth hormone treatment in growth-hormone-deficient adults: stimulation of the renin-aldosterone system. Clin Sci (Lond) 1991; 81: 587-592.
29. Herlitz H, Jonsson O, Bengtsson BA. Effect of recombinant human growth hormone on cellular sodium metabolism. Clin Sci (Lond) 1994; 86: 233-237.
30. Ross EJ, Vant Hoff W, Crabbe J, Thorn GW. Aldosterone excretion in hypopituitarism and after hypophysectomy in man. Am J Med 1960; 28: 229-238.
31. Donath MY, Zierhut W, Gosteli-Peter MA, Hauri C, Froesch ER, Zapf J. Effects of IGF-I on cardiac growth and expression of mRNAs coding for cardiac proteins after induction of heart hypertrophy in the rat. Eur J Endocrinol 1998; 139: 109-117.
32. Donath MY, Gosteli-Peter MA, Hauri C, Froesch ER, Zapf J. Insulin-like growth factor-I stimulates myofibrillar genes and modulates atrial natriuretic factor mRNA in rat heart. Eur J Endocrinol 1997; 137:309-315.
33. Tanaka N, Ryoke T, Hongo M, Mao L, Rockman HA, Clark RG, Ross J Jr. Effects of growth hormone and IGF-I on cardiac hypertrophy and gene expression in mice. Am J Physiol 1998; 275: 393-399.
34. Harder BA, Schaub MC, Eppenberger HM, Eppenberger-Eberhardt M. Influence of fibroblast growth factor (bFGF) and insulin-like growth factor (IGF-I) on cytoskeletal and contractile structures and on atrial natriuretic factor (ANF) expression in adult rat ventricular cardiomyocytes in culture. J Mol Cell Cardiol 1996; 28: 19-31.
35. Tonshoff B, Nowack R, Kurilenko S, Blum WF, Seyberth HW, Mehls O, Ritz E. Growth hormone-induced glomerular hyperfiltration is dependent on vasodilating prostanoids. Am J Kidney Dis 1993; 21: 145-151.
36. Snibson KJ, Bhathal PS, Adams TE. Overexpressed growth hormone (GH) synergistically promotes carcinogen-initiated liver tumour growth by promoting cellular proliferation in emerging hepatocellular neoplasms in female and male GH-transgenic mice. Liver 2001; 21: 149-158.
37. Ogilvy-Stuart AL. Safety of growth hormone after treatment of a childhood malignancy. Horm Res 1995; 44 Suppl 3: 73-79.
38. Tacke J, Bolder U, Herrmann A, Berger G, Jauch KW. Long-term risk of gastrointestinal tumor recurrence after postoperative treatment with recombinant human growth hormone. JPEN 2000; 24: 140-144.
39. Coster J, McCauley R, Hall J. Glutamine: metabolism and application in nutrition support. Asia Pac J Clin Nutr 2004; 13: 25-31.
40. Gouttebel MC, Astre C, Briand D, Saint-Aubert B, Girardot PM, Joyeux H. Influence of N-acetylglutamine or glutamine infusion on plasma amino acid concentrations during the early phase of small-bowel adaptation in the dog. JPEN 1992; 16:117-121.
41. Scheppach W, Loges C, Bartram P, Christl SU, Richter F, Dusel G, Stehle P, Fuerst P, Kasper H. Effect of free glutamine and alanyl-glutamine dipeptide on mucosal proliferation of the human ileum and colon. Gastroenterology 1994; 107: 429-434.
42. Gu Y, Wu ZH, Xie JX, Jin DY, Zhuo HC. Effects of growth hormone (rhGH) and glutamine supplemented parenteral nutrition on intestinal adaptation in short bowel rats. Clin Nutr 2001; 20: 159-166.
43. Jung SE, Youn YK, Lim YS, Song HG, Rhee JE, Suh GJ. Combined administration of glutamine and growth hormone synergistically reduces bacterial translocation in sepsis. J Korean Med Sci 2003; 18:17-22.
44. Buchman AL. Glutamine for short-bowel syndrome. Curr Gastroenterol Rep 2002; 4: 321.
45. Quiros-Tejeira RE, Ament ME, Reyen L, Herzog F, Merjanian M, Olivares-Serrano N, Vargas JH. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr 2004;145:157-163.