Original Article

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

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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], \(P\leq0.00001\)), 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-xylene (\(WMD = 0.37, 95\%CI [0.29, 0.44], P<0.00001\)), 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

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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 [-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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Age (year)</th>
<th>Growth hormone (mg/kg/day)</th>
<th>Glutamine (g/kg/day)</th>
<th>HCLF Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrne</td>
<td>1995</td>
<td>Clinical trial</td>
<td>Range, 28-68</td>
<td>0.14</td>
<td>OR: 0.63</td>
<td>YES</td>
</tr>
<tr>
<td>Byrne</td>
<td>1995</td>
<td>Clinical trial</td>
<td>Range, 24-68</td>
<td>0.14</td>
<td>OR/PE: 0.6</td>
<td>YES</td>
</tr>
<tr>
<td>Li N</td>
<td>1997</td>
<td>Clinical trial</td>
<td>Range, 55-67</td>
<td>0.0532</td>
<td>PE: 0.6</td>
<td>YES</td>
</tr>
<tr>
<td>Ellegard</td>
<td>1997</td>
<td>Double-blind RCT</td>
<td>Range, 30-72 Mean, 49</td>
<td>0.14</td>
<td>None</td>
<td>YES</td>
</tr>
<tr>
<td>Scolapio</td>
<td>1997</td>
<td>Double-blind RCT</td>
<td>Range, 39-69 Mean, 48.4</td>
<td>0.14</td>
<td>OR: 0.63</td>
<td>YES</td>
</tr>
<tr>
<td>Scolapio</td>
<td>1999</td>
<td>Double-blind RCT</td>
<td>Range, 39-69 Mean, 48.4</td>
<td>0.14</td>
<td>OR: 0.63</td>
<td>YES</td>
</tr>
<tr>
<td>Szkudlarek</td>
<td>2000</td>
<td>Double-blind RCT</td>
<td>Range, 32-74 Mean, 47</td>
<td>0.12</td>
<td>OR/PE: 0.56</td>
<td>NO</td>
</tr>
<tr>
<td>Jeppesen</td>
<td>2001</td>
<td>Double-blind RCT</td>
<td>Range, 32-74 Mean, 47</td>
<td>0.12</td>
<td>OR/PE: 0.56</td>
<td>NO</td>
</tr>
<tr>
<td>Scolapio</td>
<td>2001</td>
<td>Double-blind RCT</td>
<td>Range, 42-73 Mean, 65.5</td>
<td>0.14</td>
<td>None</td>
<td>OR: 0.45</td>
</tr>
<tr>
<td>Zhu W</td>
<td>2002</td>
<td>Clinical trial</td>
<td>Range, 9-67 Mean, 38.5</td>
<td>0.0532</td>
<td>OR: 0.6</td>
<td>YES</td>
</tr>
<tr>
<td>Seguy</td>
<td>2003</td>
<td>Double-blind RCT</td>
<td>Range, 19-51 Mean, 35</td>
<td>0.05</td>
<td>None</td>
<td>YES</td>
</tr>
<tr>
<td>Wu GH</td>
<td>2003</td>
<td>Clinical trial</td>
<td>Range, 7-68 Mean, 38</td>
<td>0.14</td>
<td>PE: 0.3</td>
<td>YES</td>
</tr>
<tr>
<td>Wilmore</td>
<td>2003</td>
<td>Double-blind RCT</td>
<td>Range, 18-75 Mean, 50</td>
<td>0.1</td>
<td>OR: 0.49</td>
<td>YES</td>
</tr>
</tbody>
</table>

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

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

Abbreviations: TPN, total parenteral nutrition.

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 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 may synergistically reduce bacterial translocation over time in sepsis.43 However, the potential of exogenous GLN to stimulate intestinal adaptation remains debatable.

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.8,13 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.46 But in adults, the minimal SBL is >60 cm.11 The results of Scolapio’s study showed that 8 weeks of treatment with oral GLN and a HCLF diet did not significantly improve intestinal morphology, 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


