Human growth hormone and glutamine for patients with short bowel syndrome (Review)

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[Intervention Review]

Human growth hormone and glutamine for patients with short bowel syndrome

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ABSTRACT

Background

There has been clinical enthusiasm for treating short bowel patients with human recombinant growth hormone and/or glutamine in hopes of reducing parenteral nutrition dependency. It has been more than a decade since Byrne and colleagues reported enhanced absorption of nutrients, improved weight gain, and reduction in parenteral nutrition requirements with the administration of a combination of human growth hormone (HGH) and glutamine in patients with short bowel syndrome. Other studies have reported inconsistent results.

Objectives

The purpose of this systematic review was to evaluate the efficacy of growth hormone with or without glutamine supplementation for adult patients with short bowel syndrome.

Search methods

Electronic searches were performed to identify all publications describing randomised controlled trials of the use of human growth hormone with or without glutamine for the treatment of patients with short bowel syndrome.

Selection criteria

Randomised controlled trials of human growth hormone with or without glutamine for patients with short bowel syndrome were considered for inclusion.

Data collection and analysis

Two authors independently extracted data from the published studies. The statistical analyses were performed using RevMan 5 software. Follmann's method was used for cross-over studies.

Main results

Five studies were included in the review. Human growth hormone with or without glutamine appears to provide benefit in terms of increased weight (MD 1.66 Kg; 95% CI 0.69 to 2.63;P = 0.0008), lean body mass (MD 1.93 Kg; 95% CI 0.97 to 2.90; P = 0.0001) energy absorption (MD 4.42 Kcal; 95% CI 0.26 to 8.58; P = 0.04) and nitrogen absorption (MD 44.85 g; 95%CI 0.20 to 9.49; P = 0.04) for patients with short bowel syndrome. The single RCT that focused on parenteral nutrition (PN) requirements demonstrated decreased PN volume and calories and number of infusions in patients who received HGH with or without glutamine supplementation. Only patients who received HGH with glutamine maintained statistically significant PN reductions at 3 month follow-up.

Authors' conclusions

The results suggest a positive effect of human growth hormone on weight gain and energy absorption. However, in the majority of trials, the effects are short-lived returning to baseline shortly after cessation of therapy. The temporary benefit calls into question the clinical utility of this treatment. To date, the evidence is inconclusive to recommend this therapy. Consideration should be made to studying patients during the active phase of intestinal adaptation rather than in the setting of chronic intestinal failure. The role of HGH in paediatric short bowel syndrome remains unknown.

PLAIN LANGUAGE SUMMARY

Human growth hormone and glutamine for patients with short bowel syndrome

Short bowel syndrome is a malabsorption disorder caused by the surgical removal of the small intestine, or by the complete dysfunction of a large segment of bowel. It is a challenging health problem to treat. Several small studies have assessed the benefit of providing drugs such as human growth hormone and glutamine in an attempt to improve intestinal function and wean intravenous nutrition (liquid food). The results of this review of 5 small studies suggest that human growth hormone used with or without glutamine may provide short term benefit for patients with short bowel syndrome in terms of weight gain and intestinal absorption of nutrients. However the benefits of treatment do not continue after treatment is stopped. Common side effects of treatment include peripheral edema (swelling of tissues, usually in the lower limbs), and carpal tunnel syndrome (numbness and muscle weakness in the hand). Conclusive evidence is not available to recommend this treatment. Further studies that evaluate human growth hormone treatment during the immediate phase of bowel adaptation are needed.

BACKGROUND

Patients who undergo extensive resection of the gastrointestinal tract may subsequently develop intestinal failure secondary to short-bowel syndrome. Intestinal failure occurs in the absence of minimum intestinal mass required for adequate digestion and absorption of nutrients leading to malnutrition and/or dehydration. Depending on the extent, degree, and location of the resection, patients may experience severe malabsorption of fluid, electrolytes, and other nutrients (Li-Ling 2001). Many of these patients become dependent on long-term parenteral nutrition. Due to the potential complications, cost, and quality of life issues, alternative therapies to parenteral nutrition such as aggressive intestinal rehabilitation and small bowel transplantation have been developed (Thompson 1993; Abu-Elmagd 1994).

Intestinal adaptation, first described by Flint (Flint 1912) is a process whereby the remnant bowel begins to compensate for the loss of the resected portion following small bowel resection. It is believed that this adaptive phase continues for 2 years in adults (Messing 1999;Nighttingale 1999). The exact mechanism by which these alterations in bowel morphology and function occur is not known, but the process includes both structural and functional aspects (Nighttingale 1993). During this process the bowel dilates and elongates and there is an increase in villus height, crypt depth, cell proliferation and enzyme activity. This results in enhanced fluid, electrolyte, and nutrient absorption as well as prolonged transit time (Flint 1912).

Intestinal adaptation occurs in response to enteral nutrition, intestinal secretions and hormonal factors. Trophic changes have

been observed in animals when various growth factors such as growth hormone, insulin-like growth factor-1, glucagon-like peptide-2, specific nutrients such as glutamine, short-chain fatty acids, pancreatic-biliary secretions are supplemented (Rhoads 1991; Tamada 1993; Souba 1985; Jacobs 1983; Gardemann 1992). Together these trophic stimuli allow the remnant bowel to adapt (hypertrophy). Attempts to increase the absorptive capacity of the remnant bowel have been made by promoting pharmacologic adaptation through the use of hormonal intestinal trophic factors (Lentze 1989).

Byrne and colleagues first demonstrated, through an open label clinical trial and a case series (Byrne 1995a; Byrne 1995b), the benefit to intestinal adaptation by administering growth hormone and glutamine in ten patients with remnant small intestine who had been on long term parenteral nutrition. These results attracted much interest and in the following years several other trials were published. A few case series were published suggesting the benefit of both human growth hormone (HGH) and glutamine in patients with short bowel (Scheppach 1994; Inoue 1994). However, controversy still surrounds the use of growth hormone and glutamine in these patients. The number of studies in this area is limited and the results are conflicting.

On the basis of previous animal studies, it appears that the combination of GH and glutamine has a synergistic effect on intestinal function (Gu 2001; Ziegler 1996). Glutamine is a required substrate for ornithine decarboxylase and an essential precursor for nucleotide biosynthesis. Certainly, there is no reason to suggest a negative or cancelling effect when glutamine is given with HGH. There appears to be no carry over effect using these drugs in a cross-over design, due to its confirmed short half life (Li-Ling 2001).

OBJECTIVES

The purpose of this systematic review was to evaluate the efficacy of growth hormone with or without glutamine supplementation for adult patients with short bowel syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of human growth hormone with or without glutamine for patients with short bowel syndrome were considered for inclusion. Letters, editorials, commentaries, reviews and lectures that do not contain original research data and studies that used historical controls were excluded. For studies in which further data were required the authors were contacted for further information.

Types of participants

Adult patients diagnosed with short bowel syndrome and dependent on parenteral nutrition support were considered for inclusion. Short bowel syndrome was defined as "reduction of functioning gut mass below the amount necessary for adequate digestion and absorption of nutrients".

Types of interventions

Studies in which human recombinant growth hormone with or without glutamine were compared to placebo were considered for inclusion.

Types of outcome measures

Studies were considered for inclusion if they reported on one or more of the following outcomes:
Primary outcome: Change in body weight (Kg); and
Secondary outcomes:

- Change in lean body mass (LBM) in Kg (measured using Dual energy x ray or bioelectric impedance analysis);
- Change in total energy absorption in Kcal (measured using bomb calorimetry or by subtracting the amount of energy excreted in stool output from that actually ingested);
- Changes in fat, carbohydrate and nitrogen absorption in grams (measured as the difference between intake and fecal loss);
- Change in serum level of insulin-like growth factor-1 (IGF-1) ng/mL (measured by radio-immunoassay);
- Change in parenteral nutrition requirements; and
- Adverse events related to the intervention.

Adverse events related to the intervention included:
A) Proportion of patients developing peripheral edema;
B)Proportion of patients developing arthralgia; and
C)Proportion of patients developing carpal tunnel syndrome.

Search methods for identification of studies

All publications describing randomised controlled trials of the use of human growth hormone with or without glutamine were sought through the Cochrane IBD/FBD Group Trials Register, and the Cochrane Central Register of Controlled Trials (CENTRAL) database. All studies were identified through electronic searches of MEDLINE (1966 to December 31, 2009), EMBASE (1980 to Dec 31, 2009), and CINAHL (1982 to December 31, 2009), and conference proceedings.
Databases were searched using the following search terms: "growth hormone," "glutamine," "intestinal rehabilitation," "intestinal

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