Therapeutic value of octreotide for patients with severe dumping syndrome—a review of randomised controlled trials

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Approximately 10%–50% of patients develop some manifestations of the dumping syndrome after gastric surgery. Among them, 5%–10% have clinically significant symptoms, and 1%–2% are debilitated by them.¹ Early dumping, typically starting 10–30 minutes after a meal, usually involves both vasomotor and gastrointestinal complaints such as sweating, palpitation, weakness and faintness, abdominal bloating, cramping, and profound diarrhoea. Late dumping, often occurring 2–3 hours postprandially, involves mainly vascular complaints characterised by perspiration, palpitation, mental confusion, and sometimes syncope. It is estimated that, among all affected patients, 75% have early dumping symptoms. The symptoms of early dumping probably result from rapid emptying of hyperosmolar chyme into the small bowel leading to a large fluid shift from the intravascular space into the intestinal lumen, with consequent rapid small bowel distension and an increase in both the amplitude and frequency of bowel contractions. Late dumping is a consequence of reactive hypoglycaemia resulting from an exaggerated insulin and glucagon-like peptide-1 release.² The diagnosis of late dumping syndrome can be often confirmed through frequent blood sampling after a provocation test using 75 g of orally administered glucose.

The management of the dumping syndrome can be achieved in most cases by dietary modification and adjustment of lifestyle, in particular reduction of carbohydrate intake. However, in approximately 3%–5% of patients, severe symptoms of dumping can continue despite dietary changes. This results in marked weight loss, fear of eating and outdoor activities, or even an inability to maintain full time employment. For the past decade it has been suggested that octreotide (Sandostatin SMS 210–995; Novartis Pharmaceuticals, East Hanover, NJ, USA), an analogue of somatostatin, can alleviate dumping by slowing gastric emptying, inhibiting insulin release, decreasing enteric peptide secretion, increasing intestinal absorption of water and sodium, slowing monosaccharide absorption, increasing gut transit time, and preventing haemodynamic changes. In particular, octreotide has been demonstrated to be effective in patients refractory to standard therapy.^{3 4}

Method

We have performed a systematic search for published randomised controlled trials on the effectiveness of octreotide in alleviating the

symptoms of the dumping syndrome. Electronic databases (till end of March 2000) including Medline, EMBASE, and PubMed were searched using keywords including “randomis(z)ed trial”, “dumping syndrome”, and “octreotide”. In addition, citations of relevant primary and review articles were examined.

Result

Seven randomised controlled trials (excluding one probably duplicated⁴) were identified.^{5–11} The seven trials recruited a total of 63 patients with severe symptoms of dumping. Octreotide (50 or 100 µg) was given 15–60 minutes before either a meal or a provocative dose of oral glucose (75–100 g). The following evidence of the effectiveness of octreotide for ameliorating dumping symptoms after the provocative glucose challenge were extracted from the seven trials and are summarised in table 1.

- (1) Alleviating diarrhoea, abdominal pain, dizziness, and palpitation.
- (2) Minimising changes in orthostatic pulse and blood pressure.
- (3) Minimising influence on packed cell volume and plasma osmolality.
- (4) Preventing late hypoglycaemia by reducing peak insulin concentration and prolonging maximal plasma glucose concentration.

Compared with the control cases, octreotide pretreatment resulted in significant improvement in symptoms in nearly all patients. Decreased gain in pulse rates and stabilised blood pressure were particularly recorded in four trials.^{5 6 10 11} Six trials described prevention of hypoglycaemia/rise of plasma insulin concentrations.^{5 6 8–11} One trial specifically recorded the induction of fasting migrating myoelectric complexes motility pattern (characteristic of interdigestive motility) and reduction in the duration and vigour of fed motility obtained with octreotide.⁷ However, the beneficial effect of octreotide on packed cell volume appeared uncertain.^{5 6 9–11} Furthermore, while two trials reported reduction of diarrhoea,^{5 8} three described development or worsening of this symptom.^{6 8 9}

Discussion

A recent editorial in the *British Journal of Surgery* stressed the importance of systematic reviews in assessing the effectiveness of treatment.¹² Systematic review aims to provide an unbiased summary of the evidence base to inform a clinical or policy question, to identify gaps in the research, and to improve the quality of new research. In the practice of “evidence

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Table 1 Randomised controlled trials on the effectiveness of octreotide for alleviating dumping syndrome after gastric/pancreatoduodenal surgery

Studies	Design	Method	Impact of octreotide	Side effects
Hasler <i>et al</i> , 1996 ⁵	Double blind, placebo controlled, crossover with 1 week washout	Eight patients with >2 year history received octreotide 50 µg or placebo 45 min before ingestion of 75 g glucose; 180 min follow up	Octreotide alleviated diarrhoea, dizziness, and palpitation ($p<0.001$ in all), minimised pulse and blood pressure change ($p<0.05$), and prevented late hypoglycaemia ($p<0.05$). It had no influence on packed cell volume or plasma osmolality	Painful injection (worse with placebo in four)
Gray <i>et al</i> , 1991 ⁶	Double blind, placebo controlled, crossover with 3 days' washout	Nine patients with severe dumping (4 months to 20 years) received octreotide 100 µg or placebo 30 min before ingestion of 400 ml mix of 40% glucose, 40% fat and 20% protein; 180 min follow up	Octreotide alleviated clinical dumping ($p<0.05$), minimised pulse change ($p<0.05$), and prevented late hypoglycaemia in 4 patients. It had no influence on packed cell volume or plasma osmolality	Observed* during continual octreotide treatment for an average of 5.7±1.3 months
Richards <i>et al</i> , 1990 ⁷	Double blind, placebo controlled, crossover in 2 consecutive days	Six patients with severe early dumping received octreotide 100 µg or placebo 20 min before ingestion of a 750 calorie meal containing 21 g protein, 30 g fat, and 99 g carbohydrate; 180 min follow up	Octreotide alleviated diarrhoea, abdominal pain, palpitation, and nausea in all patients, with shortened duration ($p<0.03$) and lowered vigour ($p<0.03$) of postprandial "fed" motility pattern	N/A
Geer <i>et al</i> , 1990 ⁸	Double blind, placebo controlled, crossover for 2 consecutive days	Ten patients with severe dumping (8 with early symptoms only) received 100 µg octreotide or placebo 30 min before ingestion of a 750 calorie meal containing 21 g protein, 30 g fat, and 99 g carbohydrate; 180 min follow up	Octreotide alleviated clinical dumping and abated diarrhoea ($p<0.001$) and increase in pulse or blood pressure, and prevented late hypocalcaemia. It also delayed gastric emptying. A 15 month treatment with octreotide (3–4 doses daily) continued diminution of symptoms and resulted in weight gain in all patients, and enabled 7 patients to return to work	Mild transient abdominal cramp in 4. 3 on long term treatment had diarrhoea relivable with extra dose of octreotide
Tulassay <i>et al</i> , 1989 ⁹	Double blind, placebo controlled, crossover for 2 consecutive days	Eight patients with both early and late dumping received 50 µg or placebo 15 min before ingestion of 75 g glucose; 240 min follow up	Octreotide prevented the development of both vasomotor and gastrointestinal syndromes ($p<0.001$) and packed cell volume changes. It also prevented hypoglycaemia or rise in plasma insulin and gastric inhibitory peptide concentrations ($p<0.001$)	N/A
Primrose and Johnston, 1989 ¹⁰	Randomised controlled crossover trial for 3 days	Ten patients received placebo, 50 or 100 µg octreotide 60 min before ingestion of 87.5 g glucose; 120 min follow up	Octreotide alleviated symptoms in 90% of cases (50% complete), and had a beneficial effect ($p<0.05$) on pulse, blood pressure, packed cell volume, and blood glucose. Three of 4 patients benefited from long term treatment (50 µg 3 times a day, up to 4 years)	For long treatment, 2 had severe diarrhoea, 1 existing diarrhoea was worsened
Hopman <i>et al</i> , 1988 ¹¹	Double blind, placebo controlled, crossover trial	Twelve patients received placebo or octreotide 50 µg 15 min before ingestion of 50 g glucose/m ² body surface; 210 min follow up	Octreotide alleviated symptoms in all ($p<0.05$), stabilised pulse rate ($p<0.05$), prevented hypoglycaemia ($p<0.05$), but had no effect on packed cell volume	None

*Two patients opted for surgery and had satisfactory outcome; four patients elected to stop octreotide, including two because of painful injection, one developed painful breast, and one had chest pain. Two patients required pancreatic enzyme replacement for steatorrhea during octreotide treatment.

based medicine", systematic reviewing plays a crucial part by providing the key information.

Our identified studies, admittedly involving relatively small numbers of patients, have unanimously shown short term benefit as well as promising long term results, confirming octreotide as an effective treatment for dumping syndrome. Side effects of octreotide such as steatorrhea or early morning diarrhoea associated with long term treatment were managed with pancreatic enzyme replacement or an extra dose of octreotide before bedtime.^{6,8} Notably, gallstone formation, as one of the most frequent side effects of octreotide therapy, was not observed among the identified trials. Based on their results, Geer *et al* suggested that, instead of gastrin or motilin, peptides such as pancreatic polypeptide, neurotensin, and glucagon may play a part in the development of dumping symptoms.⁸ Administration of octreotide 30 minutes before, or immediately after, a meal offers a practical and effective approach to the treatment of early and late dumping syndromes. We recommend that octreotide should be given for patients with severe or refractory dumping syndromes.

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