OCTREOTIDE IN THE PREVENTION AND TREATMENT OF GASTROINTESTINAL AND PANCREATIC FISTULAS

SUMMARY

The efficacy of octreotide in the prevention and treatment of gastrointestinal and pancreatic fistulas remains unclear. Clinical trials have not consistently shown a reduction in the development of pancreatic fistulas or overall complications. Additionally, differences in the definition of pancreatic fistula, complication endpoints, and dosing schedules, have made comparison of studies difficult. Studies on the use of octreotide for the treatment of established fistulas have demonstrated a consistent reduction in fistula output; however, there is insufficient evidence to conclude that octreotide reduces fistula closure rates or time to closure. Differences amongst the studies have again made comparisons difficult. Octreotide therapy may be useful when there is reason to believe that a reduction in fistula output would facilitate patient management. However, its use for the purpose of fistula closure or the use of doses greater than those evaluated in clinical trials cannot be recommended.

RECOMMENDATIONS

- **Level 1**
  - ➢ **None**

- **Level 2**
  - ➢ **Octreotide therapy may be used to reduce fistula output and facilitate patient fluid and electrolyte management in doses of 100 to 250 mcg subcutaneously every 8 hours.**

- **Level 3**
  - ➢ **If a clinically significant reduction in fistula output is not evident within 5-8 days, octreotide therapy should be discontinued.**

INTRODUCTION

Gastrointestinal and pancreatic fistulas are often difficult to manage and are associated with increased morbidity, often requiring longer hospital stays (1). Fistulas can often arise following abdominal surgery or trauma. In general, the more distal a fistula, the greater the fistula output volume (1,2). High-output fistulas are more likely to cause complications such as malnutrition, sepsis, fluid and electrolyte disturbances, and a lower incidence of spontaneous closure (1,2). With medical management alone there is a potential for spontaneous fistula closure, however this may take several weeks (1,2). Fistulas refractory to medical management alone generally require surgical closure (1,2).

Octreotide is an analog of somatostatin which can reduce gastrointestinal, biliary, and pancreatic secretions, as well as decrease gastrointestinal motility (1). Somatostatin is found within the pancreas, stomach, intestinal mucosa and mesenteric neurons (2). Because of its inhibitory actions, somatostatin has been used in the management of upper gastrointestinal hemorrhage, secretory diarrhea, and peptide

EVIDENCE DEFINITIONS
- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS
- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

secreting tumors (2). Octreotide has a longer half-life than somatostatin which allows for intermittent subcutaneous injections rather than a continuous intravenous infusion (1,2). Treatment with octreotide is proposed to decrease nutrient and electrolyte losses and promote fistula closure (1). Benefits of these actions would include decreased hospital stays, complication rates, and decreased overall cost of treatment (1).

LITERATURE REVIEW
Prevention of postoperative complications by administration of octreotide during or after surgery
Lowy et al. conducted a prospective, randomized trial in 110 patients to evaluate octreotide for prevention of pancreatic fistula after pancreaticoduodenectomy for malignant disease (3). Gastrointestinal reconstruction was standardized, and patients were randomized to receive 150 mcg of octreotide subcutaneously every 8 hours for 5 days vs. no treatment. The initial dose was administered after the completion of surgery or arrival to the surgical intensive care unit. The primary endpoint of the study was the development of a clinical or biochemical pancreatic anastomotic leak. A clinical pancreatic anastomotic leak was defined as the drainage of amylase-rich fluid (> 2.5 times the upper limit of normal) in association with fever, leukocytosis, and hemodynamic instability, or the need for percutaneous drainage, while biochemical pancreatic anastomotic leak was defined as drainage of amylase-rich fluid on or after postoperative day 3 that was asymptomatic and resolved spontaneously. Fifty-seven patients were randomized to receive octreotide and 53 patients received no treatment. The incidence of clinical or biochemical anastomotic leaks was not statistically different between the groups (28% vs. 21%; p-value not reported). The incidence of clinical pancreatic anastomotic leak was 12% in the octreotide group and 6% in the control group (p = 0.23). The incidence of biochemical pancreatic anastomotic leak was also not statistically different. No adverse effects could be directly related to octreotide. Based on univariate comparisons and a regression analysis; reoperative pancreaticoduodenectomy seemed to be associated with pancreatic anastomotic leaks (Class I).

Lange et al. conducted a prospective, randomized, double-blind trial to evaluate octreotide in reducing pancreatic drainage and the incidence of complications after resection of neuroendocrine tumors of the pancreas (4). Patients were randomized to receive octreotide subcutaneously every 8 hours in a dose escalating manner (50 mcg/dose on day 1, then 100 mcg/dose on day 2, then 150 mcg/dose thereafter) vs. a matching saline placebo. Treatment was continued until 3 days after drain removal. Parameters evaluated during the study included daily drain output, number of days to drain removal, and total drainage. Ten patients were randomized to receive octreotide and 11 patients received placebo. The mean and median days to drain removal, drainage per day, and total drainage were not statistically different between the two groups. Gallbladder sludge developed in 7 of 7 evaluable patients in the octreotide group and 4 of 8 evaluable patients in the placebo group (p = 0.1). There was also no statistical difference in significant complications caused by pancreatic drainage (20% in the octreotide group and 36% in the placebo group, p = 0.64) (Class I).

Stratta et al conducted a progressive randomized controlled study to evaluate octreotide after pancreas transplantation (5). The study enrolled 27 patients who were randomized to receive octreotide 100 mcg twice daily starting immediately after pancreas transplantation vs. no octreotide. Thirteen patients were randomized to the octreotide group and 12 patients to the control group. Patient survival, pancreas graft survival, rejection, infections, and operative complications were similar between the two groups. The incidence of clinically significant peripancreatic fluid collections, prolongation of ileus, and duodenal segment leaks were also similar between the two groups (Class I).

Prevention of postoperative complications by administration of octreotide before surgery
Friess et al conducted a randomized controlled multicenter study to evaluate octreotide in the prevention of postoperative complications in chronic pancreatitis patients (6). Eligibility criteria included patients with chronic pancreatitis who were suitable for pancreatic resection or pancreatic duct anastomosis. The study enrolled 247 patients who underwent one of several pancreatic operations including: Whipple procedure, pylorus-preserving pancreatic head resection, pancreaticojejunostomy, and others. Patients were randomized to receive octreotide 100 mcg subcutaneously every 8 hours vs. placebo for 8 days starting at least 1 hour prior to surgery. Post-operative complications included death; pancreatic, biliary, or intestinal anastomosis leakage; pancreatic fistula; intra-abdominal abscess; intra-abdominal fluid

collection; cardiopulmonary shock; sepsis; pulmonary insufficiency; renal insufficiency; bleeding and postoperative acute pancreatitis. One-hundred twenty-two patients were randomized to receive octreotide and 125 patients received placebo. Overall, 16% of patients in the octreotide group and 30% of patients in the placebo group had 1 or more postoperative complications (p < 0.007). The frequency of pancreatic fistula (12% vs. 28%, p < 0.05) and fluid collection (4% vs. 12%, p < 0.05) were both lower in the octreotide group. All other postoperative complications were not statistically different between the two groups. No specific adverse effects were identified with the study drug (Class I).

Yeo et al conducted a prospective, randomized double blind placebo controlled study to evaluate octreotide in the prevention of postoperative complications following pancreaticoduodenectomy (7). Patients were randomized to receive either octreotide 250 mcg subcutaneously every 8 hours starting 1 to 2 hours prior to surgery vs. matched placebo. The primary endpoints of the study included pancreatic fistula, total complications, and death. Pancreatic fistula was defined as greater than 50 mL of fluid from the surgically placed drains with amylase more than 3-fold the upper limit of normal in serum or pancreatic anastomotic disruption demonstrated radiographically. One-hundred four patients were randomized to receive octreotide and 107 patients received placebo. There was no significant difference in the rate of pancreatic fistulas (11% in the octreotide group vs. 9% in the control group). There was also no significant difference between both groups in total complication rate, mortality, or postoperative length of stay (Class I).

Pederzoli et al conducted a prospective, placebo-controlled double blind multicenter study to evaluate octreotide in the prevention of complications related to pancreatic surgery (8). Patients were randomized to receive either octreotide 100 mcg subcutaneously every 8 hours stating at least 1 hour prior to surgery vs. matched placebo. The primary endpoint was the difference in postoperative complications including death, dehiscence, pancreatic fistula, abdominal abscess, abdominal fluid collection, acute pancreatitis, shock, sepsis, respiratory failure, renal failure, and bleeding. One-hundred twenty-two patients were randomized to receive octreotide and 130 patients received placebo. The overall complication rate was significantly higher in the placebo group compared to the octreotide group (29 vs. 16%; p = 0.01). The rate of pancreatic fistula was significantly higher in the placebo group (19 vs. 9%; p < 0.05) and there was no difference in mortality between the two groups (3% for octreotide and 6% for placebo) (Class I).

Montori et al conducted a prospective, randomized, double blind, controlled study to evaluate octreotide in the prevention of pancreatic fistula after elective pancreatic resections (9). Patients were randomly assigned to receive either octreotide 100 mcg subcutaneously every 8 hours for 7 days starting within 1 hour preoperatively vs. placebo. The primary endpoint of the study was the occurrence of pancreatic fistula, defined as peripancreatic abdominal drainage with amylase concentration more than 3 times normal serum concentrations since postoperative day 3, with a volume greater than 10 mL/day. Secondary endpoints included overall morbidity (pancreatic fistula, postoperative pancreatitis, abscess, fluid collection, anastomotic leakage, bleeding, respiratory failure and renal failure) and mortality. One-hundred eleven patients were randomized to receive octreotide and 107 received placebo. Pancreatic fistula occurred in 9% of the octreotide group and 20% of the placebo group (p < 0.05) and the overall morbidity rate was 22% in the octreotide group and 36% in the placebo group (p < 0.05). Postoperative mortality rate was not significant between the two groups (Class I).

Buchler et al conducted a randomized, double-blind, placebo-controlled, multicenter study to evaluate octreotide in the reduction of postoperative complications after major elective pancreatic surgery (10). Patients were randomized to receive octreotide 100 mcg subcutaneously every 8 hours for 7 days starting within 1 hour preoperatively vs. placebo. The primary endpoint was the reduction in the rate of postoperative complications. Postoperative complications evaluated included death, leakage of anastomosis, pancreatic fistula, intra-abdominal abscess, intra-abdominal fluid collection, shock, sepsis, pulmonary insufficiency, renal insufficiency, bleeding, and pancreatitis. One-hundred twenty-five patients were randomized to receive octreotide and 121 patients received placebo. The complication rate was 32% in the octreotide group and 55% in the placebo group (p < 0.005) and the 90-day mortality rate was 3% in the octreotide group and 6% in the placebo group (p = NS). There was a significantly lower rate of pancreatic fistula in the octreotide group (18 vs. 38%; p < 0.05). High-risk patients (tumors) seemed to have a greater benefit from octreotide in regards to reduction of postoperative complications (Class I).

Benedetti et al conducted a prospective, randomized study to evaluate perioperative octreotide in prevention of technical complications after pancreas transplant (11). The study enrolled 17 patients who were randomized to receive octreotide 100 mcg subcutaneously every 8 hours for 5 days starting immediately before transplantation vs. no octreotide. Ten patients were randomized to the octreotide group and 7 to the control group. Both groups received identical immunosuppressive protocols. The two groups were compared in terms of patient and graft survival, pancreatitis, intra-abdominal infection, duodenal leak, graft thrombosis, rejection, glycemic control, and postoperative serum and urine amylase values. No patients in the treatment group developed technical complications, while 3 of 7 patients in the control group had technical complications (p = 0.05). There was no statistical difference between patient and graft survival between the two groups (Class I).

Octreotide for the treatment of established enterocutaneous pancreatic fistula
Scott el at conducted a prospective, randomized double-blind study to evaluate octreotide in the treatment of postoperative enterocutaneous fistula (12). Eligibility criteria included gastric, duodenal, pancreatic or small bowel fistula, no abscess, and no distal obstruction. Exclusion criteria included complete discontinuity, foreign body, spontaneous fistulating (Crohn's, malignancy, radiation enteritis), mucosal-skin continuity, and epithelialized track. The study evaluated 19 patients with at least 7 days of fistula output who were randomized to receive octreotide 100 mcg subcutaneously every 8 hours for 12 days vs. placebo. The primary endpoint of the study was fistula output reduction and the secondary endpoint was fistula closure defined as 2 or more successive days with no fistula output during the treatment period. Eleven patients were randomized to receive octreotide and 9 patients received placebo. About half the patients in the study had an upper gastrointestinal fistula. Median fistula losses were not statistically different between the two treatment groups (252 to 550 mL/day in the octreotide group and 202 to 400 mL/day in the placebo group). One patient in the treatment group had fistula closure and 3 patients in the placebo group had fistula closure, which was not statistically different (Class I).

Kusuhara et al conducted a randomized, placebo controlled trial to evaluate octreotide in the reduction of ileostomy output (13). Twelve patients with ileostomy following proctocolectomy for ulcerative colitis or familial adenomatosis coli were studied. Ileostomy output was assessed during three 5-day periods (no treatment, placebo, and octreotide). Ileostomy output was decreased from 997 mL during no treatment to 736 mL after octreotide treatment (p < 0.05) (Class I).

Sancho et al conducted a randomized, double-blind placebo-controlled trial to evaluate early administration of octreotide in the treatment of postoperative enterocutaneous fistula (14). The study evaluated 36 patients who were also started on total parenteral nutrition, and randomized them to receive octreotide 100mcg every 8 hours for 20 days vs. placebo. Clinical endpoints included reduction in fistula output and closure rate (no fistula output for two consecutive days, without relapse within 30 days). Fourteen patients were randomized to receive octreotide and 17 received placebo. There was no difference in the reduction of output at 24, 48 and 72 hours. The closure rate in the octreotide group was 57% and in the placebo group was 35%, which was not statistically different. There was also no difference in the time to closure between the two groups (Class I).

Nubiola-Calonge et al conducted a blind crossover trial to evaluate octreotide in the reduction of established fistula output (15). The patients were assigned to two groups; the first group received octreotide for 2 days and then placebo for 2 days (group A), while the second group received placebo for 2 days and then octreotide for 2 days (group B). After the 4-day study period all patients received octreotide. The study enrolled 14 patients who had been on parenteral nutrition, cimetidine and nasogastric suction, and during the treatment periods received octreotide 75-100 mcg every 8 hours. The primary endpoint was reduction in fistula output. Eight patients were randomized to receive treatment then placebo (group A) and 6 patients were randomized to receive placebo then treatment (group B). In the first group, an increase in fistula output was seen when octreotide was interrupted by placebo (228 mL/day vs. 498 mL/day; p = 0.014). In the second group, initiation of treatment with octreotide significantly reduced fistula output (828 mL/day vs. 247 mL/day; p < 0.01). In 11 patients there was spontaneous closure of the fistula in a mean of 4.5 days (Class I).

Torres et al conducted a prospective, randomized, controlled multicenter study to evaluate total parenteral nutrition (TPN) alone or in combination with somatostatin in the treatment of postoperative gastrointestinal fistula over a 20-day period (16). Clinical endpoints included daily fistula output, time to achieved 50% and 75% fistula output reduction and time to complete healing of fistula. Twenty patients were randomized to receive TPN and somatostatin (group B) and 20 patients received TPN alone (group A). Group A was younger and had a lower fistula output at baseline. There was not difference in the number of patients in the two groups with spontaneous fistula closure, but the mean interval of time to fistula closure was shorter in the somatostatin group (14 vs. 20 days; p < 0.05). The somatostatin group also achieved 50% and 75% reduction in fistula output sooner than the group on TPN alone, and had a lower incidence of complications (catheter, abdominal, or urinary sepsis; pneumonia; pneumothorax; wound or skin problems) (Class I).

Sitges-Serra et al conducted a prospective, randomized, controlled, double-blind cross-over study to evaluate octreotide in the treatment of established gastrointestinal fistulas (17). The study evaluated 20 patients, with group A receiving placebo for 2 days and then octreotide for 2 days, and group B receiving octreotide for 2 days and then placebo for 2 days. The study enrolled 20 patients, and during the treatment periods they received octreotide 100 mcg every 8 hours. The primary endpoint was reduction in fistula output. Thirteen patients were randomized to receive placebo followed by treatment (group A) and 7 patients were randomized to receive treatment followed by placebo (group B). In group B, an increase in fistula output was seen when octreotide was interrupted by placebo (218 mL/day vs. 436 mL/day; P < 0.05). In group A, initiation of treatment with octreotide significantly reduced fistula output (725 mL/day vs. 151 mL/day; P < 0.02). Overall, there was a 78% rate of spontaneous closure of the fistula in a mean of 5.8 days (Class I).

Huan-Long et al conducted a randomized, controlled study to evaluate octreotide in the reduction of pancreatic exocrine secretion when combined with parenteral or enteral nutrition (18). The study evaluated 17 patients after abdominal injury or operation and randomized them to receive parenteral or enteral nutrition. Patients received only nutritional support for 1 week and then in the second week were given octreotide 0.3 mg/500 mL saline infused continuously for 8 hours and 0.1 mg subcutaneous daily for 7 days. Nine patients were randomized into the parenteral nutrition group and 8 patients were randomized to receive enteral nutrition. In the parenteral nutrition group, there was a significant decrease in pancreatic juice (79.6 mL/day vs. 60.8 mL/day; p <0.05), protein (31 mg/dL vs. 22.8 mg/dL; p < 0.05) and amylase (4220 units/L vs. 3270 units/L; p < 0.05) content during the second week of treatment when octreotide was initiated. In the enteral nutrition group, there was a significant decrease in pancreatic juice (87.9 mL/day vs. 65.3 mL/day; p < 0.05), protein (36 mg/dL vs. 21.9 mg/dL; p < 0.05) and amylase (4440 units/L vs. 3670 units/L; p < 0.05) content during the second week of treatment when octreotide was initiated. Both groups also had a significant decrease in bicarbonate, potassium, sodium and chloride content in the pancreatic juice when octreotide was combined with parenteral or enteral nutrition (Class I).

Jamil et al conducted a randomized, controlled comparative study to evaluate octreotide in the management of enterocutaneous fistula (19). The study evaluated 33 patients, randomized to receive conservative treatment alone or conservative treatment and octreotide 100 mcg subcutaneously every 8 hours. Sixteen patients were randomized to receive octreotide and 17 patients did not receive octreotide. There was no significant difference between the two groups in regards to days to fistula closure (14 days in octreotide group vs. 18 days in control group; p > 0.05), length of hospital stay (15 day in octreotide group vs. 19 days in the control group) and mortality (3 patients in octreotide group vs. 2 patients in control group). There was a significantly greater cost of treatment in the group receiving octreotide (Class I).

Leandros et al conducted a prospective, randomized controlled study to evaluate somatostatin, octreotide and standard care alone in the treatment of gastrointestinal and pancreatic fistula (20). The study evaluated 48 patients who were randomized to receive standard therapy alone or in combination with somatostatin 6000 IU/day by intravenous infusion or octreotide 100 mcg subcutaneously every 8 hours. Nineteen patients were randomized to receive somatostatin, 17 received octreotide and 15 received standard medical care. The median length of hospital stay was significantly longer in the standard

treatment group (28 days); however, no difference was seen between the two treatment groups (24 days in octreotide group vs. 15 days in somatostatin group; p = 0.08). The time until restoration of oral nutrition was not significantly different between the 3 groups and the complication rates were not significantly different (67% in control group vs. 42% in somatostatin group vs. 41% in octreotide group; p = 0.35). The closure rate was lower in the control group (27%), while it was similar between the two treatment groups (84% in somatostatin group vs. 65% in octreotide group; p = 0.003), and the median time to closure was not significantly different between all 3 groups (18 days in control group vs. 10.5 days in somatostatin group vs. 16.5 days in octreotide group; p = 0.14). (Class I).

REFERENCES

1. Martineau P, Shewd JL, Denis R. Is octreotide a new hope for enterocutaneous and external pancreatic fistulas closure? *Am J Surg* 1996;172:386-395.
2. Li-Ling J, Irving M. Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials. *Br J Surg* 2001;88:190-9.
3. Lowy AM, Lee JE, Pisters PWT, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after panccreaticoduodenectomy for malignant disease. *Ann Surg* 1997;226:632-41.
4. Lange JR, Steinberg SM, Doherty GM, et al. A randomized, prospective trial of postoperative somatostatin analogue in patients with neuroendocrine tumors of the pancrease. *Surgery* 1992;112:1033-8.
5. Stratta RJ, Taylor RJ, Lowell JA, et al. Randomized trail of sandostatin prophylaxis for preservation injury after pancreas transplantation. *Transplant Proc* 1993;25:3190-2.
6. Friess H, Beger HG, Sulkowski U, et al. Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis. *Br J Surg* 1995;82:1270-3.
7. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? *Ann Surg* 2000;232:419-29.
8. Pederzoli P, Bassi C, Falconi M, et al and the Italian Study Group. Efficacy of octreotide in the prevention of complications of elective pancreatic surgery. *Br J Surg* 1994;81:265-269.
9. Montorsi M, Zago M, Mosca F, et al. Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: a prospective, controlled, randomized clinical trial. *Surgery* 1995;117:26-31.
10. Buchler M, Friess H, Klempa I, et al. Role of octreotide in the prevention of postoperative complications following pancreatic resection. *Am J Surg* 1992;163:125-30.
11. Benedetti E, Coady MD, Asolati M, et al. A prospective randomized clinical trial of perioperative treatment with octreotide in pancreas transplantation. *Am J Surg* 1998;175:14-17.
12. Scott NA, Finnegan S, Irving MH. Octreotide and postoperative enterocutaneous fistula: a controlled prospective study. *Acta Gastroenterol Belg* 1993;56:266-70.
13. Kusuhara K, Kusunoki M, Okamoto T, et al. Reduction of the effluent volume in high-output ileostomy patients by a somatostatin analogue, SMS 201-995. *Int J Colorect Dis* 1992;7:202-5.
14. Sancho JJ, Costanzo J, Nubiola P, et al. Randomized double-blind placebo-controlled trial of early octreotide in patients with postoperative enterocutaneous fistula. *Br J Surg* 1995;82:638-41.
15. Nubiola-Calone P, Badia J, Sancho J, et al. Blind evaluation of the effect of octreotide (SMS 201-955), a somatostatin analogue, on small-bowel fistula output. *Lancet* 1987;2:672-4.
16. Torres AJ, Landa JI, Moreno-Azcoita M, et al. Somatostatin in the management of gastrointestinal fistulas: a multicenter trail. *Arch Surg* 1992;127:97-9.
17. Sites-Serra A, Guirao X, Pereira JA, et al. Treatment of gastrointestinal fistulas with sandostatin. *Digestion* 1993;54(suppl 1):38-40.
18. Hang-Long Q, Zhen-Doug S, Yang Z, et al. Effect of parenteral and enteral nutrition combined with octreotide on pancreatic exocrine secretion of patients with pancreatic fistula. *Gastroenterol* 2004;10:2419-22.
19. Jamil M, Ahmed U, Sobia H. Role to somatostatin analogues in the management of enterocutaneous fistulae. *J Coll Physicians Surg Pak* 2004;14:237-40.
20. Leandros E, Antonkis PT, Albanopoulos K, et al. Somatostatin versus octreotide in the treatment of patients with gastrointestinal and pancreatic fistulas. *Can J Gastroenterol* 2004;18:303-6.

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TABLE 1: PREVENTION OF POSTOPERATIVE COMPLICATIONS WITH OCTREOTIDE

Reference	Year	Trial Type	Patients	Method	Follow-up	Treatment	Morbidity	Mortality
Lowy *et* al (3) (Class I)	1997	PRC	110	OC group: 57 Control: 53 All high-risk	30 postop days	OC 150 mcg q8 for 5 days starting postop	30 *v* 25% (NS) Pancreatic anastomotic leak: 12 *v* 6% (NS)	1 death in OC group (NS)
Lange *et* al (4) (Class I)	1992	RC, DB	21	OC group: 10 Control: 11 All high-risk	Up to 65 postop days	OC 50 mcg q8 x 3, 100 mcg q8 x 3, 150 mcg q8 starting postop	Problematic pancreatic drainage: 20 *v* 36% (NS) Gallbladder sludge: 100 *v* 50% (NS)	No death occurred
Stratta *et* al (5) (Class I)	1993	PRC	25	OC group: 13 Control: 12	10 postop months	100 mcg q12 for mean of 8 days starting postop	Similar in two groups Graft survival: similar in two groups	No deaths
Friess *et* al (6) (Class I)	1995	MC, RC, DB	247	OC group: 122 Control: 125 All low-risk	90 postop days	OC 100 mcg q8 for 8 days starting > 1 hour preop	16 *v* 30% (P < 0.007) PF: 10 *v* 22% (P < 0.05)	2 *v* 1% (NS)
Yeo *et* al (7) (Class I)	2000	PRC, DB	211	OC group: 104 (91 high-risk, 13 low-risk) Control: 107 (98 high-risk, 9 low-risk)	Up to 24 postop months	OC 250 mcg q8 x 7 days starting within 2 h preop	40 *v* 34% (NS) PF: 11 *v* 9% (NS) Mean hospital stay: 9 days in each group	0 *v* 1% (NS)
Pederzoli *et* al (8) (Class I)	1994	PRC, MC, DB	252	OC group: 122 (76 high-risk, 46 low-risk) Control: 86 high-risk, 44 low-risk)	90 postop days	OC 100 mcg q8 x 7 days starting > 1 hours preop	16 *v* 29% (P = 0.01) High-risk: 22 *v* 35% (NS) Low-risk: 4 *v* 18% (P = 0.05) PF: 9 *v* 19% (P < 0.05)	3 *v* 6% (NS)
Montorsi *et* al (9) (Class I)	1995	PRC, MC, DB	218	OC group: 111 (8 CP) Control: 107 (10 CP)	60 postop days	OC 100 mcg q8 x 7 days starting > 1 hour preop	22 *v* 36% (P < 0.05) PF: 9 *v* 20% (P < 0.05)	8 *v* 6% (NS)
Buchler *et* al (10) (Class I)	1992	MC, RC, DB	246	OC group: 125 (68 high-risk, 57 low-risk) Control: 121 (71 high-risk, 50 low-risk)	90 postop days	OC 100 mcg q8 x 7 days starting > 1 hour preop	32 *v* 55% (P < 0.005) High-risk: 38 *v* 65% (P < 0.01) Low-risk: 25 *v* 42% (NS) PF: 18 *v* 38% (P < 0.05)	3 *v* 6% (NS)
Benedetti *et* al (11) (Class I)	1998	PRC	17	OC group: 10 Control: 7	6 postop months	100 mcg q8 x 5 days starting preop	0 *v* 3 (P = 0.05) Graft survival: 90 *v* 86% (NS)	1 death in control group (NS)

DB, double-blind; ECF, enterocutaneous fistula; MC, multicenter; NS, not significant; OC, octreotide; PF, pancreatic fistula; (P)RC, (prospective) randomized controlled; SOM, somatostatin; *v*, versus

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TABLE 2: TREATMENT OF ESTABLISHED FISTULA WITH OCTREOTIDE

Reference	Year	Trial type	Subjects	Method	Treatment	Output reduction	Closure rate	Other
Scott *et* al (12) (Class I)	1993	PRC, DB	17 ECF, 2 PF (all > 7 days)	OC group: 11 Control: 8	OC 100 mcg q8 x 12 days	Similar in the two groups	1 *v* 3 (NS)	–
Kusuhara *et* al (13) (Class I)	1992	RC	12 ECF	First 5 days: no treatment Second 5 days: OC or placebo Third 5 days: reverse	OC 100 mcg q8	OC group: from 997(52) to 736(28) g/day (P < 0.05) Placebo had no effect	–	–
Sancho *et* al (14) (Class I)	1995	MC, PRC, DB	26 ECF, 5 PF (all > 50mL/day and < 8 days)	OC group: 14 Control: 17	OC 100 mcg q8 x 20 days	66(4.3) *v* 68(4.7)% by 24 hours (NS) 60(4.6) *v* 57(4.3)% by 48 hours (NS) 62(5) *v* 66(4.9)% by 72 hours (NS)	57 *v* 37% (NS) Closure time: 7(3) *v* 12(7) days (NS)	Injection pain in 16%; 4 deaths (2 each)
Nubiola-Calong *et* al (15) (Class I)	1987	PRC, blind, cross-over	14 ECF	Group A: OC then placebo, 2 days each (n = 8) Group B: placebo then OC, 2 days each (n = 6)	OC 75 – 100 mcg q8	Group A: from 228 mL/day after OC to 498 mL/day (P = 0.014) Group B: from 828 to 247 mL/day (P < 0.01)	79% in 2 – 10 days	1 allergic reaction, 1 cholestasis, 2 deaths
Torres *et* al (16) (Class I)	1992	MC, PRC	33 ECF, 7 PF, all > 150 mL/day	SOM group: 20 Control: 20	SOM 250 mcg/hr for 20 days	50% reduction: 5.2 *v* 9.8 days (P < 0.05) 75% reduction: 7.5 *v* 13.7 days (P < 0.01)	85 *v* 80% (NS) Closure time: 13.9 *v* 20.4 days (P < 0.05)	Complications: 35 *v* 79% (P < 0.05); 2 patients had hyperglycemia
Sitges-Serra et al (17) (Class I)	1993	PRC, DB, cross-over	20 ECF (all > 29 days)	Group A: placebo then OC, 2 days each (n = 13) Group B: OC then placebo, 2 days each (n = 7)	OC 100 mcg q8	Group A: from 725 to 151 mL/day (P < 0.02) Group B: 218 mL/day after OC to 436 mL/day (P < 0.05)	78% by 5.8 days	Continual treatment changed all high-output fistulas into low ones; injection pain: 15%; 2 deaths
Haun-Long et al (18) (Class I)	2004	RC	20 PF	PN + OC (n = 9) EN + OC (n = 8)	OC 0.3 mg infusion, then 0.1 mg daily x 7 days	PN: 79.6 mL/day to 60.8 mL/day (P < 0.05). EN: 87.9 mL/day to 65.3 mL/day (P < 0.05). No difference between two groups	–	OC reduced protein, amylase, and electrolyte content of pancreatic juices
Jamil et al (19) (Class I)	2004	RC	33 ECF	OC group: 16 Control: 17	OC 100 mcg q8 till fistula closure	–	Overall 100% 14 v 17.7 days (NS)	Hospital stay: 15 v 19 days (NS) 3 deaths in octreotide group, 2 death in control group
Leandros et al (20) (Class I)	2004	PRC	38 GF 13 PF	SOM group: 19 OC group: 17 Control: 15	SOM 6000 IU/day IV infusion OC 100 mcg q8	–	84.2 v 64.7 v 26.7% (P = 0.003) SOM v OC (NS) Closure time: 10.5 v 16.5 v 16 days (NS)	Similar complication rates; 2 deaths (both in control group); treatment group had shorter hospital stay

DB, double-blind; ECF, enterocutaneous fistula; EN, enteral nutrition; GF, gastric fistula; MC, multicenter; NS, not significant; OC, octreotide; PF, pancreatic fistula; PN, parenteral nutrition; (P)RC, (prospective) randomized controlled; SOM, somatostatin; *v*, versus

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