OCTREOTIDE IN THE PREVENTION AND TREATMENT OF GASTROINTESTINAL AND PANCREATIC FISTULAS

SUMMARY

Octreotide has been used for the prevention and treatment of fistulas, however, its effectiveness is unclear. Studies have not consistently shown a reduction in the development or healing of pancreatic fistulas nor in overall complications. There is insufficient evidence to conclude that octreotide reduces fistula closure rates or time to closure. Octreotide therapy may be useful when there is reason to believe that a reduction in fistula output would facilitate patient management. Its use for the purpose of fistula closure or the use of doses greater than those evaluated in clinical trials is not recommended.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Octreotide therapy may be used to reduce fistula output in doses of 100 to 250 mcg subcutaneously every 8 hours.**
  - **If a clinically significant reduction in fistula output is not evident within 5 - 8 days, octreotide therapy should be discontinued.**
- **Level 3**
  - **Octreotide does not reduce time to fistula closure or closure rate**

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 from abdominal surgery or trauma. Gastrointestinal fistulas may form between the digestive tract lumen and skin, the bladder, or another abdominal cavity or viscous lumen (1). A pancreaticocutaneous fistula forms between the pancreatic duct and the skin. 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). Typical management of enteric fistulas include correction of electrolyte imbalances, repletion of ongoing losses, skin protection, prevention of infections and total parenteral or enteral nutrition (1,2). With medical management alone there is a potential for spontaneous fistula closure, however this may take several weeks (1,2). Fistulas refectory to medical management alone will need to be surgically closed (1,2).

Octreotide is an analog of somatostatin which can reduce gastrointestinal, biliary, and pancreas 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.

Approved 06/20/2005
Revised 10/06/2009, 11/2/2017

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 single-institution, prospective, randomized trial to evaluate octreotide for prevention of pancreatic fistula after pancreaticoduodenectomy for malignant disease (3). Eligibility criteria included patients with biopsy-proven or suspected malignant disease, no extrapancreatic disease, no evidence of tumor enhancement of the superior mesenteric artery or celiac axis, and a patent superior mesenteric-portal venous confluence. The study enrolled 110 patients who underwent pancreaticoduodenectomy for biopsy-proven or suspected disease, of which 46 patients received preoperative chemoradiation with continuous-infusion 5-fluorouracil. Pancreaticoduodenectomy included distal gastrectomy in all patients, and after tumor resection, electron-beam intraoperative radiation therapy was delivered to the bed of the resected pancreas. Gastrointestinal reconstruction was standardized, and after surgery patients were randomized to receive 150 mcg of octreotide subcutaneously every 8 hours for 5 days or 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 median age was 63 years and the two groups were similar with respect to tumor type, percent receiving preoperative chemoradiation and intraoperative radiation therapy, and percent undergoing reoperative pancreaticoduodenectomy. The incidence of clinical or biochemical anastomotic leaks were not statistically different between both groups (28% in octreotide group vs. 21% in control group, 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) and the incidence of biochemical pancreatic anastomotic leak were also not statistically different. There was 1 (2%) perioperative death in the octreotide group and none in the control group. No adverse effects could be directly related to octreotide and based on univariate comparisons and a stepwise 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). Eligibility criteria included patients scheduled to undergo surgery at the NIH for pancreatic endocrine tumor. Exclusion criteria included patients with diabetes. The minimum operation necessary to remove the tumor was performed, and drains were placed after pancreatic incision (two Penrose and one triple lumen). After the surgery, 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) or 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 median age was 46 years (range, 23 to 69). 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 in the safety and efficacy in minimizing early preservation injury after pancreas transplantation (5). The study enrolled 27 patients who were randomized to receive octreotide 100 mcg twice daily starting immediately after pancreas transplantation or no octreotide. Thirteen patients were randomized to the octreotide group and 12 patients to the control group. The mean age was 35 years and both groups were similar regarding demographic, clinical, and donor characteristics. 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)

Droeser et al. conducted a retrospective review of the clinical data of patients undergoing pancreatic resection who developed a post-operative pancreatic fistula (6). The aim was to compare patients receiving post-operative prophylaxis with octreotide versus those who did not, to evaluate whether post-operative octreotide attenuated the severity of post-operative pancreatic fistula. Twenty-two patients received octreotide within 24 hours after surgery, and 56 control patients received no octreotide. Most patients underwent either a pancreaticoduodenectomy (n=51) or a pancreatic resection (n=20). There were no differences in baseline demographic or operative characteristics between the groups except for a shorter operative time in the control group. Patients in the octreotide group received 100 mcg subcutaneously every 8 hours for a mean of 11.2 ± 1.3 days. The primary endpoints were the grade of post-operative pancreatic fistula (ISGPF criteria) and the amount of lipase activity within the drainage at post-operative day 3, 5, and 7. The secondary endpoints were overall mortality, ICU stay, and post-operative hospital stay. Overall, there was a significantly higher incidence of severe post-operative pancreatic fistula (Grade B or C) in the patients treated with octreotide. This was also independently associated with the lipase activity level following surgery. Sensitivity analysis did not demonstrate that octreotide had a significant effect on the lipase activity, despite a significantly higher lipase activity at POD 3 in the octreotide group. Overall survival, ICU stay, and hospital were all comparable between both groups. (Class II)

Fernandez-Cruz et al. conducted a prospective randomized controlled trial in patients undergoing elective pancreaticoduodenectomy to evaluate the effect of prophylactic octreotide on pancreatic exocrine secretion and the development of clinically relevant post-operative pancreatic fistula (7). Patients were eligible for enrollment if they were undergoing an elective pancreaticoduodenectomy, and were excluded if they had non-resectable disease or if their surgery was converted to a different operation. Patients were randomized to either the octreotide group or the placebo group. Patients in the treatment group received octreotide 100 mcg subcutaneously every 8 hours for 10 days starting during the procedure (immediately following pancreaticoduodenectomy). Thirty-two patients were enrolled in the octreotide group and thirty patients were enrolled in the placebo group. The primary endpoint was the effect of perioperative octreotide on pancreatic remnant exocrine secretion and the rate of development of clinically relevant post-operative pancreatic fistula (ISGPF Grade B or C). There was no significant difference overall between the two groups in terms of median pancreatic output, and this remained consistent when broken down by pathological diagnosis and pancreatic duct size. In both groups, pancreatic secretion amount was lower in patients with adenocarcinoma versus periampullary tumors. There was also no significant difference in terms of the development of clinically relevant post-operative pancreatic fistula, mortality, complications, or hospital length of stay. Overall, this trial does not support the routine use of perioperative octreotide to reduce pancreatic secretion or post-operative pancreatic fistula formation. (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 (8). 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: left resection, Whipple procedure, duodenum-preserving pancreatic head resection, pancreaticojejunostomy, and others. Patients were randomized to receive octreotide 100 mcg subcutaneously every 8 hours or placebo for 8 days starting at least 1 hour prior to laparoscopy. Post-operative complications evaluated

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. The median age was 48 years and the two groups were similar with respect to underlying disease and surgery performed. Overall, 16.4% of patients in the octreotide group and 29.7% 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%, $p<0.05$) was lower in the octreotide group. All other postoperative complications were not statistically different between the two groups. There were 2 deaths within 90 days of surgery in the octreotide group and 1 death in the placebo group. No specific adverse effects were identified with the study drug. (Class I)

Yeo et al. conducted a progressive randomized double-blind placebo controlled study to evaluate octreotide in the prevention of pancreaticoduodenectomy postoperative complications (9). Eligibility criteria included patients undergoing a pancreaticoduodenectomy. The study enrolled 211 patients who were eligible for the final analysis. Patients were randomized to receive either octreotide 250 mcg subcutaneously every 8 hours starting 1 to 2 hours prior to surgery or 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. The mean age was 64 years and the two groups were similar regarding gender and preoperative factors. 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 progressive placebo-controlled double-double blind multicenter study to evaluate octreotide in the prevention of complications related to pancreatic surgery (10). Eligibility criteria included adult patients undergoing elective pancreatic resection or drainage procedures for tumors of the periampullary region, or for chronic pancreatitis. Exclusion criteria included emergency surgery, total pancreatectomy, pancreatic transplantation and pancreatic resection combined with substantial intestinal resection. The study evaluated 252 patients. Patients were randomized to receive either octreotide 100 mcg subcutaneously every 8 hours stating at least 1 hour prior to surgery or 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 mean age was 53 and the two groups were similar regarding sex, underlying illness, preoperative morbidity, and type of operation. 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, controlled, randomized, double blind study to evaluate octreotide in the prevention of pancreatic fistula after elective pancreatic resections (11). Eligibility criteria included candidates for an elective pancreatic resection for neoplastic of chronic inflammatory disease of the pancreas and the periampullary region, and those with solid neoplasm's or inflammatory diseases requiring an additional partial pancreatic resection. Exclusion criteria included patients aged less than 18 and greater than 75, very high-risk patients (American Society of Anesthesiologists, class III and IV), patients with ongoing acute pancreatitis, those treated with octreotide or somatostatin within the last 48 hours and those undergoing operations other than resection, total pancreatectomy, or emergency pancreatic surgery. The study evaluated 218 patients, who were randomly assigned to receive either octreotide 100 mcg subcutaneously every 8 hours for 7 days starting within 1 hour preoperatively or

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. The mean age was 58.2 years and the two groups were similar with regards to gender, types of operation, and underlying disease. 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 (12). Eligibility criteria included patients with pancreatic or periampullary tumors and those suffering from chronic pancreatitis who were suitable for pancreatic resection. Exclusion criteria included emergency surgery of the pancreas, total pancreatectomy, pancreatic transplantation, or elective pancreatic-cyst anastomosis. The study evaluated 246 patients who were randomized to receive octreotide 100 mcg subcutaneously every 8 hours for 7 days starting within 1 hour preoperatively or 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 median age was 51 years and the two groups were similar regarding underlying disease, surgery performed, and preoperative morbidity. The majority of patients underwent pancreaticoduodenectomy. The complication rate was 32% in the octreotide group and 55.4% in the placebo group ($p<0.005$) and the 90-day mortality rate was 3.2% in the octreotide group and 5.8% in the placebo group (p=NS). There was a significantly lower rate of pancreatic fistula in the octreotide group (18 vs. 38%; $p<0.05$). Also, in this study, high-risk patients (tumors) seemed to have a greater benefit from octreotide in regard 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 (13). The study enrolled 17 patients who were randomized to receive octreotide 100 mcg subcutaneously every 8 hours for 5 days starting immediately before transplantation or 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. The mean age was 35 years and the two groups were similar in regard to demographic and clinical characteristics. 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)

Graham et al. prospectively evaluated patients at elevated risk of developing POPF (pancreatic duct size $\leq$ 3 mm) receiving preoperative octreotide compared to low risk patients (>3 mm duct size) and a historically matched cohort of control patients (14). Both the low-risk group and the historical cohort (consisting of both low and high-risk patients) did not receive octreotide. Patient receiving octreotide were treated with a 20 mg depot intramuscular injection 1 hour prior to induction of procedure and continued on an intravenous infusion of 25 mcg/hour for 24 hours. The historical cohort of control patients was treated by the same 2 surgeons conducting the procedures on the other two groups. One hundred and six patients were included in the control group (44 high-risk and 62 low-risk). Thirty-six patients were included in the high-risk group and thirty-two were included in the low-risk group. The incidence of POPF was significantly higher in the high-risk group vs the low-risk group, and the incidence in both groups was

similar to the historical cohort. The use of preoperative depot octreotide did not reduce the incidence of POPF in high-risk patients. (Class II)

Octreotide for the treatment of established enterocutaneous pancreatic fistula

Scott et al. conducted a prospective randomized double-blind study to evaluate octreotide in the treatment of postoperative enterocutaneous fistula (15). 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 or 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 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 (16). Twelve patients with ileostomy following proctocolectomy for ulcerative colitis or familial adenomatosis coli were studied. The study was carried out 2 to 3 months after surgery. Ileostomy output was assessed during three 5-day periods (no treatment, placebo, and octreotide). Ileostomy output was decreased from 997g during no treatment to 736g 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 (17). Eligibility criteria included all patients with postoperative enterocutaneous fistula of less than 8 days with a daily output greater than 50 mL. Patients with fistulas arising from neoplastic or irradiated tissues were excluded. 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 or 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 (18). 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 patient received octreotide. Eligibility criteria included persistent fistula drainage for at least 7 days and not originating from cancerous or necrotic bowel. 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 (19). Eligibility criteria included patients with postoperative gastrointestinal fistulas with an output higher than 150 mL/day. Exclusion criteria included greater than a 1000mL/48hours leakage, use of greater than 30 units of insulin per day, intra-abdominal sepsis, intra-abdominal foreign bodies, or fistula arising from a cancerous area. The study evaluated 40 patients, with group A receiving TPN alone, and group B receiving TPN plus somatostatin 250 mcg/hour for 20 days. 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 (13.86 vs. 20.4 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 (20). 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; $p<0.02$). Over all 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 (21). 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. Clinical endpoints included collection of pancreatic juice for determination of volume, protein, amylase, bicarbonate, potassium, sodium and chloride content.

Nine patients were randomized into the parenteral nutrition group and 8 patients were randomized to receive enteral nutrition. There was no statistical difference between the two groups regarding the clinical endpoints before or after the initiation of octreotide. 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 (22). Eligibility criteria included enterocutaneous fistula from esophagus to colon, while those needing surgery or where spontaneous closure was not possible were excluded. The study evaluated 33 patients, and they were randomized to receive conservative treatment

alone or conservative treatment and octreotide 100 mcg subcutaneously every 8 hours. Clinical endpoints included time to fistula closure, length of hospital stay, cost of treatment and mortality.

Sixteen patients were randomized to receive octreotide and 17 patients did not receive octreotide. There was no significant difference between the two groups in regard to days to fistula closure (14 days in octreotide group vs. 17.7 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 (23). 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. Clinical endpoints included length of hospital stay, days until oral nutrition, presence of complications, fistula closure, and outcome on discharge.

Nineteen patients were randomized to receive somatostatin, 17 received octreotide and 15 received standard medical care. The three groups were not similar in regard to age. 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 (66.7% in control group vs. 42.1% in somatostatin group vs. 41.2% in octreotide group; $p= 0.35$). The closure rate was lower in the control group (26.7%), while it was similar between the two treatment groups (84.2% in somatostatin group vs. 64.7% 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. Droeser RA, Jeanmonod P, Schuld J, Moussavian MR, Schilling MK et al. Octreotide prophylaxis is not beneficial for biochemical activity and clinical severity of postoperative pancreatic fistula after pancreatic surgery. *Digestive Surgery* 2012; 29:484-491.
7. Fernández-Cruz L, Jimenez Chavarria E, Taura P, Closa D, Boado MA et al. Prospective randomized trial of the effect of octreotide on pancreatic juice output after pancreaticoduodenectomy in relation to histological diagnosis, duct size and leakage. *HPB (Oxford)* 2013; 15:392-399.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. Graham JA, Johnson LB, Haddad N, Al-Kawas F, Carroll J et al. A prospective study of prophylactic long-acting octreotide in high-risk patients undergoing pancreaticoduodenectomy. *Am J Surg* 2011; 201:481-485.
15. Scott NA, Finnegan S, Irving MH. Octreotide and postoperative enterocutaneous fistula: a controlled prospective study. *Acta Gastroenterol Belg* 1993; 56:266-270.
16. 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; 7:202-205.
17. 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; 82:638-641.
18. 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; 2:672-674.
19. Torres AJ, Landa JI, Moreno-Azcoita M, et al. Somatostatin in the management of gastrointestinal fistulas: a multicenter trail. *Arch Surg* 1992; 127:97-99.
20. Sites-Serra A, Guirao X, Pereira JA, et al. Treatment of gastrointestinal fistulas with sandostatin. *Digestion* 1993;54(suppl 1):38-40.
21. 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; 10:2419-2422.
22. Jamil M, Ahmed U, Sobia H. Role to somatostatin analogues in the management of enterocutaneous fistulae. *J Coll Physicians Surg Pak* 2004;14: 237-240.

23. 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.

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Dominick Curry, PharmD; Brandon Hobbs, PharmD
Editors: Michael L. Cheatham, MD, Chadwick Smith, MD
Last revision date: November 2, 2017

Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net