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Somatostatin analogues in the prevention of pancreas-related complications after pancreatic resection

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Abstract
Background/Purpose. The Achilles' heel of operative pancreatectomies is the pancreaticoenterostomy for proximal resections and the pancreatic parenchymal closure for distal resections. Inhibition of pancreatic exocrine secretions by somatostatin analogues has been suggested to decrease pancreas-specific complications, but this topic remains controversial.
Methods. We performed a randomized, prospective, placebo-controlled, multicenter trial of the use of perioperative vapreotide, a potent somatostatin analogue, in pancreatic resections for presumed neoplasms in 381 patients without chronic pancreatitis. We also reviewed the literature on the use of somatostatin and its analogues after pancreatectomy.
Results. When compared to the placebo, perioperative vapreotide had no effect on overall pancreas-specific complications (30.4% vs 26.4%), mortality (0% vs 1.4%), overall complications (40% vs 42%), and duration of hospitalization; there were no differences in complications per type of resection with use of vapreotide — proximal versus distal resection. Seven other prospective, randomized trials provide differing results.
Conclusions. Our study with vapreotide failed to show any benefit when administered perioperatively (and for 7 days postoperatively) on pancreas-specific complications after major pancreatectomy in patients without chronic pancreatitis. The use of perioperative analogues that suppress pancreatic exocrine secretion seems not to be warranted as routine treatment.

Key words Somatostatin · Octreotide · Vapreotide · Pancreatic resection · Pancreatic fistula · Pancreaticoduodenectomy · Pancreatectomy

In the past decade, pancreatic resection has been used with ever-increasing frequency to treat many pancreatic disorders. This marked increase in major pancreatectomy is a direct result of the combination of improved safety, a decrease in the mortality associated with these procedures secondary to increased experience with the operations, and improvements in perioperative care. No longer are operative mortality rates too high to justify resection. Mortality rates at tertiary referral centers with dedicated experience are less than 5% and are less than 2% in some centers.

However, the major surgical complication of pancreatic resection remains the postoperative exocrine fistula/leak. Pancreatic fistula/leak after pancreatic resection with or without pancreaticoenteric anastomosis is responsible for a substantial proportion of the morbidity and can contribute to the mortality of these operations. The incidence of pancreatic fistula/leak after pancreaticoduodenectomy has not changed much since Whipple's original report[1] and varies from 2% to as high as 38% depending on the series;[2–8] therefore, the pancreatic anastomosis is considered the Achilles' heel of the procedure. One must remember when reviewing the literature that to date there is no consensus regarding the definition of pancreatic fistula/leak; hence it is difficult to estimate the true frequency of pancreatic fistula after pancreatic resection, because surgeons use a different set of criteria for the definition of leak.

A number of technical and pharmacologic interventions have been suggested to decrease the frequency of pancreatic fistula/leak after pancreatic resection without an accepted consensus of success.[9–11] The most common pharmacologic approach has been the use of somatostatin and, more recently, its long-acting synthetic analogues (octreotide and vapreotide). Somatostatin and its analogues inhibit secretion of multiple gastrointestinal hormones such as cholecystokinin (CCK), gastrin, pancreatic polypeptide, motilin, secretin, glucose-dependent insulinotropic peptide (GIP), and vasoactive intestinal polypeptide (VIP), as well as inhibiting gastric secretion and gallbladder motility.

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However, more important to this discussion is the effect of these long-acting somatostatin analogues on pancreatic function.

In the pancreas, somatostatin acts in a paracrine manner to inhibit exocrine secretion, as well as inhibiting the release of the hormones insulin and glucagon. The theory underlying the use of a somatostatin analogue is that by decreasing the volume of pancreatic exocrine secretion, the incidence of pancreatic fistula/leak would be decreased, because the pancreaticoenteric anastomosis or site of pancreatic parenchymal closure will heal better. Therefore, the use of somatostatin analogues in the prevention of pancreas-related complications after pancreatic resection has appealed to many surgeons. In 1979, Klempa et al.[12] reported on the use of somatostatin to reduce the incidence of complications after pancreatic resection. At least four other studies have addressed the use of prophylactic somatostatin in the prevention of pancreas-related complications.[13–16] One limitation of somatostatin is its very short half-life, and thus several analogues have been developed pharmacologically that have a much greater metabolic stability and longer duration of action. Since 1992, eight large controlled trials have been conducted primarily in academic centers to evaluate the efficacy of somatostatin analogues in the prevention of intra-abdominal complications after pancreatic resection (Table 1).[8,17–23] Other smaller, uncontrolled or retrospective trials using octreotide have been reported as well.[24–27]

In 2003, the senior author coordinated a study, conducted by The Pancreatic Surgery Group at 16 academic centers in the United States, aimed at determining prospectively if vapreotide, a more potent somatostatin analogue, would decrease pancreas-specific complications in a prospective, double-blinded, placebo-controlled trial.[22] This carefully carried out multicenter trial, although funded by the industry, was conducted by an industry-independent research firm (Target Research Associates, New Providence, NJ, USA), used intention-to-treat analysis with objective criteria of pancreas-specific complications, and was monitored by a separate, independent, data safety monitoring committee.

This study involved 381 patients 18 years of age or older undergoing either proximal or central pancreatectomy with pancreaticoenteric anastomosis or distal pancreatectomy with or without pancreaticoenteric anastomosis. These patients were randomized preoperatively to receive 0.6 mg of vapreotide acetate or placebo subcutaneously 2 h before operation and then every 12 h thereafter for 7 days postoperatively. Vapreotide, a potent synthetic analogue of somatostatin, is a cyclic octapeptide with a high affinity for somatostatin receptor subtypes 2 and 5 and some affinity for subtype 4. This somatostatin analogue has been shown to decrease pancreatic exocrine secretion by more than 75%.[28] Patients with chronic pancreatitis were specifically excluded from this study, because the study was designed to select patients undergoing elective pancreatic resection for presumed neoplasms in whom the pancreatic parenchyma would be expected to be otherwise normal and thus at high risk for anastomotic fistula/leak. The firm fibrotic glands of patients with chronic pancreatitis have a lower risk of developing anastomotic failure.

When the interim analysis was carried out after about 50% of the planned number of patients had been recruited and followed up for 45 days postoperatively, the study was closed, because no statistical differences were found. Two hundred and seventy five patients completed the trial (135 in the vapreotide arm and 140 in the placebo arm). Patients were followed up for a minimum of 45 days. The indications and type of pancreatic resection were distributed evenly between groups (Table 2). There were no differences in pancreas-specific complications (placebo, 26.4%; vapreotide, 30.4%; $P = 0.47$), mortality (placebo, 1.4%; vapreotide, 0%), overall complications (placebo, 42%; vapreotide 40%; $P = 0.72$), or duration of postoperative hospitalization. A post-hoc, subgroup analysis according to the type of pancreatic resection also found no differences between different types of operations (pancreaticoduodenectomy: pla-

Table 1. Prospective randomized controlled trials of somatostatin analogues for the prevention of complications after pancreatic resection

Reference	Year	Country	Setting	Number of patients	CP/other	SA	Pancreatic fistula/leak (SA vs control)	Mortality (SA vs control)
Buchler et al.[16]	1992	Germany	MC	248	112/136	Octreotide	18% vs 38% ($P < 0.05$)	3% vs 6% (NS)
Pederzoli et al.[17]	1994	Italy	MC	252	95/157	Octreotide	9% vs 19% ($P < 0.05$)	3% vs 6% (NS)
Montorsi et al.[18]	1995	Italy	MC	218	18/200	Octreotide	9% vs 20% ($P < 0.05$)	8% vs 6% (NS)
Friess et al.[19]	1995	Germany	MC	247	247/0	Octreotide	10% vs 22% ($P < 0.05$)	2% vs 1% (NS)
Lowy et al.[20]	1997	USA	SC	110	5/105	Octreotide	12% vs 6% (NS)	0.8% vs 0% (NS)
Yeo et al.[21]	2000	USA	SC	211	22/189	Octreotide	11% vs 9% (NS)	0% vs 1% (NS)
Sarr et al.[22]	2003	USA	MC	275	0/275	Vapreotide	30% vs 26% (NS)	0% vs 1.4% (NS)
Suc et al.[23]	2004	France	MC	230	30/200	Octreotide	17% vs 19% (NS)	12% vs 7% (NS)

CP, chronic pancreatitis; SA, somatostatin analogue; MC, multicenter; SC, single center; NS, not significant

Table 2. Indications and type of pancreatic resection in the vapreotide study

	Placebo (n = 140)	Vapreotide (n = 135)
Pathology (%)		
Benign neoplasm	23	21
Malignant	70	68
Pancreatic ductal	36	44
Ampullary	14	8
Duodenal	3	3
Bile duct	4	4
IPMN	1	0
Neuroendocrine	7	7
Cystadenocarcinoma	0	1
Other	6	1
Nonneoplastic	7	10
Type of resection (%)		
Pancreaticoduodenectomy	77	79
Classical	46	52
Pylorus-preserving	31	27
Distal pancreatectomy	19	19
Central pancreatectomy	4	2

IPMN, intraductal papillary mucinous neoplasm

cebo, 24%; vapreotide, 27%; distal pancreatectomy: placebo, 27%; vapreotide, 42%). As other studies have demonstrated, this study showed that pancreas-related complications were more frequent in patients found intraoperatively to have a soft pancreatic parenchyma than in those with a firm pancreas; the administration of vapreotide made no difference in these subgroups either.

The overall conclusion of this study was that vapreotide administered preoperatively and for 7 days postoperatively offers no therapeutic benefit in reducing postoperative pancreas-related complications in patients undergoing elective pancreatic resection for causes other than chronic pancreatitis.[22]

Two other prospective, randomized, but single-center studies conducted in the United States using perioperative octreotide have drawn similar conclusions in patients undergoing elective pancreatectomy, one at the MD Anderson Cancer Center[20] and the other at the Johns Hopkins Hospital.[21] In contrast, four multicenter, prospective, randomized, controlled trials carried out in Europe support the use of perioperative octreotide to decrease the complication rate of pancreatic resection.[16–19] The most recent report, a multicenter, prospective trial originating in France from the French Associations for Surgical Research, reached a conclusion that lies between those of the previous studies. Although they do not recommend the routine use of octreotide in all patients undergoing pancreatectomy, they concluded that prophylactic octreotide may be useful in patients in whom a pancreaticojejunostomy is to be performed, or in those patients with a pancreatic duct diameter of less than 3 mm, or both.[23] This latter study, as with most all these studies, is not without its limitations. Biologic glue was used more frequently in the octreotide group than in the controls, and it was only after a subgroup analysis that the differences favoring octreotide became evident.

The reasons behind the almost diametrically opposite results of the efficacy of perioperative somatostatin analogues in patients undergoing elective pancreatectomy in Europe and in the United States remain largely unknown. Because all these studies differ in terms of study design, diagnosis, operative procedures, drug or drug dosage, time of administration, and the rate and definition of pancreatic fistula, comparisons have been very difficult.[29] Among the findings that all the published trials have in common is that none has demonstrated a decrease in the overall mortality rate secondary to the use of somatostatin analogues. This observation is related, in part, to the low risk of postoperative death after elective pancreatectomy.

The efficacy of somatostatin analogues for protection against anastomotic leaks may be affected by several factors:

1. A single-patient study demonstrated significant fluctuations in enzyme concentrations after administration of octreotide, which resulted in production of low volumes of pancreatic juice with high enzyme concentrations, which could be detrimental for fistula prevention or closure.[30]
2. The inhibitory effects of octreotide on pancreatic secretion have been reported to diminish with repeat applications.[31]
3. Somatostatin and its synthetic analogues cause a decrease in splanchnic blood flow that theoretically may interfere with anastomotic healing.[32,33]
4. Somatostatin and its analogues have been shown to alter T cell function, which may also affect postoperative immune function.[34]

In addition, some authors have suggested that the benefits of somatostatin analogues may be more evident in patients undergoing resection at low-volume centers with higher leak rates;[23] but these opinions are not based on any conclusive evidence and should not give a false sense of confidence to the surgeon to attempt the occasional Whipple procedure.

In summary, the use of somatostatin analogues preoperatively and for 5–7 days postoperatively in an attempt to prevent pancreas-related complications after pancreatic resection remains at best controversial and cannot be recommended as routine therapy. Solid evidence for its efficacy is lacking; however, its use in patients with a soft pancreatic parenchyma, in whom the risk of a pancreatic leak is greater, may be justified, but the cost/benefit ratio remains unproven.

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