J Gastrointest Surg (2015) 19:2038–2044
DOI 10.1007/s11605-015-2925-x

ORIGINAL ARTICLE

Octreotide Does Not Prevent Pancreatic Fistula Following Pancreatoduodenectomy in Patients with Soft Pancreas and Non-dilated Duct: A Prospective Randomized Controlled Trial

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Received: 8 June 2015 / Accepted: 11 August 2015 / Published online: 25 August 2015

Abstract

Background Whether octreotide prevents pancreatic fistula following pancreatoduodenectomy is controversial and it is believed to be beneficial in soft glands and normal-sized ducts. The aim of this study is to assess the potential value of octreotide in reducing the incidence of pancreatic fistula, postoperative complications, morbidity and hospital stay in patients with soft pancreas and non-dilated ducts.

Methods A total of 109 patients undergoing elective pancreatoduodenectomy with soft pancreas and non-dilated duct were randomized to octreotide group versus no octreotide—the control group. Surgical steps were standardized and incidences of pancreatic fistula, complications, death and hospital stay were assessed.

Results There were 55 patients in octreotide group and 54 in the control group. Demographic features and pancreatic duct diameter of the groups were comparable. The rates of clinically significant pancreatic fistulae (grades B and C) were 10.9 and 18.5 % (p=ns), and morbidity was 18 and 29.6 % (p=ns), respectively. Patients who received octreotide resumed oral diet early and had a shorter hospital stay.

Conclusion This study demonstrated no statistical difference in pancreatic fistulae with the use of octreotide, though there was a trend towards fewer incidences of pancreatic fistulae, morbidity and shorter hospital stay.

ClinicalTrials.gov Identifier: NCT01301222

Keywords Pancreatic fistula · Octreotide · Pancreaticoduodenectomy · Randomized controlled trial

Introduction

Pancreatoduodenectomy (PD) is commonly performed worldwide for treatment of tumours involving the periampullary region and the head of the pancreas. The mortality of PD, in recent years, has reduced to less than 5 % in high-volume centres.[1–4] This is believed to be owing to the better intensive care rather than a decrease in the incidence of pancreatic fistula or other complications. Postoperative pancreatic fistula (POPF) and the associated complications remain the major cause for morbidity after pancreatoduodenectomy with reported incidence varying from 10 to 30 %.[1,3–5] The reported incidence of POPF has been reported as 5 to 30 % in high-volume centres.[4–6] As POPF is the single determinant factor which might affect a patient's immediate and long-term outcomes, surgeons use various techniques in pancreatic anastomosis like the use of adhesive sealants around the anastomosis, use

Presented as oral paper in IHPBA World Congress, 2012. Kurumboor P, Kamalesh NP, Pramil K, Vipin IS, Shylesh A, Varma D, et al. A prospective randomized controlled trial on the use of octreotide in patients with soft pancreas undergoing pancreaticoduodenectomy: interim analysis. *HPB* 2012; 14:225.

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of transanastomotic stents and use of various systemic pharmacological agents to decrease the incidence of POPF.[7]

Various factors like the age of the patient, co-morbid illness, neoadjuvant chemoradiation, intraoperative blood loss, soft pancreas and non-dilated duct have been implicated as factors predisposing to the development of POPF.[7,8] Of these factors, soft pancreas and non-dilated duct have been consistently identified to be associated with a higher incidence of POPF after PD.[8,9] Various pharmacological interventions were attempted to decrease pancreatic exocrine secretion to decrease the incidence of pancreatic fistula. Somatostatin, a native tetradecapeptide was used a few decades back as continuous infusion to cut the complication rate after PD.[10] Later on, octreotide, a potent synthetic octapeptide analogue of native somatostatin, was widely preferred for the same purpose due to its longer half-life.[11] However, whether somatostatin or octreotide exerts a potential significant beneficial effects in terms of decreasing POPF and or other complications has never been addressed in the 'high-risk' glands, i.e. soft glands with non-dilated duct. This prospective randomized controlled, single-institution trial was designed to evaluate whether the use of octreotide in this specific group of patients with soft pancreas and non-dilated pancreatic duct (high risk) can decrease the incidence of POPF or other complications following PD.

Methods

Study Period

This study was conducted between September 2010 and December 2014 in the Department of GI Surgery, PVS Memorial Hospital, Kochi, India. Patients aged between 35 and 75 years who underwent an elective PD for periampullary or pancreatic tumours were recruited to the study based on the preoperative imaging, usually a contrast CT scan and/or endosonography that showed a normal pancreas and non-dilated duct. Non-dilated for the purpose of the study was identified as duct not visualized on a contrast CT scan. Patients with age >75 years, documented evidence of chronic pancreatitis, documented dilatation of the pancreatic duct on imaging, previous pancreatic surgery, previous gastric surgery or vagotomy were excluded. During the study period, 192 patients underwent pancreatoduodenectomy for various indications in our unit, of which 119 patients (62 %) were eligible for the study with the abovementioned criteria. The surgical team explained the protocol to the patients and recruited eligible subjects. Informed written consent was obtained and patients were randomized using computer-generated random numbers using a sealed envelope method. The randomization process was carried out during the operation once the surgeon assessed the operability and soft nature of the gland. This study was approved by hospital ethics committee and was registered in Clinical trials.gov (NCT01301222).

Surgical Technique

All procedures were performed as open classical pancreatoduodenectomy by standard technique. Those who were randomized to octreotide group were given subcutaneous administration of 100 mcg of octreotide (Inj. Octreotide acetate 100 mcg; Sun Pharmaceutical Industries Ltd.) before transection of the neck of the pancreas while the control group (no octreotide group) did not receive the same. Octreotide was continued in the study group with a dose of 100 mcg every 8 h for the next 5 days. A biopsy was obtained from the cut surface to assess the non-tumour parenchyma of the pancreas, and the diameter of the pancreatic duct was measured. All patients underwent reconstruction as pancreatojejunostomy, hepaticojejunostomy and gastrojejunostomy. All pancreatic anastomoses were performed by one of the three consultants using end-to-side, duct-to-mucosa technique using interrupted 4-0 polygalactin sutures and outer 3-0 polypropylene sutures using standard techniques. An internal 5F transanastomotic plastic feeding tube stent was used in most of the cases. Surgeons were asked to record the details of the state of the pancreas including friability, eccentric position of the main pancreatic duct, the duct size and the poor suture-holding ability of the gland and to assess the technical difficulties of the pancreatic anastomosis in the operation notes. Further reconstruction was completed as an end-to-side hepaticojejunostomy using interrupted 4-0 polygalactin in the same jejunal limb, antecolic gastrojejunostomy and a feeding jejunostomy in that order. Drainage tubes were placed in the right sub-hepatic region and lesser sac close to the pancreatojejunostomy. Patients in the octreotide group were given 100 mcg of octreotide subcutaneously every 8 h for the next 5 days, and the control group received routine postoperative care. The patients in the control group were administered octreotide as per the discretion of the surgeon if they develop significant pancreatic fistula or complications in the postoperative period. All patients received third-generation cephalosporin plus ornidazole prophylaxis and proton-pump inhibitors. The patients were shifted out of ICU when they are hemodynamically stable, and their further postoperative care was closely monitored.

Data Collection and Perioperative Management

Patient demographic features, preoperative laboratory parameters and imaging characteristics were recorded systematically in a prospective database. Details of the intraoperative parameters like texture of the pancreas, pancreatic duct size, friability of the pancreas while anastomosis, technical difficulty, the

use of pancreatic stent and pathologic diagnosis were also recorded.

The serum amylase values were measured on the first postoperative day. The daily outputs of both drains and nasogastric tube were measured, and drain amylase values were measured on the first, third, fifth postoperative days and whenever clinically indicated, further in the postoperative course in both groups. Drains were removed after the fifth day if the drain amylases were low or as per clinician's judgement. The nasogastric tube was removed if the output was less than 300 ml/day, usually by the fifth day, and started with liquid diet initially and semisolid diet gradually. The primary end points of the study were pancreatic fistula, complications or death. Postoperative pancreatic fistula was graded as per International Study Group of Pancreatic Fistula as ISGPF grades A, B or C.[12] Patients who had high nasogastric aspirate beyond the fifth postoperative day and those suspected to have POPF underwent imaging to rule out intra-abdominal collections. Other outcome measures like the day of nasogastric tube removal, day of resumption of oral liquids, semisolid diet and hospital stay were documented and analysed in both groups.

Statistical Analysis

The required sample size was determined assuming a clinically relevant leak rate of 30 % in the control group. It was assumed that a reduction of the leak rate to 10 % in the octreotide group to achieve a 20 % decrease in leak rate would be clinically significant. With alpha and beta errors of 5 and 15 %, respectively, a total of 108 patients were required. Statistical analysis was done using Student's *t* test for continuous variables and chi-square tests for categorical variables using SPSS version 19. Results are reported as mean±standard error of the mean or as percentages for categorical variables. A p value of <0.05 was considered to indicate statistical significance.

Results

A total of 119 patients were eligible for the study of that 10 were excluded (10 patients had firm pancreas on assessment during surgery). Finally, the study population consisted of 109 patients, 55 in the octreotide group and 54 in the control group (no octreotide group) (Fig. 1). An interim analysis was conducted in 2012 and study was completed when it attained the sample size. The demographic parameters, preoperative laboratory parameters and perioperative findings were comparable and are detailed in Table 1. Noticeably, the incidence of preoperative cholangitis and preoperative biliary stenting and the number of periampullary lesions, the tumour size, the pancreatic duct size and the texture of the pancreas were comparable. The histology of non-tumour pancreas showed normal anatomy in 93 % in the octreotide group and 91 % in the control group and the remaining patients had mild periductal inflammation and or mild fibrosis.

Serum amylase values on day 1 were significantly higher in the octreotide group versus controls (265.7±277 vs. 181±138 U/l, p=<0.04). The drain output values and the amylase levels on postoperative day 3 were not statistically different though the octreotide group had higher drain amylase values compared to the control group (4281.1±9950 vs. 2572.6±3296 U/l, p=<0.08, ns). The same was comparable on day 5 between two groups (Table 2). Similarly, the day of removal of nasogastric tube was comparable between groups. However, the patients tolerated oral liquids (6.4 vs. 8 days, p=<0.01) and semisolid diet (10.3 vs. 11.7 days, p=<0.03) significantly early in the octreotide group compared to controls. No patient experienced any serious adverse event in the octreotide arm.

Pancreatic Fistula and Complications

The incidence of different grades of POPF according to ISGPF definition was comparable between both groups. Grade A POPF were 49 and 44 % between octreotide and control groups, respectively (p=0.6). The incidence of grades B and C POPF in the octreotide groups were 9.1 and 1.8 % and that in control groups were 16.6 and 18.5 %, respectively (p=ns). The clinically significant POPF (grades B and C together) were also similar, 10.9 and 18.5 %, respectively (p=0.26). The morbidity rates were also comparable (18 and 30 %, p=0.16) between these groups. Various complications like wound infections, respiratory infections, intra-abdominal abscess, reoperation and the incidence of delayed gastric emptying were statistically not different between the groups. However, when the change in line of treatment were compared (including drainage of abscess, retained drain at the time of discharge from the hospital, crossover to octreotide arm etc.), these incidences were significantly higher in the control group compared to octreotide (13 % in octreotide group vs. 30 % in controls, p=<0.03). Similarly, the hospital stay was significantly prolonged in the control arm compared to the octreotide arm (Table 3). The mortality rates in both groups were comparable, one patient in the octreotide group expired on the 13th postoperative day due to acute myocardial infarction and one patient in the control group died on the tenth postoperative day due to secondary haemorrhage.

Discussion

This prospective randomized controlled trial failed to show any benefit of use of octreotide to decrease the incidence of POPF or complications following PD in the select group of patients with soft gland and non-dilated duct. The use of somatostatin or its synthetic analogues have been assessed in

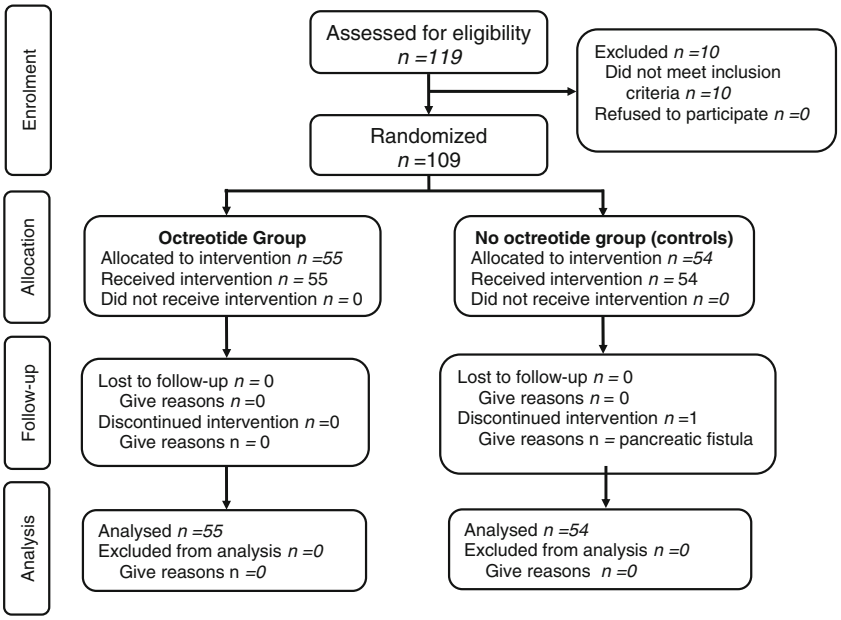

Fig. 1 Selection of the study groups according to the CONSORT template

many previous trials. To date, seven trials have compared somatostatin vs. control and 13 trials have compared the use of octreotide vs. control to decrease postoperative complications or POPF after pancreatic surgery.[13] However, a direct comparison between the trials is difficult due to different inclusion criteria in these studies such as inclusion of patients who underwent procedures other than PD (distal pancreatectomy, pancreatojejunostomy),[14–16] inclusion of patients who had preoperative chemoradiation[17] and inclusion of patients with both firm and soft pancreas together[14–18] and due to different definitions used for reporting the incidence of pancreatic fistula. It is generally believed that the benefit of octreotide in preventing POPF is most likely in those patients with high risk of developing POPF, i.e. those with soft pancreas and non-dilated pancreatic duct. Due to the varying inclusion criteria and non-uniformity of reporting of POPF, it remains still unclear whether octreotide is effective in decreasing the incidence of POPF or complications in those patients who are believed to have high risk for developing POPF. This study has included a highly selective group of patients with soft pancreas and non-dilated pancreatic duct (the first of its kind to include only this select group of "high-risk glands")

Table 1 Demographic features, laboratory parameters and intraoperative factors of the study groups

Parameters	Octreotide (n=55)	No octreotide (n=54)	p value
Age (years)	58±9.2	56±11.6	0.312
Male to female	31:24	35:19	0.366
Systemic illness	24 (43.6 %)	27 (50 %)	0.505
Haemoglobin (g/dl)	12.5±1.47	12.14±1.45	0.121
S. bilirubin (mg/dl)	6.2±5.1	7.6±7.4	0.164
S. protein (g/dl)	6.9±0.49	6.76±0.7	0.091
S. albumin (g/dl)	3.87±0.45	3.74±0.48	0.373
Preop cholangitis	7 (12.7 %)	8 (14.8 %)	0.751
Preop biliary stenting	9 (16.3 %)	11 (20.3 %)	0.588
Periampullary	48 (87.2 %)	47 (87 %)	0.970
Pancreatic duct (mm)	3.46±0.7	3.28±0.8	0.167
Friable pancreas	8 (14.5 %)	11 (20.3 %)	0.642
Technical difficulty	18 (32.7 %)	16 (29.6 %)	0.121
Tumour size (cm)	2.19±1.3	2.55±3.06	0.239
Normal histology of non-tumour pancreas	51 (92.7 %)	49 (90.7 %)	0.141

Table 2 Serum amylase, drain output, amylase values and postoperative data of the study groups

Parameters	Octreotide (n=55)	No octreotide (n=54)	p value
Day 1 serum amylase (U/l)	265.72±227	181.04±138.3	<0.047
Day 1 drain amylase (U/l)	1763.36±3176.3	1423.5±1675.5	0.081
Day 1 drain output (ml)	60.7±95.2	48±48.3	0.256
Day 3 drain amylase (U/l)	4281.9±9950.1	2572.66±3296.2	0.083
Day 3 drain output (ml)	41.9±84.7	47.1±74.9	0.308
Day 5 drain amylase (U/l)	1782.31±4292	1012.9±1324.9	0.120
Day 5 drain output (ml)	17.1±21.8	12.9±17.2	0.219
NG tube removal (days)	5.51±2.75	6.09±2.86	0.148
Oral liquids (days)	6.38±2.7	8±3.71	<0.012
Semisolid diet (days)	10.29±2.91	11.76±4.16	<0.031

with nearly 90 % of patients who have normal pancreatic parenchyma in the non-tumour pancreas in the final histology.

A major issue in interpreting the trials comparing the use of octreotide in PD is the fact that the definition of POPF used in these studies is not uniform. Only few studies comparing somatostatin and its analogue octreotide have reported the incidence of clinically significant POPF.[12] The ISGPF definition and the grading of POPF as grades A, B and C has gained widespread acceptance and made the reporting of POPF uniform. Only three trials comparing the use of somatostatin or its analogue have reported POPF using the ISGPF definition and have demonstrated no difference in the incidence of POPF with or without use of the drugs.[19–22] This issue of non-uniformity of reporting of the results of POPF with respect to ISGPF definition has been addressed in previous systematic reviews and meta-analysis as well.[13,22] The current study has categorised POPF using ISGPF definition, and accordingly, there were 6 (10.9 %) clinically significant fistulae in octreotide group and 10 (18.5 %) in the controls (p=ns). This indicates a trend towards decrease in clinically significant POPF, probably a study with a larger sample size would show up the clinical implication of this difference. There was no statistical difference with respect to grades A, B and C fistulae in both groups as well. Similarly, there was no difference in overall complications or morbidity, and particularly, there was no difference in the reoperation rate as well. The lack of difference is possibly due to the failure of octreotide to demonstrate any impact in the occurrence of POPF. McMillan et al. in a recent multi-institutional prospective study including a large number of subjects have drawn similar conclusions.[23]

In this study, though not statistically significant, the octreotide group had early removal of nasogastric tubes and

Table 3 Pancreatic fistulae, complications, morbidity and hospital stay of the study groups

Parameters	Octreotide (n=55)	No octreotide (n=54)	p value
Grade A POPF	27 (49 %)	24 (44.4 %)	0.626
Grade B POPF	5 (9.1 %)	9(16.6 %)	0.237
Grade C POPF	1 (1.81 %)	1 (1.85 %)	0.989
Significant POPF	6 (10.9 %)	10 (18.5 %)	0.261
Morbidity	10 (18.1 %)	16 (29.6 %)	0.161
Complications			
Wound infection	13 (23.6 %)	14 (25.9 %)	0.781
Respiratory	8 (14.5 %)	7 (13.7 %)	0.810
Intraabdominal abscess	3 (5.4 %)	2 (3.7 %)	0.662
Reoperation	1 (1.8 %)	2 (3.7 %)	0.547
Retained drain	4 (7.2 %)	8 (14.8 %)	0.208
Delayed gastric emptying	3 (5.4 %)	5 (9.2 %)	0.446
Change of treatment	7 (12.7 %)	16 (29.6 %)	<0.03
Readmission	3 (5.4 %)	3 (5.5 %)	0.981
Hospital stay	11.75±3.02	13.27±4.25	<0.02
Mortality	1 (1.81 %)	1 (1.85 %)	0.989

low incidence of delayed gastric emptying. This could be the reason for a significant shorter hospital stay (11.7 vs. 13.3 days, p=<0.01) observed in the octreotide group in the current study, considering the fact that clinically relevant POPF and morbidity in both groups were similar. In studies comparing pancreatic juice output with and without administration of octreotide has not shown any significant decrease in output of pancreatic juice with the use of octreotide.[21,24] Octreotide has been observed to improve the gastric emptying time and prolongation of the mouth-to-caecal emptying time in healthy volunteers.[25,26] Hence, early resumption of diet and early discharge from the hospital could be attributed to the effect of octreotide on gastrointestinal secretion and motility, rather than the beneficial effect of the drug in decreasing POPF.

There are a few limitations for the current study. This was not a blinded study and there was no placebo administered. However, since the definitions of POPF, complications, removal of nasogastric tube drains etc. were defined before the study, we have tried to eliminate the possible bias. The dose of octreotide used was 100 mcg thrice daily in this study; many studies have used varying doses from 100 to 250 mcg thrice daily.[14–19] It remains unclear whether the higher dose than used in this study would have changed the result in a different manner. Similarly, it remains to be studied whether a study with a bigger sample size would have demonstrated the incidence of POPF/morbidity with the use of octreotide, and with this respect, the study is probably underpowered. Since this is a select group of patients with soft pancreas and small ducts, there are practical difficulties in recruiting a large number of patients and probably would require a multi-institutional study. In this study, financial consideration of using the drug was not assessed. Finally, one should be able to predict the risk for developing POPF or complications and identify the high-risk group preoperatively using preoperative parameters or fistula risk score as employed in some studies.[7,8,23,27] We have not employed any such predictive scores in this study, and it remains unclear whether a selective policy in administering octreotide in such a group would be of any relevance in clinical practice.

In conclusion, this randomized controlled trial assessing the role of octreotide in preventing POPF or its complications in the selective group of soft pancreas and non-dilated duct showed no statistical difference in POPF with the use of octreotide.

Conflict of Interest The authors declare that they have no competing interests.

Financial Disclosures Nil

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