

High dose omeprazole heals pancreatic fistula; A case series

Abstract

Introduction: Pancreatic fistula is a serious complication after pancreatic and peripancreatic organ surgery. No clear management modality is fool proof. Increased Gastrin level is known to reduce Secretin. Omeprazole is the first proton pump inhibitor and in use since in the last 40years. Thus, a high dose of Omeprazole is likely to suppress the Secretin and likely to reduce the fistula output and thus improve the healing.

Materials and methods: Confirmed pancreatic fistula patients as defined by an international consensus group were included in this prospective study. Patients with ascites and fistula healing in five days were excluded. Bacterial culture positive drain fluid patients were not excluded. All received 60mg of Omeprazole 12hourly and continued for 2months after the closure of fistula. The drain fluid volumes were measured daily and amylase periodically during the follow up.

Result: There were 39 cases in 13years (2005 to 2017) with 35 males and 4 females. All the fistulae closed in 7-24days (mean 11.777 SD +/- 3.882). One case developed a pseudocyst after early stoppage of Omeprazole, but it, resolved with another course. Second, end PF required elective fistulo-enterostomy for recurrent fistula.

Conclusion: High dose Omeprazole hastens up the healing of pancreatic fistula. Further studies are needed.

Keywords: pancreatic fistula, high dose omeprazole, open main pancreatic duct, postoperative pancreatic fistula, end duct fistula

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Introduction

Pancreatic Fistula (PF) is still regarded as a major complication.¹ The only therapy known is a stent placed across the defect of pancreatic duct during the ERCP session in stable patients with pancreatic trauma.² No other known non-invasive therapy available for neither PF nor any probable healing time frame. Omeprazole came as the first Proton pump inhibitor and is in clinical use for close to 40years and is known to cause drastic reduction of gastric acid secretion and raise the serum gastrin level due to gastric an-acidity. Elevated Gastrin inhibits Secretin-induced pancreatic ductal secretion,³ which is rich in bicarbonate and forms the bulk of pancreatic juice.⁴ When the bulk of secretion reduces, pressure will drop, thus reducing the ductal the fistula output volume and the PF is likely to heal faster.

Materials and methods

All the patients with drain output with elevated amylase three times more than serum amylase on or beyond third postoperative day even with bacterial culture positive were included for this prospective study from 2005-2017 (13years). Three patients with biochemically proven PF and dried up in 3-5days were excluded. The cases details, the causes of the fistula are given on table number one. All patients were in the hospital till the closure of the fistula except a lady with grade III pancreatic injury, who underwent laparoscopic peritoneal drainage and feeding jejunostomy (FJ) was discharged for home care. The drain volume was measured on a daily basis. The drain fluid (pancreatic juice) was fed to the patients through the FJ tube. Patients without FJ it was discarded and was replaced by IV normal saline till oral feed was started. Omeprazole was given 60mg 12hrly per oral or FJ, once the PF was confirmed after the third day. All received vitamin

C 500mg daily along with Omeprazole. The drain was slightly pulled out once the output was nil to negligible and if no drainage was seen for three days, an USG was done to rule out any collection before removal of the drain. The same dose of the medication continued for a total period of 2 months to have a complete healing. But the home care lady stopped after 2 weeks only of her own. All were kept on follow up.

Results

There were 39 patients after exclusion of three cases. The age range was from 23-68 years (mean 44.391 SD 11.603) with male to female ratio 35:4. The cases details, the causes of the fistula are given (Table 1). The highest fistula daily output volume varied from 60 to 600mL (Mean 336.759 SD 144.99mL). In all cases the fistula fluid amylase was more than 10 times that of serum. Lower volume fistula healed faster than the higher volume ones. At least in three [3/39=7.7%] cases, the duct was open with normal pancreas. (Two cases of grade III injury and one radical gastrectomy involving distal pancreatectomy and splenectomy and segmental colectomy, pancreatic closure were accidentally missed). All these three cases, the volume of drain came down but the amylase level kept on going high (Table 2). All the fistulae dried up in 7 to 24days after (mean 11.777 SD 3.883). During the follow up period of 10 to 84months (mean 40.608 SD +/-23.776), there were two death (34th day post Whipple's procedure of Acinetobacter septicemia and cancer stomach after 13months) unrelated to the study after closure of PF. The home care lady stopped the medication after 15days of closure of PF developed pseudocyst (Figure 3). It regressed with the same medication and later developed stricture at the injury site with distal dilatation of the

duct (Figure 3). Two cases were having recurrence of fistula after 8 weeks of Omeprazole. One of them, a case of chronic pancreatitis with proximal ductal obstruction due to stone, underwent elective fistulo-enterostomy after the third recurrence. The other, following Necrosectomy, was having scanty discharge, possibly related to left

over minimal necrosed tissue for 6 months then it stopped. All other cases the drug was stopped after two months following removal of drain and then tapered to 20mg 12hrs for a variable period 4 weeks to 12 weeks.

Table 1 (Causative factors of PF)

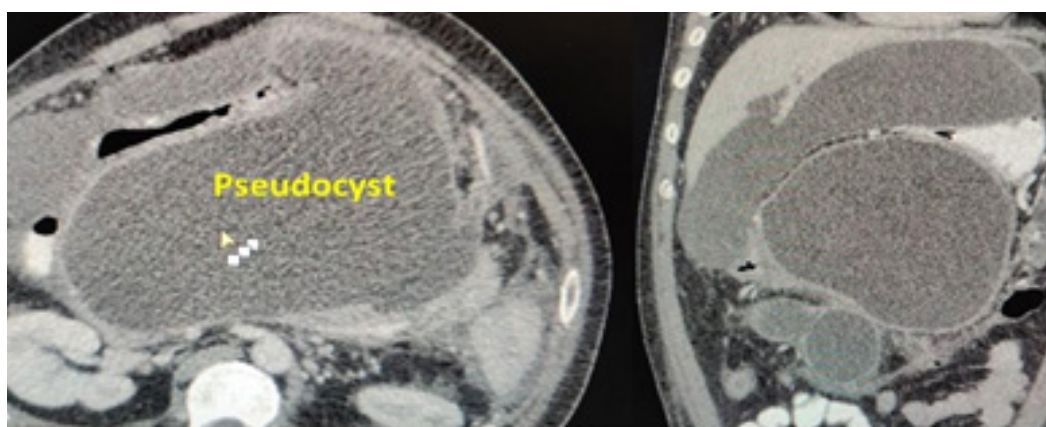
Causes of fistula	n	Death	M	F
External drainage of pseudocyst	18 ^a	0	18	0
Necrosectomy	6	0	6	0
pancreatic abscess drainage	2	0	2	0
Distal pancreatectomy	8 ^b	0	6	2
Duct closure over the stent	1 ^c	0	1	0
Gr.III pancreatic injury with- drain	2	0	0	1
Whipple	1	1 ^d	1	
Mucinous cyst adenoma(head)	1	0	0	1
Total	39	1	35	4

- a. External drainage- Head pseudocysts with gastric outlet obstruction/ jaundice-5 and infected pseudocyst-12, (image-1) Very high-pressure large pseudocyst compressing the stomach with poor nutrition-1 (image-2)
- b. Distal pancreatectomy- 8 [Solid Papillary tumor-1, Ca pancreas-1, Cystic neoplasm tail- 4. Pancreatic tail Necrosis -1, Cancer stomach involving splenic hilum needing spleen and pancreatic tail excision-1]
- c. Duct closure- suspected haemosuccus pancreaticus, opened the duct, but bleed was from stomach hence the duct was closed in anaemia with B negative group
- d. Whipple's- Secondary bleeding due to Acinetobacter sepsis

Table 2 Relation of fistula volume and amylase level in normal pancreas

Cases	S amylase-d3	Df amylase d3	D3 dfv	D12-15 dfa	dfv
Gd III injury -1	28	29684	475	83900	125
Gd III injury-2	124	3980	520	74200	55
Radical gastrectomy	188	37800	490	78800	35

S=serum, D3=Day three, D12-15- day 12 to 15, Df=Drain fluid, dfv=Drain fluid volume, dfa=drain fluid amylase



Large Pseudocyst Ext drainage 2.4 L

Figure 1 Large pseudocyst compressing stomach and duodenum- External tube drainage done.

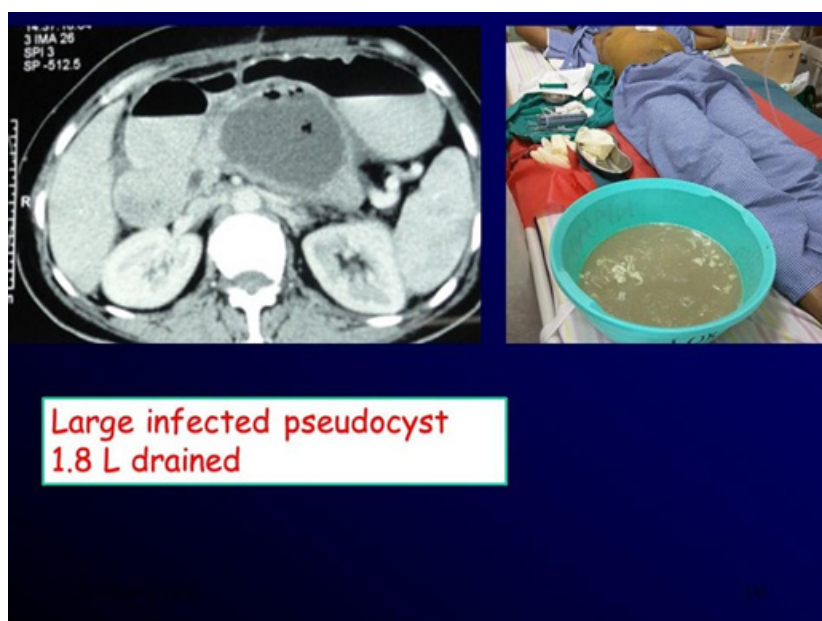


Figure 2 Large infected Pseudocyst -process of external drainage.

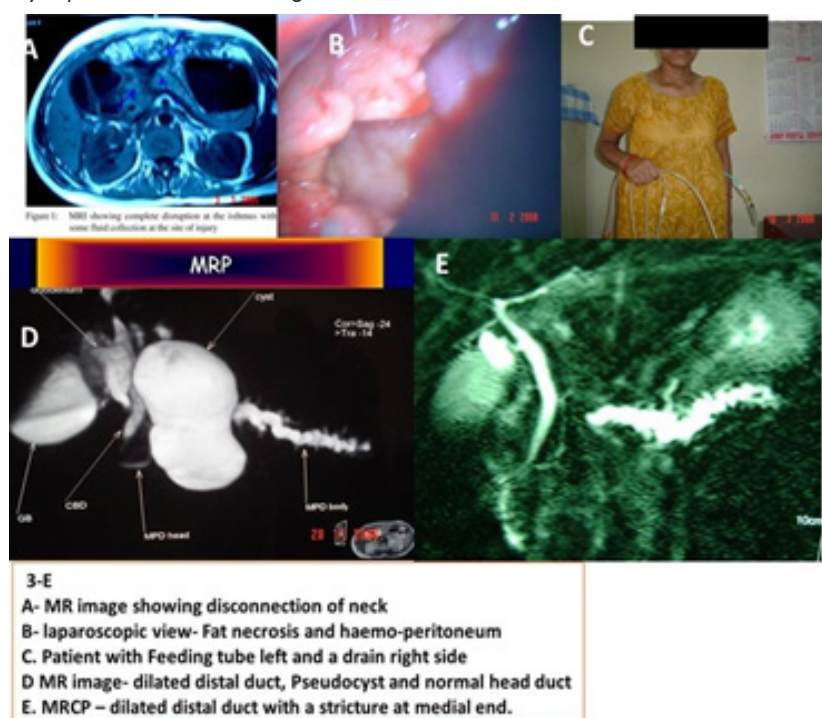


Figure 3

Discussion

An all-inclusive definition of PF is, drain output of any measurable volume on or after postoperative day 3 with amylase content greater than 3 times the serum amylase activity⁶. All the present cases the amylase level were much more than ten times then the serum amylase thus fulfilling the PF criteria. The principal determinants of closure of an external pancreatic fistula are the anatomy of the fistulous tract (end versus side, main duct versus side branch), the presence of downstream ductal obstruction, ongoing peripancreatic inflammation and etiology of the fistula (inflammatory versus postoperative. Side fistula heals faster and fistula with onward flow obstruction unlikely

to heal as per fluid dynamics. In our relatively larger case series (Table 1) 12 PF cases were post-operative/ trauma with the main duct fistula and rest all fit into the inflammatory group. Fistulogram can be done in the post-operative period in presence of a drain. It can differentiate the anastomotic leak (immediate visualization of bowel lumen without a tract) is likely to heal faster (2.7days) vis a vis late healing (9.8days) with a definite tract. But if there is fluid collection and a fistulous tract heals late⁸. However, the authors have not explained the reason behind the early or late healing. In the present study fistulogram was never a routine test. Various therapy has been used for faster healing. Besides the conservative wait and watch therapy, invasive therapy like Naso-pancreatic drainage (NPD) and Trans papillary stents

(TPS)¹⁴ is used with relatively good healing rates, but the technical failure rates are rather high (Table 3)^{9,10,11,12}. The mean healing period varies between 8.8 days to 154 days (Table 3). Obviously, conservative therapy taking longer time and shortest time is with NPD groups (Table 3). In the present series, PF healed in 11.7 days, that to without any pancreatico-enteric continuity in most of the cases and majority were of inflammatory origin. An end inflammatory fistula is known as a distinct entity as spontaneous closure is exceedingly uncommon. Surgery is almost always required and is successful in the majority

of cases.⁷ Only one of our cases required fistulo-enterostomy due to repeated recurrence of PF due to a stone blocking the duct distal to the leak. The use of Somatostatin analogues is still, matter of controversy in the management of PF. On a randomized placebo-controlled study, only 15% (45 of 300) reached the end point¹⁴. Somatostatin is a gut hormone and is very costly. It is a generalized gut depressant that reduces the blood flow as well. In one metaanalysis, effects of Somatostatin on PF are not seen.¹⁵

Table 3 (Discussion Table)

Author	Year	n	Types of fistula	Therapy	Healing rate	MHT (days)
Howard TJ ¹¹	1998	15	Post-operative	conservative	13/15(86%)	77
		15	Inflammatory side	conservative	8/15(53%)	154
Costamagna G ¹²	2001	16	Post-operative	NPD	09 NPD/ 8 failed	8.8 (2-33) #.
Rana SS ¹³	2010	23		NPD	21/23(2 failed)	14-56
Bakker OJ ¹⁴	2011	19	Post Necrosectomy	TPS		71
		16		conservative		120
Faccioli N ⁸	2012	35/84	Post-Whipple *	conservative	41.7%	2.7
		49/84			58.3%	9.8
Present	2021	39	Mixed	Medical	37/39(94.87%)	11.77**

MHT, mean healing time in days; * anastomotic leak cases, NPD, naso pancreatic drainage; TPS, trans papillary Stent; #- one death, ** one recurrence; F- I, Fistula from directly from bowel (no fistula tract); F2, Fistula tract opening to bowel anastomosed to pancreas

In the present study, no used this controversial and costly Somatostatin, but have used Omeprazole, the longest used safe Proton pump inhibitor, which is easily available and cheap and whose safety profile is known. It is also found to be safe for high up to 60mg 6hourly dose for a longer period 1-43months as in case of Zollinger Ellison syndrome with no evidence of hematologic, biochemical, or gastric toxicity^{16,17,18}. Omeprazole 60 mg 12hourly used per enteral route for 8 weeks and usual dose 20mg 12hourly for another 4weeks continuously without any side effect. However, it was repeated in a few cases after an interval. PPI is used in chronic pancreatitis to lower the dose of oral pancreatic enzyme supplementation and for symptom reduction in chronic pancreatitis.¹⁹ Omeprazole is primarily metabolized through the CYP2C19 enzyme, a member of the P450 mixed-function oxidases group.²⁰ Thus, Omeprazole toxicity appears to be oxidative and preventable with antioxidant therapy, including Vitamin C. It is a safe and efficacious addition to treatments requiring the use of proton pump inhibitors to avoid toxicity in long use.²¹ On review the literature it was found that, Rabepazole 20mg a day reduces the pain in chronic pancreatitis faster than Famotidine along with conventional treatment and MRI on 7day of treatment, was accompanied by a reduction of the pancreas size and the diameter of the main pancreatic duct.²² With the same principle of reducing intraductal pressure to get relief of pain in chronic pancreatitis, the same dose is used with a success rate of 96% at the end two weeks and 95% weight gain at one year.²³ The mechanism of action of Omeprazole or that to any PPI is possibly a feedback of gut hormones regulating the exocrine secretion. It is proved that Omeprazole deduces the gastric acidity and thus serum Gastrin level rises. The raised serum Gastrin, inhibits Secretin. Low Secretin level reduces the pancreatic juice output. But Secretin only inhibits ductular secretion and not the enzyme acinar juice. The volume of ductular secretion constitutes 80% of volume and is rich in bicarbonate. Thus, reduces the fistula output and helps in the healing process of PF explains it well.^{3,4,19,22,23}

Conclusion

Omeprazole 60 mg twice daily is useful in hastening the healing of PF. Further randomized studies are necessary for confirmation.

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

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