Original article

Octreotide plus Total Parenteral Nutrition in Patients with External Digestive Tract Fistulas – An Evaluation of our Experience

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SUMMARY

Objective: We conducted a retrospective study to evaluate the use of total parenteral nutrition (TPN) and octreotide (OC), in comparison to standard treatment for the management of external digestive tract fistulas (EDTF) at a major tertiary referral University Hospital.

Patients: We analyzed the clinical course of 112 patients with EDTF treated from 1978 to 2001. Thirty-nine patients admitted during the period 1978-1990 (group A) and 73 patients admitted during the period 1991-2001 (group B) were studied. Group A received standard supportive treatment while group B received standard supportive treatment in combination with TPN and OC. The main outcome measures were the duration of hospitalization, the fistula spontaneous closure time, the mortality rate and complications of treatment.

Results: A dramatic reduction (81±4.5%) in fistula output was observed within 48 hours after administration of TPN and OC in group B compared to group A ($p<0.05$). The incidence of spontaneous fistula closure was increased from 64% in group A to 81% in group B ($p<0.05$) and the mean fistula closure time decreased from 38±2.7 in group A to 17±1.8 days in group B ($p<0.05$). Complications occurred in 61.5% of group A patients and in 45% of patient group B respectively ($p<0.05$). The direct fistula related mortality was 7.5% and 2% respectively ($p<0.05$).

Conclusions: The introduction of TPN and OC in EDTF ameliorated in a statistically significant way all the parameters of EDTF healing that were studied. Although fistula related direct mortality was decreased, further studies with well-designed comparative prospective trials are needed.

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Keywords: digestive tract fistulas, octreotide, total parenteral nutrition

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INTRODUCTION

Fistula management has been challenging physicians for centuries. Management of external digestive tract fistulas (EDTF) and of biliary-pancreatic fistulas has been traditionally associated with high morbidity rates of up to 65%and mortality rates of up to 40%.[1-7] Although the causality of these high mortality rates is multifactorial, it is generally emphasized that mortality rate is higher in patients with underlying infections, malnutrition and high-output fistulas. The great importance of nutritional support during fistula therapy has been shown by Chapman et al.[8]

Nonetheless, in patients diagnosed with an EDTF, a high morbidity, prolonged hospitalization and high mortality rate has already been reported.[9-14] The role of nutritional support in decreasing the number of deaths

Abbreviations

TPN*=total parenteral nutrition,* ***OC****=octreotide,* ***EDTF****=external digestive tract fistulas*

caused by enterocutaneous fistulas still remains controversial.[15-17]

It seems that conservative treatment with only total parenteral nutrition (TPN) succeeds in closing between 60-75% of fistulas [18]. Octreotide (OC) as an adjuvant therapy to standard fistula management has been reported to decrease fistula output.[19-24] However its role in shortening the fistula closure time still remain to be proven[25] as OC use in recent studies showed no overall advantage compared to standard treatment and was associated with increased morbidity including severe septic complications.[26]

We compared disease outcome of 73 patients with EDTF treated with peripheral TPN and OC during the period 1991-2001 with that of 39 patients treated during the period 1978-1991, when only the usual conventional treatment was applied as the routine method.

PATIENTS AND METHODS

Hospital and clinic medical records were retrospectively reviewed at the Academic Department of Surgery of our University Hospital, from March 1978 to September 2001 in order to trace all patients with EDTF. Only patients with fistulas documented by fistulography, intraluminal contrast dye injection or chemical analyses of fistula output (such as bilirubin or amylase levels), without distal obstruction were included in the study. High output fistulas were defined as those that drained over 500 ml per 24 hours while low output fistulas were defined as those that drained less than 500 ml per 24 hours.

One hundred and twelve patients with a total of 119 fistulas were reviewed. Thirty-nine of these patients [group A], who had been hospitalized before 1991, were managed by standard therapy which included nasogastric suction, antibiotics, intravenous supportive measures (IV glucose, crystalloid solutions and electrolytes). Fistula output and clinical and laboratory manifestations of infection (complete blood count, erythrocyte sedimentation rate and C reactive protein) were recorded. Local skin care was applied daily. Nutritional support was preferably administered by adequate oral intake or by tube feeding with high calorie liquefied diets.

Since 1991, when an artificial nutritional support team was introduced in our Department, 73 patients [group B] with EDTF have been treated with combination of TPN and OC (0.1 mg tid) as an adjunct to standard treatment. No oral intake or tube feeding was allowed during the first week of treatment. In group B, supportive measures, control of sepsis, control of fistula effluent and local skin care were also included. Patients on TPN [group B] received 10-16 gr of nitrogen and 1500-2500 kcal daily via a peripheral vein. In all patients with gastrointestinal and biliary fistulas, TPN and OC were started one or two days after fistula diagnosis. Routine laboratory tests were performed as needed in order to monitor the metabolic effects of the fistula, of TPN, as well as to prevent possible hyperglycemia related to OC administration. If case that the fistula had not healed after 26±5 days of OC administration, its use was reassessed including other options.

Fistulas that closed without primary operative intervention were considered to be those that a spontaneously closed. Some of these patients had some other kind of minimal surgical procedures, such as drainage of a fistula related abscess. Fistula output was recorded on a daily basis (milliliters per day), while reduction of fistula output (mean [±SEM]) and time for the complete fistula healing (mean [± SEM] number of days) was also evaluated.

Data is expressed as standard error of the mean (SEM). Statistical analysis was performed using x^2-test and student's t-test. A p value of <0.05 was considered significant at the 5% level of statistical significance.

RESULTS

Patients' clinical and demographic characteristics are shown in table 1. Fistula etiology, location and output are shown in tables 2, 3, and 4. The two groups were comparable in age and gender distribution and in the proportion of high output fistulas (38.5 % vs. 42.5%). In group B, there was a significantly higher number ($p<0.05$) of patients with primary malignant disease compared to group A (Table 5). However fistulas in patients

Table 1. Demographic characteristics of patients with external digestive tract fistulas

Characteristic	Group A*	Group B**
No of patients	39	73
Gender (Male/Female)	24/15	42/31
Mean age (years)	58.7	57
No of fistulas	42	79

***Group A:** patients with external digestive tract fistulas admitted during the period 1978-1990 and treated with standard treatment.*

****Group B:** patients with external digestive tract fistulas admitted during the period 1991-2001 and treated with octreotide and total parenteral nutrition plus standard treatment.*

Table 2. Causes of external digestive tract fistulas in the two patient groups.

Causes of fistula	Group A No (%)	Group B No (%)
Postoperative	35 (90)	60 (82)
Traumatic	2 (5)	11 (15)
Spontaneous	2 (5)	2 (3)

Table 3. External digestive tract fistula origin in the two groups of patients

Fistula origin	Group A	Group B
Oesophagus	2	2
Stomach	1	2
Duodenum	11	17
Small intestine	8	21
Colon	7	9
Biliary tree	6	10
Pancreas	4	12
Total	39	73

Table 4. External digestive tract fistula output in the two groups of patients

Type of fistula output	Group A No (%)	Group B No (%)
Low output (<500ml/24h)	24 (61.5%)	42 (57.5%)
Mean low output volume (ml/24h)	*271±27*	*278±16*
High output (>500ml/24h)	15 (38.5%)	31 (42.5%)
Mean high output volume (ml/24h)	*726±42*	*756±31*

Table 5. Primary disease that caused external digestive tract fistula.

Primary Disease	Group A (N=39)	Group B (N=73)
Cancer*	8	21
Gastroduodenal ulcer/complications	8	9
Trauma*	2	11
Extrahepatic biliary tree disease/complications	3	5
Hydatic cyst of liver	4	6
Diverticulitis	4	5
Inflammatory bowel disease (I.B.D.)	3	4
Miscellaneous	7	12

* Statistically significant difference ($p<0.05$) between the two groups

with malignant diseases were not that of neoplastic disease origin but were postoperative ones. About half of the patients in both groups had signs of sepsis (52% vs 47%) and the difference was not significant ($p=0,55$, Fisher's exact test).

In addition a higher percentage of patients, were referred to our institution from other regional hospitals during the 1991-2001 period compared to the 1978-1990 period (27% vs. 5%, $p<0.05$). The majority of these patients (17/20), mainly those with traumatic postoperative fistulas (10 patients), were referred from Albanian hospitals, in an extremely critical condition with sepsis and severe electrolyte abnormalities. The remaining seven patients referred from Albanian hospitals were referred because of postoperative complications related to cancer (n=3), peptic ulcer disease (n=2), pancreatitis (n=1) and diverticulitis (n=1).

The introduction of TPN and OC therapy resulted in a rapid and significant decrease in fistula output. A mean reduction of 81.7 ± 4.5 % for fistulas output of group B was achieved (mean reduction 84% in high and 77% in low output fistulas). This dramatic fistula output reduction was observed within 48-72 hours after TPN and OC administration especially in the high output group fistulas. Fistula output was not influenced by the time of treatment initiation or fistula anatomical site.

Twenty-seven (69%) patients in group A and 59 (81%) patients in group B had been exclusively treated conservatively. Ten (26%) patients in group A and nine (12%) patients in group B, failed initial conservative management and underwent a primary surgical fistula repair. The remaining 7 patients, 2 from group A and five from group B, underwent some other kind of minimal surgical procedures, mainly drainage of a fistula related abscess. These patients formed the group of minimal surgery assisted conservative treatment (Table 6).

The incidence of spontaneous fistula closure was increased from 64% (25/39 patients) in group A to 89% (65/73 patients) in group B ($p<0.05$). In addition seven patients of each group had successful primary surgical fistula repair so the overall incidence of fistula closure by both conservative and surgical repair still remained significantly higher in group B compared to group A (90.4% vs. 82%, $p<0.05$). The mean closure time for fistulas that closed spontaneously was decreased from 38±2.7days (range from 10 to 93 days) for group A fistulas, to 17.2±1.8 days (range from 7 to 43 days) for group B fistulas ($p<0.05$) (Table 7).

Two fistulae of group A relapsed after initial success-

Table 6. Definite treatment of external digestive tract fistula in the two groups.

Definite treatment	Group A No (%)	Group B No (%)
Conservative	27 (69)	59 (81)
Conservative+minimal surgery	2 (5)	5 (7)
Operative*	10 (26)	9 (12)

* Failure of conservative treatment during the same admission.

Table 7. Fistula outcome in both groups with external digestive tract fistula.

Fistula outcome	Group A No (%)	Group B No (%)
Spontaneous closure	25 (64)	62 (85)
Surgical closure	7 (18)	7 (10)
Failure after surgical repair	1 (2.5)	1 (1)
Fistula relapse after conservative treatment	2 (5)	-
Deaths during conservative treatment*	2 (5)	2 (3)
Deaths during surgical treatment*	2 (5)	1 (1)
Closure time** (days)	38±2.7	17.2±1.8

** Fistula open.*
*** Mean closure time ± SEM for spontaneous closure.*

Table 8. Complications during treatment of external digestive tract fistulas.

Types of Complications	Group A (39 patients) No (%)	Group B (73 patients) No (%)
Total number of patients with complications	**24 (61)**	**33 (45)**
Intraabdominal sepsis	20 (51)	29 (40)
Pneumonitis	3 (8)	6 (8)
Urinary infections	2 (5)	4 (5)
Pleural infusion	2 (5)	2 (3)
Malnutrition	23 (60)	18 (25)
Electrolyte imbalance	16 (41)	17 (23)
Anemia	13 (33)	22 (30)
Haemorrhage from fistula	3 (8)	2 (3)
Haemorrhage from digestive tract	3 (8)	2 (3)
DVT/ PE*	4 (10)	2 (3)
Liver dysfunction	4 (10)	4 (5)
ARDS/MOF*	2 (5)	4 (5)
Cardiac problems	3 (8)	4 (5)
Wound infection	8 (20)	13 (18)
Dermatitis, Skin maceration	16 (41)	8 (11)

**DVT=deep vein thrombosis*
PE= pulmonary embolism
ARDS=acute respiratory distress syndrome
MOF=multiple organ failure

ful conservative treatment. These fistulas had a successful surgical repair. Surgical treatment has failed to repair an enterocutaneous fistula in a Crohn's disease patient in group A and a traumatic pancreatic fistula in group B. The first patient was successfully treated operatively, during the same admission. The second patient in group B underwent a distal pancreatectomy but unfortunately the fistula relapsed after a few days.

Morbidity assessment in both groups showed that complications were much more frequent in group A patients who were treated with standard therapy (Table 8). Twenty-four (61.5%) patients of group A, and 33 (45%) patients of group B, experienced 106 and 129 complication episodes respectively ($p<0.05$). Sepsis had been the most frequent serious complication that led to conservative and surgical treatment failure as well as patient morbidity and mortality. The introduction of TPN and OC significantly reduced metabolic and water-electrolyte abnormalities in group B compared to group A (41% vs 23%, $p<0.05$). These electrolyte abnormalities in group A included mainly hyponatremia (24%, hypokalemia or hyperkalemia (15%) and hypocalcemia (2%), while in group B they included hyponatremia (15%), hypokalemia (6%) or hyperkalemia (2%). Cutaneous complications such as dermatitis and skin maceration were also markedly reduced in group B.

Four (10%) patients in group A and three (4%) patients in group B died. In group A, two patients died from uncontrolled intraabdominal sepsis, one from multiple organ failure and one from acute heart failure. In group B, two patients died from multiple organ failure due to uncontrolled sepsis and one from pulmonary embolism. The direct fistula related mortality was 7.5% in group A and 2 % in group B ($p<0.05$). Three of the patients who died (2 from group A and 1 from group B) had undergone an attempt for surgical fistula closure. Stepwise regression analysis showed that the most important factor for predicting survival was fistula closure ($F=25,1$ $p<0,01$), followed by absence of malnutrition ($F=16$, $p<0,05$), absence of sepsis ($F=12,2$, $p<0,05$) and absence of electrolyte abnormalities ($F=4,2$, $P<0,05$).

On admission, 60 % of group A patients had significant malnutrition (serum albumin < 3.5 g/dl), whereas

severe malnutrition occurred in 75 % of group B patients. Negative nitrogen balance was reversed in 90% of group B patients after 8-10 days of TPN administration. Except of some cases of hyperosmolar thrombophlebitis no other side effects or complications attributable to TPN or OC were observed. In patients with underlying sepsis that occurred prior to drainage of intraabdominal or fistulous tract abscesses transient hyperglycemic episodes were noticed during treatment.

DISCUSSION

Gastrointestinal cutaneous fistulas still remain a serious problem of current surgical practice. The predominant causes of death in patients with EDTF have been and still remain malnutrition, electrolyte abnormalities, and sepsis.[18] This is especially true in patients with high-output duodenal or jejunal fistulas, in whom mortality rate remains approximately 35%.[9,26,27] Although the reported rates of spontaneous closure tend to increase, the morbidity rates remain still high.[1,3,8,28-30] Furthermore several authors have demonstrated the detrimental effects of malnutrition and sepsis in the management of fistulas.[8,15,18,29,30]

In this study it was shown that the main advantage of TPN and OC introduction was the rapid decrease of fistula output (81,7±4.5 %) leading to hastening of fistula closure. In group B the mean fistula closure time was 17.2±1.8 days and it was significantly shorter compared to standard treatment in group A which was 38 ± 2.7 days [$p<0.05$]. Total parenteral nutrition has been shown to reduce by 90% the volume of gastropancreatic secretions in experimentally produced fistulas.[27] Current management which is based on TPN, sepsis control and local skin care succeeds in fistula closing rates ranging from 30% to 75%.[16, 27, 28,29]

TPN use has been historically associated with fistula spontaneous closure times of 30 to 50 days[14,27,29] while somatostatin and OC use has been reported to reduce digestive fistula activity in fewer than 16 days and occasionally within 24 hours.[19-26] A randomized however not placebo-controlled trial using a model of continuous somatostatin infusion plus TPN compared to TPN alone, showed a significant reduction in the time required for "spontaneous fistula healing "from 20 days to 14 days.[22]

Two prospective placebo-controlled trials did not show any improvement in fistula closure rate using OC and TPN versus TPN monotherapy.[23,31] Another study[26] had also failed to demonstrate significant improvement in the long-term outcome of complicated fistulas using OC therapy. According to that study prolonged therapy failed to affect the outcome parameters studied, particularly fistula duration, spontaneous closure rate, and length of hospitalization. In addition there was a significantly higher incidence of septic and thrombotic complications associated with OC use. In complicated enterocutaneous fistulas, the use of OC showed no benefit and it seemed to be associated with increased morbidity. In contrast, our study demonstrated that in good hands the combination therapy of TPN and OC is safe and effective and leads to significantly improved outcome for patients with postoperative external digestive tract fistulas.

So, TPN combined with OC succeeded in closing 89% of fistulas in this unselected patient cohort reported herein, an outcome similar to that reported by other authors [19-26] In addition, the combined treatment of TPN and OC significantly increased the overall rate of spontaneous fistula healing by 25% compared with standard medical treatment (89% vs. 64%, $p<0.05$). The study did not include a group of patients that received TPN alone, because the combination of TPN and OC was considered as the optimal therapy, since the reduction of fistula output with OC was desirable to achieve a quick improvement in critically ill patients.[30] Besides, it has been shown by the majority of studies that octreotide or somatostatin reduces the closure time and the period of hospitalization and it improves the quality of life of patients with gastrointestinal tract fistulae.[31-34] No important side effects with OC treatment were observed in our study, as reported. This was in contrast with other studies, reporting that octreotide might have contributed to cardiac morbidity in patients with pancreatic fistulas.[35]

Metabolic disorders and physical discomfort caused by corrosive fluids are related to fistula output.[11,27] By reducing the volume and enzymatic content of gastrointestinal fistulas, TPN and OC facilitated the management of fluid and electrolyte abnormalities, metabolic and nutritional disorders as well as of local skin damage. In addition TPN and OC combination treatment succeeded in reducing morbidity in group B and this outcome was statistically significant ($p<0.05$). In addition, there was no evidence of increased septic complications. The majority of hypeglycemic events occurring during TPN and OC management were diagnosed prior to drainage of intraabdominal or fistulous tract sepsis as already reported.[29]

Better results were also obtained with surgical fistula repair in patients of group B and this may be attributed to the improvement of nutritional status with TPN during perioperative period. There is evidence that the prophylactic pharmacotherapy with somatostatin-14 admin-

istered as a continuous intravenous infusion produces a significant decrease in fistula formation and secretion events after pancreaticoduodenectomy.[36,37] Other studies however do not support this opinion and report that prophylactic octreotide should not be used, as there is no convincing evidence for its efficacy so far.[26,38]

In conclusion, the present study demonstrated that regardless of EDTF type, the introduction of TPN and OC in the standard treatment of EDTF, optimized treatment efficacy by reducing hospitalization time, increasing closure rate, accelerating fistula closure rate and decreasing fistula related morbidity and mortality.

REFERENCES

1. Edmunds H.Jr, Williams GM, Welch CE. External fistulas arising from the gastrointestinal tract. Ann. Surg 1960; 152: 445-470.
2. Halversen RC, Hogle HH, Richards RC. Gastric and small bowel fistulas. Am J Surg 1969; 118: 968-972.
3. Lorenzo GA, Beal JM. Management of external small bowel fistulas. Arch Surg 1969; 99: 394-396.
4. Nassos TP, Braasch JW. External small bowel fistulas: current treatment and results. Surg Clin North Am 1971; 51: 687-692.
5. Nemhauser GM, Brayton D. Enterocutaneous fistulas involving the jejuno-ileum. Am Surg 1967; 33: 16-20.
6. Roback SA, Nicoloff DM. High output enterocutaneous fistulas of the small bowel. Am J Surg 1972; 123: 317-322.
7. West JP, Ring EM, Miller RE. A study of the causes and treatment of external postoperative intestinal fistulas. Surg Obstet Gynecol 1961; 113: 490-496.
8. Chapman R, Foran B, Dunphy JE. Management of intestinal fistulas. Am J Surg 1964;108:157-164.
9. Meguid MM, Campos ACL. Preface: Surgical management of gastrointestinal fistulas. Surg Clin North Am 1996; 76: 11-13.
10. Fischer JE. The pathophysiology of enterocutaneous fistulas. World J Surg 1983; 7: 446-450.
11. McIntyre PB, Ritchie JK, Hawley PR, et al. Management of enterocutaneous fistulas: a review of 132 cases. Br J Surg 1984; 71: 293-296.
12. Rinsema W, Gouma DI, von Meyenfeldt MF, et al. Primary conservative management of external small-bowel fistulas. Acta Chir Scand 1990; 156: 457-462.
13. Schein M, Decker GAG. Postoperative alimentary tract fistulas. Am J Surg 1991; 161: 435-438.
14. Kuvshinoff BW, Brodish RJ, McFadden DW, et al. Serum tranferrin as a prognostic indicator of spontaneous closure and mortality in gastrointestinal cutaneous fistulas. Ann Surg 1993; 217: 615-623.
15. Reber HA, Roberts C, Way L, et al. Management of external gastrointestinal fistulas. Ann Surg 1978; 188: 460-467.
16. Soeters PB, Ebeid AM, Fischer JE. Review of 404 patients with gastrointestinal fistulas: impact of parenteral nutrition Ann Surg 1979; 190: 189-202.
17. Machado MC, Monteiro da Cunha JE, Bacchela T, et al. Surgical treatment of persistent intestinal fistula associated with abdominal evisceration. Int Surg 1988; 73: 133-134.
18. Berry SM, Fischer JE. Enterocutaneous fistulas. Curr Probl Surg 1994; 31: 473-554.
19. Nubiola P, Badia JM, Martinez-Rodenas F, et al. Treatment of 27 postoperative enterocutaneous fistulas with the long half-life somatostatin analogue SMS 201-995. Ann Surg 1989; 210: 56-58.
20. Nubiola-Calogne P, Sancho J, Segura M, et al. Blind evaluation of the effects of OC (SMS 201-995), a somatostatin analogue, on small-bowel fistula output. Lancet 1987; 2: 672-74.
21. Borison Dl, Bloom AD, Pritchard TJ. Treatment of enterocutaneous and colocutaneous fistulas with early surgery or somatostatin analog. Dis Colon Rectum 1992; 35: 635-639.
22. Torres AJ, Landa JI, Moreno-Azcoita M, et al. Somatostatin in management of gastrointestinal fistulas: A multicenter trial. Arch Surg 1992; 127: 97-100.
23. Sancho JJ, Di Constanzo J, Nubiola P, et al. Randomized double-blind placebo-controlled trial of early OC in patients with postoperative enterocutaneous fistula. Br J Surg 1995; 82: 638-641.
24. Paran H, Neufeld D, Kaplan O, et al. OC for treatment of postoperative alimentary tract fistulas. World J Surg 1995; 19: 430-434.
25. Martineau P, Shwed JA, Denis R. Is OC a new hope for enterocutaneous and external pancreatic fistulas closure? Am J Surg 1996; 172: 386-390.
26. Alvarez C, McFadden DW, Reber HA. Complicated enterocutaneous fistulas: failure of OC to improve healing. World J Surg 2000; 24: 533-538.
27. Sitges-Serra A, Jaurrieta E, Sitges-Creus A. Management of postoperative enterocutaneous fistulas: The role of parenteral nutrition and surgery. Br J Surg 1982; 69: 147-150.
28. Prickett D, Montgomery R, Cheadle WG. External fistulas arising from the digestive tract. South Med J 1991; 84: 736-739.
29. Rose D, Yarborough MF, Canizaro PC, et al. One hundred and fourteen fistulas of the gastrointestinal tract treated with total parenteral nutrition. Surg Gynecol Obst 1986; 163: 345-350.
30. Memon AS, Siddiqui FG. Causes and management of postoperative enterocutaneous fistulas. J Coll Physicians Surg Pak 2004; 14: 25-28.
31. Gonzalez-Pinto I, Gonzalez EM. Optimizing the treatment of upper gastrointestinal fistulae. Gut 2001; 49: iv22-31.
32. Hesse U, Ysebaert D, De Hemtinne B. Role of somatostatin-14 and its analogues in the management of gastrointestinal fistulae: clinical data. Gut 2001; 49: iv11-iv21.
33. Hashimoto N, Yasuda C, Ohyanagi H. Pancreatic fistula after pancreatic head resection: incidence, significance

and management. Hepatogastroenterology 2003; 20: 1658-1660.
34. Alivizatos V, Felekis D, Zorbalas A. Evaluation of the effectiveness of octreotide in the conservative treatment of postoperative enterocutaneous fistulas. Hepatogastroenterology 2002; 49: 1010-2.
35. Barnett SP, Hodul PJ, Creech S, et al. Octreotide does not prevent postoperative pancreatic fistula or mortality following pancreaticoduodenectomy. Am Surg 2004; 70: 222-226.
36. Gouillat C, Gigot JF. Pancreatic surgical complications-the case for prophylaxis. Gut 2001; 49: iv32-39.
37. 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: 190-199.
38. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000; 232: 419-429.