RESEARCH ARTICLE

Clinical Efficacy of Endoscopic Pancreatic Drainage for Pain Relief with Malignant Pancreatic Duct Obstruction

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Abstract

Objective: This study was conducted to investigate the efficacy of pancreatic drainage for pain relief in advanced pancreatic cancer. Method: Seventy-one patients with pancreatic carcinoma were divided into two groups: dilated and non-dilated pancreatic ducts. All patients underwent endoscopic retrograde cholangiopancreatography (ERCP), endoscopic biliary stenting and pancreatic stenting. Visual Analog Scale (VAS) scores, pain remission rates and survival time were evaluated during follow-up. Results: The post-ERCP VAS score of the dilated group was lower than that of the non-dilated group at 1 and 3 months post-ERCP. There was no difference at 6 months. The pain remission rate in the dilated duct group was significantly higher than that in non-dilated duct group in 1 and 3 months post-ERCP. The median survival times were 8.17 and 8.22 months respectively. Conclusion: Endoscopic pancreatic drainage can relieve pain of advanced pancreatic cancer accompanied by safe dilation of the pancreatic duct.

Keywords: Pancreatic cancer - ERCP - pancreatic drainage - pain relief

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Introduction

Pancreatic cancer is a highly malignant gastrointestinal cancer with an insidious onset. It usually does not cause any specific symptoms in early stages. Therefore, it is difficult to detect and treat in early stages (Saif, 2011). The incidence and mortality rates of pancreatic cancer have gradually increased in China (Chen et al., 2013). The intractable pain caused by pancreatic cancer affects the life quality of the patients (Lee et al., 2012). With the progression of the disease, more than half of the patients will demonstrate symptoms of obstructive jaundice and abdominal pain, especially for the patients in the moderate and advanced stages of pancreatic carcinoma (Huggett and Pereira, 2011). We found that some patients with dilated pancreatic ducts had severe pain. Consequently, much attention has focused on relief of the pain of pancreatic duct distension. Palliative treatment is an important means by which the life quality can be improved in advanced or end stage disease (Kruse, 2010). The aim of the present study was to determine the effects of endoscopic pancreatic drainage on pancreatic cancer pain associated with dilated pancreatic ducts.

Materials and Methods

Objects and grouping

This was a prospective study. A total of 76 cases of pancreatic carcinoma admitted from September 2009 to September 2012 were enrolled. The inclusion criteria were as follows: (1) visual analogue score (VAS) ≥ 4; (2) no radiotherapy, chemotherapy, or analgesics were used before enrollment; (3) the main clinical symptoms were pain in upper abdomen/lower back, jaundice, anorexia, and weight loss. Magnetic resonance imaging (MRI) or computed tomography (CT) report indicated space-occupying lesions in the pancreas. Two cases were confirmed as pancreatic carcinoma by fine needle aspiration (FNA) followed by histopathological examination, and the other 74 were diagnosed by clinical symptoms, radiology examination, and laboratory inspection. The 76 patients were divided into two groups, the dilated group (with dilated pancreatic duct, 42 cases) and the normal group (with normal pancreatic duct, 34 cases) based on CT, magnetic resonance cholangiopancreatography (MRCP) and ERCP images. Pancreatic duct dilatation was defined as a diameter of the main pancreatic duct was dilated more than 5 mm at the widest point.

Therapeutic treatment

ERCP exanimation was conducted by JF-240, TJF-260V electronic duodenoscope (Olympus, Japan). Surgical instruments included standard ERCP catheter, duodenal papilla incision knife (Olympus, Japan), super lubricious hydrophilic guide wire (0.025 inch, Olympus, Japan), yellow zebra guide wire (0.035 inch, Boston,

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USA), red zebra guide wire (0.025 inch, Boston, USA), dilating bougie of biliary duct and pancreatic duct (Cook, USA), 5 Fr plastic pancreatic drainage stent (Cook, USA), metal biliary drainage stent (Boston, USA), ERBE ICC200 high-frequency electricity generator (ERBE, Germany); Iohexol injection was used as contrast medium (Yangtze River Pharm, China). The length of stent depended on the distance from the distal end of stenosis to the opening of the papilla. All patients routinely received ERCP examination. Following pancreatic intubation, contrast medium was injected slowly to determine whether the pancreatic duct was dilated. All the patients received endoscopic sphincterotomy prior to stent insertion. All strictures of the biliary duct and the pancreatic duct were expanded using dilators before stenting, and pancreatic stent and metal biliary stent were subsequently inserted over guide wires. The distal end of the stent was placed to extend 0.5-1.0 cm beyond the stenosis. The guide wire and endoscope were withdrawn and radiographic images were collected (Figure 1).

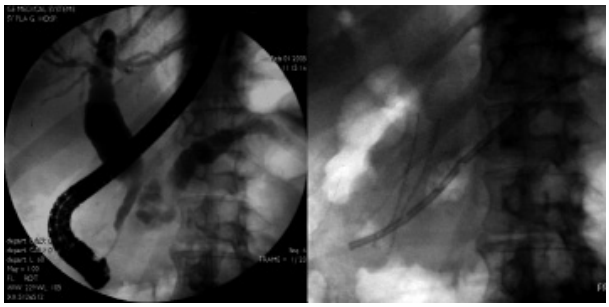

Figure 1. Image of Dilated Duct and Stent Placement

Post-ERCP examination

Blood amylase, total bilirubin, AKP, and ALT of the patients were observed and recorded pre- and post-ERCP. VAS of abdominal pain was recorded pre-ERCP. All the patients underwent abdominal fluoroscopy and BUS or CT at 3 and 6 months. The patients were followed up at one week, 1, 3 and 6 months post-ERCP up to death, and the survival times, VAS and pain remission rates were recorded. No patients received analgesics during the 3 months post-ERCP. Some, including most of the non-dilated group received analgesics 3 months after ERCP. Complications related to the operation such as bleeding, fever, hyperamylasemia, pancreatitis, and stent displacement were also documented.

Abdominal pain

The degree of abdominal pain was scored by VAS. Complete remission means painless (CR); partial remission (PR) was defined as obvious relief of pain compared with pre-treatment, and rare disturbance of sleep; mild remission (MR) was defined as relief, but with remaining obvious pain and sleep disturbance; no remission (NR) was defined as no relief of pain compared with pre-treatment. The effects were evaluated according to WHO Response Evaluation Criteria in Solid Tumors and CR and PR were both considered to be measures of effectiveness. The rate of pain remission was defined as the proportion of patients with CR and PR in all the patients.

Statistical analysis

The data were analyzed by SPSS 13.0. Measurement data were presented in x±s. The intergroup comparison of pain remission rate was investigated by $\chi 2$ test; the intergroup comparisons of blood amylase and median survival time were conducted by t-test. The intra-group VAS was compared by single factor F test and the intergroup VAS was compared by t-test. The difference is considered as significant when $p<0.05$.

Results

General Data

During the enrollment period, about 22.6% (42/186) of the patients with dilated ducts had pain, and about 18.7% (34/182) of the patients with normal ducts had pain. Four cases of dilated pancreatic duct were excluded due to failure of pancreatic stent implantation (3 cases of failed pancreatic intubation, and 1 of failed pancreatic stent placement). Finally, 38 cases were included in the dilated duct group. The success rate of pancreatic intubation was 90.5% (Table 1). One case with a non-dilated pancreatic duct was excluded because of pancreatic intubation failure. Finally, 33 cases were taken into the non-dilated duct group. The success rate of pancreatic intubation was 97.1%, and there was no statistically significant difference in the pancreatic intubation success rates between the two groups ($\chi^2=2.38$, $p>0.05$). The average age of patients in the dilated duct group (22 males and 16 females) was 68.2±17.9 and in the non-dilated duct group (21 males and 12 females) was 65.1±14.4. The differences in patient age and gender were not statistically significant (t=0.06, $p>0.05$). In this respect, the two groups were comparable. The total bilirubin, ALT, and AKP of all patients before operation were 74.6±12.0 mmol/L, 256.2±32.0 U/L, and 297.5±37.3 U/L, respectively. There was no significance difference between the median survival time of the dilated duct group (8.17 months) and the non-dilated duct group (8.22 months) (t=0.19, $p>0.05$).

Table 1. Clinical Characteristics of Two Groups (x±s)

	Dilated Ducts (38 cases)	Non-dilated Ducts (33 cases)	Statistics
Male, female	22, 16	21, 12	t=0.09
Average age (y)	68.2±17.9	65.1±14.4	t=0.06
Success rate of pancreatic intubation	90.5%	97.1%	$\chi_2=2.38$
Median survival time (m)	8.17	8.22	t=0.19

Post-ERCP examination

Of all patients, the levels of serum total bilirubin, ALT, and AKP were significantly lower than those pre-ERCP (23.7±6.5 mmol/L vs 74.6±12.0 mmol/L, $p<0.05$; 79.2±18.8 U/L vs 256.2±32.0 U/L, $p<0.05$; 108.9±223.8 U/L vs 297.5±37.3 U/L, $p<0.05$). The blood amylase level of the dilated duct group, one day post-ERCP was (62.7±27.3) U/L, while that of the non-dilated duct group was (76.2±21.6) U/L. The difference was not statistically significant (t=0.07, $p>0.05$). There was one case each group that developed hyperamylasemia and post-ERCP

pancreatitis. Both resolved after 5 days of symptomatic therapy. All the pancreatic duct stents in patients remained in place 3 and 6 months after insertion. Nine cases in the dilated duct group (23.7%), and 8 in the non-dilated duct group (24.2%) were complicated by displacement and obstruction of the biliary stent, without statistically significant difference between the two groups (χ^2=1.97, p>0.05). Both covered and uncovered biliary stents were used. Only covered metal biliary stents migrated. Because we dilated all strictures before stent insertion, it is possible that this had an effect on stent migration. All patients with displacement and obstruction of the biliary stent received ERCP replacement or superposed biliary stent implantation. No complications including bleeding, perforation, and displacement of pancreatic stent were observed in any of these cases. According to the follow-up results 3 months post-ERCP, no further dilation was seen in any patients, and no improvement of dilated pancreatic ducts was observed in dilated group.

Abdominal pain

There was 35 cases of epigastric pain, 1 of back pain, 2 of mixed pain and 15 of post-prandially worsened pain in the dilated pancreatic duct group. There were 29 cases of epigastric pain, 2 of back pain, and 2 of mixed pain. There was 1 case of post-prandially worsened pain in the non-dilated pancreatic duct group. No patients received analgesics until 3 months after ERCP. Figure 2 presents the pre- and post-ERCP VAS results of the patients from both groups. The VAS of the dilated duct group one week post-ERCP was significantly lower than that of pre-ERCP and of the non-dilated duct group (F=0.574, F=0.691, both p<0.05); the VAS one month post-ERCP was significantly lower than that of the pre-ERCP and the non-dilated duct group (F=0.602, F=0.499, both p<0.05); the VAS 3 months post-ERCP was significantly lower than that of pre-ERCP and of the non-dilated duct group (F=0.883, F=0.892, both p<0.05). The VAS 6 months post-ERCP was not significant different from that pre-ERCP and from the non-dilated duct group (F=2.776, F=3.260, both p>0.05). It is shown in Table 2 that the pain remission rate of the dilated duct group one month post-ERCP was 74.3%, while that of the non-dilated duct group was 16.1%, which was a statistically significant difference between the two groups

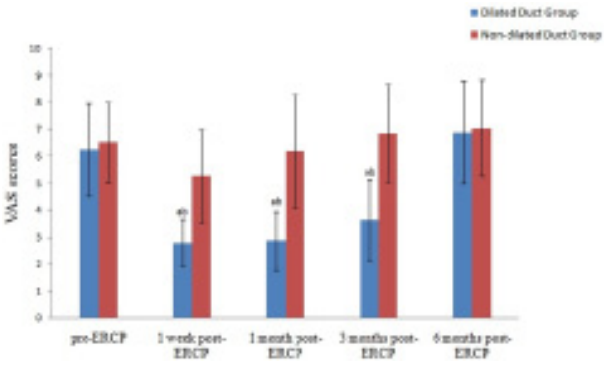

Figure 2. VAS Scores Pre- and Post-ERCP of The Two Groups (x±s) VAS is visual analogue scale; a compared with the same group prior treatment, p<0.05; b compared with the normal group, p<0.05

Table 2. Pain Relief of The Dilated Duct and Non-Dilated Duct Groups 1 and 3 Months Post- ERCP (Number of Cases)

Group	N	CR	PR	MR	NR	Remission rate (%)
1 month post-ERCP						
Dilated	35	5	21	9	0	74.3%[a]
Normal	31	0	5	7	19	16.1%
3 months post-ERCP						
Dilated	29	2	14	10	3	55.2%[a]
Normal	24	0	4	8	9	16.7%

[a]compared with the normal group, p<0.05

(χ^2=18.57, p<0.05). The pain remission rate of the dilated duct group three months post-ERCP was 55.2%, while that of the non-dilated duct group was 16.7%, representing a statistically significant difference between the two groups (χ^2=11.43, p<0.05).

Discussion

Currently, endoscopic biliary drainage has become a common treatment to relieve jaundice in patients with unresectable pancreatic cancer (Maosheng et al., 2001). According to previous studies (Decker et al., 2011; Adams et al., 2012), pancreatic cancer patients who received metal stent biliary drainage had a better patency, and lower incidence of complications than those treated by plastic biliary stent. Therefore, in this study, all patients were treated with metal stent biliary drainage, and the results showed that jaundice was significantly improved a week after the biliary drainage to basically normal total bilirubin levels.

In the present study, 55.3% (42/76) of patients had pancreatic duct dilatation and preoperative enhanced CT or MRCP clearly showed whether there is pancreatic duct dilatation. ERCP intraoperative cholangiopancreatography allowed accurate identification of the tumor site, the length of narrowed segment, and the extent of pancreatic duct dilatation. A number of studies (Mazaki et al., 2010; Choudhary et al., 2011; Mazaki et al., 2013) have shown that pancreatic stents can reduce the incidence of post-ERCP pancreatitis. Therefore, in the present study, the patients without dilated pancreatic ducts all received pancreatic stents implantation, not only to reduce the incidence of post-ERCP pancreatitis, but also to prevent the secondary pancreatic duct outlet obstruction caused by biliary metallic stent implantation. Lee et al (Lee et al., 2012) reported a success rate of pancreatic duct intubation of 96%, which is similar to that of the patients without pancreatic duct dilatation (97.1%) in the present study. However, the success rate of pancreatic duct intubation of the dilatation group (90.48%) is lower than the non-dilated duct group, because significant stenosis of pancreatic duct in some cases resulted from tumor tissue hyperplasia. The guide wire failed to traverse the stenosis of pancreatic duct, which led to failure of pancreatic duct cannulation. Overall, both the difficulty and danger of pancreatic duct intubation are greater than that of bile duct intubation.

The biliary stent insertions were successful in all patients in this study. From the univariate analysis, the

data support the use of a metallic-type stent, in patients having no jaundice, or pain, with a history of prior ERCP and a proximal biliary stone causing cholangitis (Salehimarzijarani et al., 2012). However, no cholangitis was found in our study. Cholangitis may be associated with abdominal pain and jaundice and can be avoided with adequate biliary drainage. There was no significant difference in the incidence of obstruction and biliary stent migration between the two groups and no significant difference in levels of postoperative serum amylase. We did find post-ERCP pancreatitis and hyperamylasemia. The incidence of hyperamylasemia (2.63% vs 3.03%) and pancreatitis (2.63% vs 3.03%) were similar between the two groups. Repeated cannulation was difficult. However, pancreatic duct drainage rapidly resolved the obstructions. There were no instances of perforation, bleeding, pancreatic duct stent migration and other complications. No pancreatic duct dilatation was observed in non-dilated duct group during follow-up period. In the present study, the incidence of complications was similar to that of previous reports (Zhou et al., 2011), and the results indicate that the pancreatic stents may improve the patency of pancreatic ducts and reduce the incidence of ERCP complications in the non-dilated duct group. No improvement in anorexia or weight loss was found in either group.

Pancreatic duct obstruction resulting from the compression of pancreatic tumor causes pancreatic duct dilatation and increased pressure, thus inducing pancreatic hypertensive pain. A similar study confirmed that PD stenting achieved significant pain relief and short-term improvement of the quality of life in the majority of patients with PD obstruction due to pancreatic carcinoma (Wehrmann et al., 2005). In the present study, a large amount of pancreatic juice mixed with white protein plugs was seen after pancreatic duct drainage in the dilated duct patients. Therefore, the abdominal pain of patients in the dilatation group can ease as early as one day after the ERCP, and a significant decrease can be seen one week, one and three months after the operation, which are improvements compared with the non-dilated duct group. As no patients received analgesics in 3 months post-ERCP, we concluded that the pain remission was completely due to pancreatic stent insertion. Although some patients in the two groups received analgesics after 3 months post-ERCP, the VAS of abdominal pain showed no significant difference between the two groups 6 months post-ERCP. The results confirmed that the pancreatic duct drainage can reduce the pressure in the pancreatic duct dilatation cases and help to reduce the abdominal pain. For patients in the non-dilated duct group, there was no significant difference in the VAS of abdominal pain pre- and post-ERCP, which indicated that the pancreatic duct drainage cannot improve the abdominal pain of patients without pancreatic duct dilatation.

However, significant differences in the VAS was found six months after ERCP in patients in the dilatation duct group, suggesting that with the progression of the disease, the increase, proliferation and metastasis of tumor involved the sensory nerves around the pancreas or retroperitoneal plexus, and thus making the pain worse and independent of duct dilatation. Yet, no significant difference in the VAS was found during the 6 months after ERCP in the non-dilated group, suggesting that the analgesics resulted in pain relief. No statistical difference in the VAS can be found 6 months after ERCP between the dilatation group and non-dilated duct group. Therefore, the long-term treatment of pancreatic cancer pain shall adopt a comprehensive treatment encompassing medication (Uomo, 2011), ganglion block (Wyse et al., 2011) or high-intensity focused ultrasound (Wang et al., 2011) etc. In the present study, one month after the operation, the pain remission rate (74.3%) of dilatation group was significantly higher than that of the non-dilated duct group (16.1%) and three months after ERCP, the pain remission rate (55.2%) of dilatation group is also significantly higher than that of the non-dilated duct group (16.7%). However, as the disease progressed, the pain remission rate of the dilatation group gradually reduced while the abdominal pain of some patients in the non-dilated duct group showed slight relief, because biliary stenting may reduce the patient's biliary pressure, relieve obstructive jaundice, which enables the bile excretion into the intestinal tract, and thereby improves the digestion and abdominal distension of patients, and relieves the abdominal pain of some patients.

In the present study, there was no significant difference in the median survival time between the dilatation group (8.17 months) and non-dilated duct group (8.22 months), indicating that the pancreatic duct drainage does not prolong the lifetime of patients with pancreatic cancer, and the pancreatic duct dilatation is also not an indicator of life expectancy. Pancreatic duct drainage can reduce the associated pain of advanced patients with pancreatic duct dilatation, but cannot prolong life expectancy.

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