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Is constant negative pressure for external drainage of the main pancreatic duct useful in preventing pancreatic fistula following pancreatoduodenectomy?

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ABSTRACT

Background: This study sought to investigate the utility of constant negative pressure for external drainage of the main pancreatic duct in preventing postoperative pancreatic fistula (POPF) after pancreatoduodenectomy.
Methods: Only patients with soft pancreas were included. In the former period (July 2013 to May 2015), gravity dependent drainage was applied (gravity dependent drainage group), and in the latter period (June 2015 to November 2016), constant negative pressure drainage (negative pressure drainage group) was applied to the main pancreatic duct stent.
Results: There were 37 patients in the gravity dependent drainage group and 39 patients in the negative pressure drainage group. Clinically relevant POPF occurred in 21 patients (56.8%) in the gravity dependent drainage group and 13 patients (33.3%) in the negative pressure drainage group ($p = 0.040$). The incidence rate of major complications (Clavien-Dindo grade > III) was significantly lower in the negative pressure drainage group (13.2%) compared to the gravity dependent drainage group (48.7%) ($p = 0.001$). In-hospital stay was also significantly shorter in the negative pressure drainage group compared to the gravity dependent drainage group (median 25 vs. 33 days, $p = 0.024$). Multivariate analysis demonstrated that the gravity dependent drainage was one of the independent risk factors for the incidence of POPF (odds ratio, 3.33; $p = 0.032$).
Conclusions: In patients with soft pancreas, the incidence rate of clinically relevant POPF may be reduced by applying constant negative pressure to the pancreatic duct stent. It also has a potential to reduce overall incidence of major complications and shorten in-hospital stay after pancreatoduodenectomy.

Introduction

Post-operative pancreatic fistula (POPF) is the most deleterious complication that induces life-threatening event after pancreatoduodenectomy [1]. There have been a number of reports that attempted to reduce the incidence of POPF [2–4]. Those include technical arrangement of the reconstruction method for pancreatojejunostomy [5,6], prophylactic use of octreotide [7,8], and drainage of pancreatic juice from the main pancreatic duct using external pancreatic duct stent to reduce the leakage of pancreatic juice into abdominal cavity [9,10]. Because large amount of pancreatic juice secreted from soft pancreas is a definitive risk factor for POPF, the external drainage of the pancreatic juice using a pancreatic duct stenting is a useful way to reduce the incidence of POPF following pancreatoduodenectomy [10].

There have been a few previous reports that compared the negative pressure drainage and gravity dependent drainage of the pancreatic duct stent in pancreatoduodenectomy [11–13]. In these reports, negative pressure drainage showed some beneficial effects in reducing the incidence of POPF. Nevertheless, the impact was modest and the real benefit of negative pressure drainage of the pancreatic duct is still unclear. Moreover, previous studies included patients with hard pancreas, in whom pancreatic juice secretion is

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scarce and the benefit of negative pressure drainage of pancreatic juice may be limited. The study should be performed only in patients with soft pancreas who secrete rich amount of pancreatic juice from the remnant pancreas and suffered from high incidence of POPF.

In the present study, we only included the patients with soft pancreas and sought to determine whether constant negative pressure drainage is beneficial in preventing clinically significant POPF as well as other major complications following pancreatoduodenectomy.

Patients and methods

Patients

The study protocol has been approved by the research institute's committee on human research (approved number 2018–0100). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

Patients who underwent pancreatoduodenectomy in the First Department of Surgery, Nagoya University Hospital from July 2013 to November 2016 were included. All patients with narrow main pancreatic duct diameter (less than 3 mm) or soft pancreatic texture (irrespective of the diameter of main pancreatic duct) determined by an intraoperative finding were subjected for the analysis. Patients with pancreaticojejunostomy by Kakita's method [5], invagination [3,14], and two layered anastomosis were excluded, and only those with Blumgart anastomosis were included to avoid the impact of different anastomotic technique on the incidence of POPF. During the study period, there was no patient without pancreatic duct stenting. Patients with hard pancreas determined intraoperatively were also excluded, because these patients may not secrete high amount of pancreatic juice. In the former period (July 2013 to May 2015), gravity dependent drainage was applied for the pancreatic duct stent (gravity dependent drainage group). And in the latter period (June 2015 to November 2016), constant negative pressure was applied using CLIO DRAIN VAC (Sumitomo Bakelite Co. Ltd. Tokyo, Japan) (negative pressure drainage group) (Fig. 1). During the study period, perioperative management did not change except for the type of drainage of the pancreatic duct stent.

Surgical techniques

Four board certified hepato-biliary -pancreatic surgeons (Y.Y., J.Y., G.S., and T.I.) by the Japanese Society of Hepato-Biliary-Pancreatic Surgery mainly performed surgeries. All of the patients underwent either a subtotal-stomach preserving (SSPPD), a pylorus-preserving (PPPD), or a conventional pancreatoduodenectomy. The stomach was cut 3 cm proximal to the pylorus in SSPPD. The proximal duodenum was preserved 2–4 cm distal to the pylorus in PPPD. Portal vein resection and reconstruction was performed in patients with tumor invasion. In all patients, reconstruction were performed by a modified Child's method. It means that the anastomosis was performed between the jejunum and the pancreas, bile duct, and stomach in order through the mesocolon. The end-to-side pancreaticojejunostomy was performed by duct-to-mucosa technique using 5–0 absorbable monofilament and with Blumgart method using 4–0 non-absorbable monofilament in all patients [6,15]. A 4 to 7.5-Fr polyethylene knotted pancreatic duct stent depending on the size of the main pancreatic duct (Sumitomo Bakelite Co. Ltd. Tokyo, Japan) was inserted into the main pancreatic duct of the remnant pancreas, and the stent was exteriorized through the end of the blind loop of the jejunum for external drainage. The externalized stent was then connected to either a gravity dependent drainage bag or a constant negative pressure bag (Fig. 1). These bags were kept at floor level whenever possible. In addition, an 8-Fr polyethylene jejunal tube was separately inserted as the route of enteral nutrition and pancreatic juice replacement. At the end of operation, 19-Fr Silicone drains were routinely placed in the dorsal and ventral aspects of the pancreaticojejunostomy.

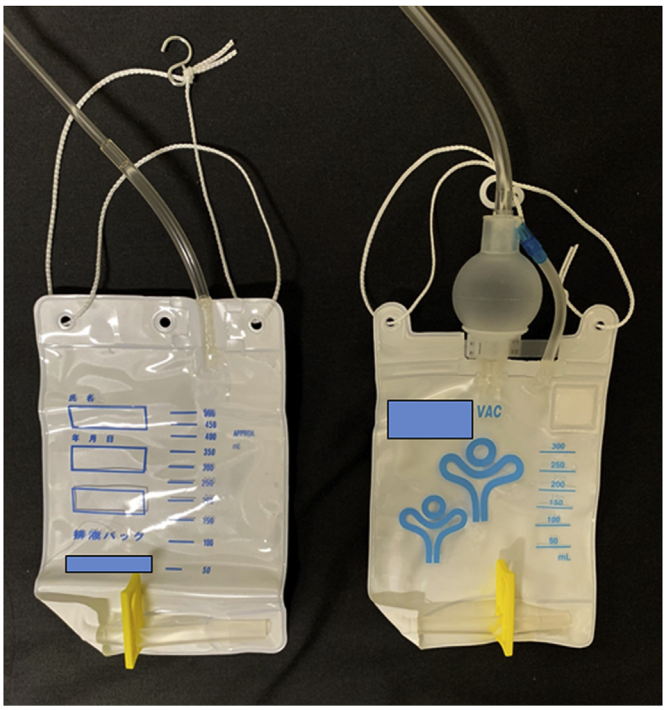

Fig. 1. Gravity dependent drainage bag (left) and negative pressure drainage bag (right). Approximately 20–40 cmH_2O negative pressure is applied by squeezing the ball between the tube and bag (left).

Perioperative management

The perioperative patient management was standardized as follows. All patients received intravenous antibiotics intraoperatively and for two or three days after surgery. Enteral nutrition and replacement of pancreatic juice was started from postoperative day (POD) 1 [16]. The amylase levels in discharge fluid from the peripancreatic drains were measured on POD 1, 3, and 7. The drains were removed if discharge fluid was clear and the levels of amylase were less than 3 times of the institutional upper limit of serum amylase (125 IU/L). Otherwise, these were left, and then exchanged twice a week until the evidence of POPF or infection of the drainage tract had completely disappeared. Pancreatic duct stent had never been removed until all peripancreatic drains were removed.

Analyzed factors

The preoperative patient's characteristics including age, gender, body mass index, type of diseases, comorbidities, and main pancreatic duct diameter measured by preoperative computed tomography images were recorded. Intraoperative factors including

operative method, portal vein resection, texture of the pancreas, estimated blood loss, and operation time were recorded. The amylase levels in the drained fluid were measured on POD 1 and 3. The daily output volume of pancreatic juice from the pancreatic duct stent was monitored on POD 1 to 7 every day at 2 p.m. Postoperative outcomes including overall mortality, overall morbidity, duration of drainage, and the length of hospital stay after surgery were also recorded.

The postoperative complication after pancreatoduodenectomy was graded according to the Clavien-Dindo classifications of surgical complications [17]. Postoperative pancreatic fistula and delayed gastric emptying were classified according to the definition of the International Study Group of Pancreatic Surgery [18–20]. Informed consent was obtained from all individual participants included in this study.

Statistical analysis

All data were reported as the mean ± standard deviation or the median with interquartile range. The student t-test or Mann-Whitney *U* test was used for continuous data. χ [2] -test was used for categorical data. Univariate and multivariate analysis were used to explore the risk factors of POPF. Clinical variables that showed a p value of less than 0.2 by univariate analysis were selected for multivariate analysis. Cut-off values were determined using a receiver operating characteristic curve analysis. A value of $p < 0.05$ was considered statistically significant. All of the statistical analyses were performed using JMP version 11.0 (SAS Institute INC., Cary, NC).

Results

Preoperative patient's characteristics

One-hundred and thirty-four patients underwent pancreatoduodenectomy during the study period (Fig. 2). Among them, 16 patients without Blumgart anastomosis and 42 patients with hard pancreas were excluded. Thus, 76 patients who were with soft pancreas and underwent Blumgart anastomosis during the study period were included for the final analysis. A gravity dependent drainage was applied in 37 patients, whereas a negative pressure drainage was applied in 39 patients. There was no significant difference in age, gender, body mass index, and type of diseases between the gravity dependent drainage group and negative pressure drainage group (Table 1). Among preoperative comorbidities, the proportion of patients with diabetes mellitus was significantly lower in the negative pressure drainage group. The main pancreatic duct diameter measured by CT scan images were not significantly different between the two groups.

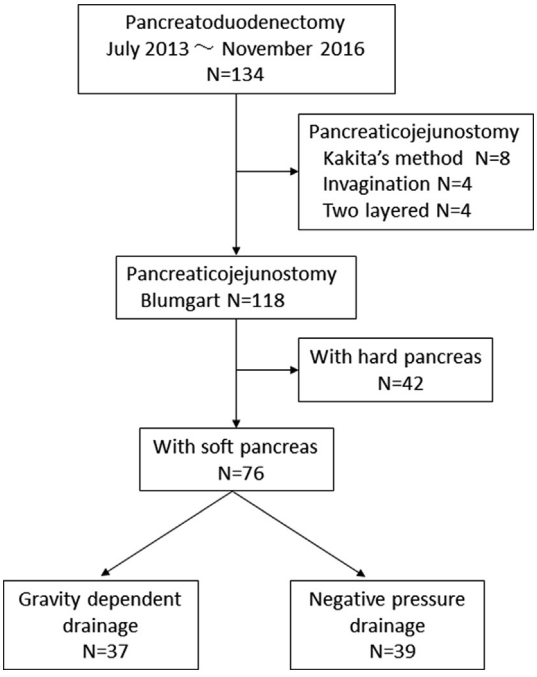

Fig. 2. Flow chart of the studied patients.

Intraoperative factors

More than 90% of the patients underwent SSPPD in both groups (Table 2). The rate of portal vein resection, estimated intraoperative blood loss, and operation time were all comparable between the two groups.

Daily amount of pancreatic juice discharge from the pancreatic duct stent

After surgery, the amount of daily pancreatic juice output from the pancreatic duct stent increased gradually and reached to plateau level on POD 5 (Fig. 3). Although the amount of pancreatic juice output tended to be higher in the negative pressure drainage group on POD 2 to 5, there was no significant difference between the two groups.

Postoperative outcomes

There was no surgery-related death. Although the rate of total complications was similar in the two groups, major complications classified as Clavien-Dindo classification grade III and IV in the gravity dependent drainage group were observed more than that in the negative pressure drainage group ($p = 0.001$). There was one patient with grade IV complication in each group. One patient in the gravity dependent drainage group was admitted to the intensive care unit because of aspiration pneumonia, and the other patient in the negative pressure drainage group was admitted to the intensive care unit because of heart failure. Both of them recovered swiftly and discharged from the hospital on POD 48 and 18, respectively. There was no incidence of grade C POPF in both groups. The total incidence rate of POPF was almost identical between the two groups. However, the rate of clinically relevant POPF (grade B) in the negative pressure drainage group was significantly lower compared to that in the gravity dependent drainage group (13.3% vs. 56.8%, $p = 0.040$) (Table 3). The duration of drainage was shorter and the median length of hospital stay was significantly shorter in the negative pressure drainage group than the gravity dependent drainage group ($p = 0.024$).

Risk factors of POPF

Finally, univariate and multivariate analyses were performed by including the possible risk factors of clinically relevant POPF. Among all clinical variables, BMI (>21 kg/m^2), presence of diabetes mellitus, main pancreatic duct diameter (<3 mm), operation time (>380 min), and method of drainage showed a p value less than 0.20 by univariate analysis. With multivariate analysis, gravity dependent drainage was identified as one of the independent risk factors for the incidence of POPF (odds ratio, 3.33; 95% confidence interval, 1.11–11.03; $p = 0.032$) (Table 4).

Table 1
Preoperative patients' characteristics.

	Gravity dependent drainage (n = 37)	Negative pressure drainage (n = 39)	*P*
Age (years)	64 [60–73]	69 [58–76]	0.380
Gender (male:female)	28:9	22:17	0.077
Body mass index	21.1 [19.7–22.8]	21.2 [20.3–23.3]	0.554
Diseases, n (%)			0.703
Pancreatic cancer	3 (8.1%)	5 (12.8%)	
Bile duct cancer	14 (37.8%)	17 (43.6%)	
Ampullary cancer	7 (18.9%)	4 (10.3%)	
Cystic neoplasm	6 (16.2%)	8 (20.5%)	
Others	3 (8.1%)	5 (12.8%)	
Comorbidities, n (%)			
Obstructive jaundice	16 (43.2%)	24 (61.5%)	0.110
Cholangitis	7 (18.9%)	9 (23.1%)	0.657
Diabetes mellitus	12 (32.4%)	4 (10.3%)	**0.018**
Pancreatitis	2 (5.4%)	4 (10.3%)	0.433
Main pancreatic dut diameter (mm)	2.4 [2.0–3.0]	2.6 [2.1–3.0]	0.231

Note, continuous data are shown with median [interquartile range].

Table 2
Intraoperative factors.

	Gravity dependent drainage (n = 37)	Negative pressure drainage (n = 39)	*P*
Operative method			0.471
PD	2 (5.4%)	1 (2.6%)	
PPPD	1 (2.7%)	0 (0%)	
SSPPD	34 (91.9%)	38 (97.4%)	
Portal vein resection	3 (8.1%)	2 (5.1%)	0.600
Blood loss (ml)	796 [371–1379]	826 [606–1294]	0.461
Operation time (min)	458 [375–568]	430 [350–519]	0.141
Allogeneic blood transfusion	5 (13.5%)	11 (28.2%)	0.116

Note, continuous data are shown with median [interquartile range].
PD, conventional pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; SSPPD, subtotal stomach-preserving pancreatoduodenectomy.

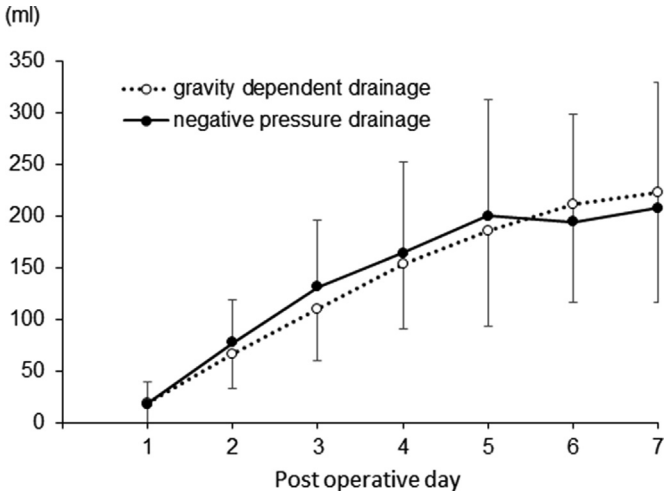

Fig. 3. Daily amount of pancreatic juice from pancreatic duct stent in the gravity dependent drainage group (n = 37) and negative pressure drainage group (n = 39) (Mean ± S.D.).

Disccusion

POPF remains the leading cause of morbidity and sometimes leads to lethal complications following pancreatectomy. The rate of POPF still remains high, ranging approximately 30–40%, even in high volume centers [21,22]. Since our institution is a high-volume center of cholangiocarcinoma, large proportion of patients who underwent pancreatoduodenectomy are with soft pancreas with small main pancreatic duct and normal pancreatic secretory function. Therefore, the incidence rate of POPF is relatively higher compare to other institutions. Nevertheless, we have been trying to arrange various surgical techniques and patient managements to reduce the incidence of POPF following pancreatoduodenectomy [16]. Routine use of exteriorized pancreatic duct stent to completely drain pancreatic juice secreted from the remnant pancreas is one of these approaches. In the former period in our institution, the exteriorized pancreatic duct stent was connected to a simple bag and let the pancreatic juice being drained by gravity. In such case, drainage was sometimes unstable depending on the relative position of drainage bag to the patients' body or the remnant pancreas. We thought that this problem could be resolved by using constant negative pressure bag. Therefore, from June 2015, the use of constant negative pressure bag was started for patients who underwent pancreatoduodenectomy. The aim of this study was to evaluate the usefulness of the negative pressure bag as compared to the simple bag in terms of the incidence of POPF and other complications following pancreatoduodenectomy. Because the pancreatic anastomosis techniques may have significant influence on the incidence of POPF [3,23], only patients who underwent pancreatojejunostomy with the Blumgart technique [15], which was introduced and continuously performed from 2013 in our institution, were included in this study. Moreover, only patients with soft pancreas who may have normal pancreatic juice secretional capacity was included.

Unexpectedly, the daily amount of drained pancreatic juice was not significantly different between patients with gravity dependent drainage group and negative pressure drainage group throughout the postoperative course. Because all patients were with soft pancreas, the total incidence rate of POPF was extremely high (almost 70%) in both groups. However, the incidence rate of clinically relevant POPF (grade B) was significantly lower and the length

Table 3
Postoperative outcomes.

	Gravity dependent drainage (n = 37)	Negative pressure drainage (n = 39)	*P*
Mortality	0 (0%)	0 (0%)	1.000
Morbidities[a]			
Total complications (Grade I-IV)	31 (83.8%)	28 (71.8%)	0.210
Major complications (Grade III-IV)	18 (48.7%)	5 (13.2%)	**0.001**
Infectious complications	10 (27.0%)	8 (20.5%)	0.653
Amylase level in drainage fluid on POD 3 (IU/L)	398 [114–2137]	1057 [313–2340]	0.183
Post-operative pancreatic fistula			
Total	26 (70.3%)	27 (69.2%)	0.922
Biochemical leakage[b]	5 (13.5%)	14 (35.9%)	
Grade B POPF	21 (56.8%)	13 (33.3%)	**0.040**
Grade C POPF	0 (0%)	0 (0%)	
Duration of drainage (days)	28 [9–34]	20 [7–30]	0.091
Delayed gastric emptying (Grade A-C)[c]	8 (21.6%)	5 (12.8%)	0.309
Postoperative hospital stay (days)	33 [22–41]	25 [16–33]	**0.024**

Note, continuous data are shown with median [interquartile range].
POPF, postoperative pancreatic fistula.
[a] Complications were graded according to the Clavien-Dindo classification.
[b] Biochemical leakage = Amylase level in drained fluid on POD 3 more than 3 times upper limit of institutional normal serum amylase level.
[c] Delayed gastric emptying was graded by the definition of the International Study Group of Pancreatic Surgery.

Table 4
Factors associated with the incidence of clinically relevant POPF.

Variables	No. of patients	No. of patients with POPF (%)	Univariate		Multivariate	
			Odds ratio (95% C.I.)	*P* value	Odds ratio (95% C.I.)	*P* value
BMI				0.069		**0.014**
≤21 kg/m^2	31	10 (32.3)	1.00		1.00	
>21 kg/m^2	45	24 (53.3)	2.40 (0.92–6.23)		4.14 (1.33–14.74)	
Diabetes mellitus				0.108		0.390
No	60	24 (40.0)	1.00		1.00	
Yes	16	10 (62.5)	2.50 (0.80–7.78)		1.80 (0.47–7.42)	
MPD diameter				**0.003**		**0.001**
≥3 mm	19	3 (15.8)	1.00		1.00	
<3 mm	57	31 (54.4)	6.36 (1.66–24.25)		8.58 (2.17–46.48)	
Operation time				0.118		0.072
≤380 min	25	8 (32.0)	1.00		1.00	
>380 min	51	26 (51.0)	2.21 (0.81–6.03)		2.91 (0.91–10.21)	
Method of drainage				**0.040**		**0.032**
Negative pressure	39	13 (33.3)	1.00		1.00	
Gravity dependent	37	21 (56.8)	2.63 (1.03–6.66)		3.33 (1.11–11.03)	

POPF, postoperative pancreatic fistula; 95% C.I., 95% confidence interval; BMI, body mass index; MPD, main pancreatic duct.

of postoperative hospital stay was significantly shorter in the negative pressure drainage group compared to the gravity dependent drainage group. These results indicated that the severity of POPF was alleviated by applying negative pressure to the pancreatic duct stent. With multivariate analysis, along with other risk factors of POPF such as greater BMI and smaller main pancreatic duct diameter, the gravity dependent drainage was identified as one of the independent risk factors of clinically relevant POPF.

There are three previous reports pertaining to the pancreatic duct stent with negative pressure [11–13]. In 2009, Lee et al. reported results of prospective randomized pilot trial comparing gravity dependent drainage and closed suction drainage of the pancreatic duct in pancreticojejunostomy [11]. In their study, a total of 110 patients were enrolled and 55 were allocated to each group. The incidence rate of pancreatic fistula defined by ISGPF criteria (including grade A, B, and C) was significantly lower in the closed suction group (25.5%) compared to that in the gravity dependent drainage group (43.5%) ($p = 0.045$). However, the incidence rate of grade B and C fistula was not significantly different between the two groups (9.1% in the closed suction group vs. 10.9% in the gravity dependent drainage group). They concluded that the closed suction drainage was only effective to reduce the incidence of grade A pancreatic fistula. The amount of drained pancreatic juice was significantly higher in the closed suction group only on POD 1, and thereafter there was no significant difference until POD 7 between the two groups. It should be noted that more than half of the patients were with hard pancreas in this study and the proportion of soft pancreas was higher in the gravity dependent drainage group (41.8%) compared to the closed suction group (30.9%).

In 2010, Kim et al. also reported the usefulness of negative pressure external drainage of the pancreatic duct in pancreatoduodenectomy in reducing the incidence of POPF [12]. They compared the postoperative outcomes between the patients with negative pressure external drainage of the pancreatic duct and those with internal stent. This was not a study comparing the patients with and without negative pressure external drainage. Thus the superiority of external drainage with negative pressure to that without negative pressure was not clarified. Moreover, this study was a retrospective data analysis, and the criteria of selecting the negative pressure external drainage or the internal stent were not

clearly shown.

More recently, Minagawa et al. reported the impact of intermittent negative pressure external drainage of the pancreatic duct on the postoperative complications after pancreaticojejunostomy by comparing the outcomes with gravity dependent drainage [13]. Similar to our study, they formerly used gravity dependent drainage of the pancreatic duct and in the later period they started to use negative pressure drainage. The amounts of drained pancreatic juice were not significantly different between the two groups throughout the postoperative course as was observed in our study. Nevertheless, they showed that the incidence rates of POPF, abdominal abscess, and wound infection were significantly lower in the negative pressure drainage group compared to gravity dependent drainage group. In accordance with the results in the present study, the incidence of POPF was significantly lower in the negative pressure drainage group when restricted to patients with a soft pancreas.

This study includes several limitations. First, the design of the study was retrospective analysis and the number of patients was small. Additionally, as discussed in the above paragraphs, the results in our study are partly inconsistent with the previous studies. Moreover, the mechanism reducing the incidence of POPF without significantly increasing drained amount of pancreatic juice is still unclear. It could be speculated that the intra-pancreatic duct pressure occasionally increases depending on the position of the bag in gravity dependent group, whereas the pressure is kept constant in the negative pressure drainage group irrespective of the position of the bag. This difference may lead to the slight difference of the daily amount of pancreatic juice drainage during early postoperative period, and reflected on the incidence of clinically significant POPF. A large scale prospective randomized study should be performed to clarify the real benefit of negative pressure for the external pancreatic drainage stent especially in patients with soft pancreas.

In conclusion, this study demonstrated that the application of negative pressure for the external pancreatic drainage stent contributed in reducing clinically relevant POPF and shortened postoperative length of hospital stay in patients undergoing pancreatoduodenectomy for soft pancreas. Although, the application of negative pressure to the pancreatic duct stent did not seem to significantly increase the drained amount of pancreatic juice as compared to the gravity dependent drainage, it may at least reduce the severity of POPF.

Disclosure/conflicts of interest

All authors do not have any financial and direct or indirect personal relationships with other people or organizations that could potentially and inappropriately influence (bias) this work.

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