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Clinical outcome of endoscopic therapy in patients with symptomatic pancreas divisum: a Dutch cohort study

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ABSTRACT

Background and study aims Although the majority of patients with pancreas divisum (PDiv) are asymptomatic, a subgroup present with recurrent pancreatitis or pain for which endoscopic therapy may be indicated. The aim of this study was to evaluate success rates and long-term outcomes of endoscopic treatment in patients with symptomatic PDiv.

Patients and methods A multicenter, retrospective cohort study was performed. Patients with symptomatic PDiv presenting with recurrent acute pancreatitis (RAP), chronic pancreatitis (CP), or chronic abdominal pancreatic-type pain (CAP) who underwent endoscopic retrograde cholangiopancreatography (ERCP) between January 2000 and December 2019 were included. The primary outcome was clinical success, defined as either no recurrent episode of acute pancreatitis (AP) for RAP patients, no flares for CP patients, or absence of abdominal pain for patients with CAP after technically successful ERCP.

Results In 60 of 81 patients (74.1 %) a technically successful papilla minor intervention was performed. Adverse events were reported in 30 patients (37 %), with post-ERCP pancreatitis in 18 patients. The clinical success rate for patients with at least 3 months of follow-up was 42.6 %, with higher rates of success among patients presenting with RAP (44.4 %) as compared to those with CP (33.3 %) or CAP (33.3 %). Long-term sustained response was present in 40.9 % of patients with a technically successful intervention. In patients with RAP who did not completely respond to treatment, the mean number of AP episodes after treatment decreased significantly from 3.5 to 1.1 per year, and subsequently the interval between AP episodes increased from 278 to 690 days ($P = 0.0006$). A potential predictive factor of failure of clinical success after technically successful ERCP, at univariate analysis, was male sex (OR = 0.25, $P = 0.02$).

Conclusions Endoscopic therapy in patients with symptomatic PDiv is moderately effective, with its highest yield in patients presenting with RAP. Future studies are needed to assess factors predictive for success of endoscopic therapy and potential risk factors for relapse after ERCP.

Introduction

Pancreas divisum (PDiv) is the most common pancreatic anomaly and is present in approximately 2 % to 10 % of the general population [1–3]. PDiv results from failure of fusion of the ventral and dorsal pancreatic ducts during embryogenesis [4]. Subsequently, pancreatic exocrine secretions are predominantly drained through the relatively small duct of Santorini and minor papilla into the duodenum.

Although the majority of patients with PDiv are asymptomatic, there are subgroups with either recurrent symptoms of acute pancreatitis (RAP), flares of chronic pancreatitis (CP) or chronic abdominal pancreatic-type pain (CAP) [5–7]. A relative obstruction of outflow of pancreatic juice through the minor papilla has been proposed as a cause of recurrent pancreatitis [6, 7]. Endoscopic treatment may relieve symptoms in patients with PDiv and can be considered in patients with recurrent and/or severe symptoms [8, 9]. It aims at improving ductal outflow, by either performing a minor papilla sphincterotomy or stenting in case of a dorsal pancreatic duct stricture.

While endoscopic therapy in the management of patients with symptomatic PDiv is commonly applied in clinical practice, there is limited high-quality evidence to support this strategy. Only one small randomized trial in patients with RAP has been published, the results of which were hampered because it was not blinded and the sample size consisted of only 19 patients [10]. Several retrospective studies have reported a significant improvement in the disease course for symptomatic patients with PDiv after endoscopic therapy, although reported efficacy rates are highly variable, ranging from 8 % to 94 % [8, 11]. These results are difficult to interpret and to compare, given the significant variations in the definition of successful therapy, as well as large variations in definitions of subgroups of PDiv patients. In the majority of the studies, a subjective endpoint, self-perceived improvement, was used, and sample sizes were rather small. As a result, the exact role of endoscopic therapy in the management of symptomatic PDiv remains unclear.

Given the low incidence of symptomatic PDiv, multicenter studies are required to obtain a more accurate estimate of the yield of endoscopic therapy and to identify potential predictors of success. This current multicenter study aimed to analyze the short-term and long-term efficacy and safety of endoscopic treatment in a large cohort of patients with symptomatic PDiv, with uniform definitions of outcome and subgroups of patients (i. e. RAP, CP and CAP). In addition, predictive factors for successful endoscopic treatment were studied.

Patients and methods

Study design and study population

A multicenter retrospective cohort study was performed in the Departments of Gastroenterology and Hepatology at three Dutch tertiary referral centers for pancreaticobiliary diseases. Patients with symptomatic PDiv who underwent endoscopic retrograde cholangiopancreatography (ERCP) with the primary intention to perform a minor papilla sphincterotomy and/or dorsal duct plastic stent placement between January 2000 and December 2019 were identified from local endoscopy databases (Endobase or Clinical Assistant (RVC)). In this dedicated electronic endoscopic reporting system, all endoscopic procedures and reports are prospectively registered. Patients were eligible for inclusion if symptomatic PDiv had been confirmed prior to ERCP at consultation at the outpatient clinic and after exclusion of other causes of pancreatitis by a standardized diagnostic work-up. Symptomatic PDiv was further classified according to type of clinical presentation: (1) RAP, (2) CP, and (3) CAP. RAP was defined as more than one episode of proven acute pancreatitis (i. e. 2/3 of the following; acute upper abdominal pain, lipase and/or amylase > 3x upper limit of normal, signs of acute pancreatitis on computed tomography). CP was defined according to the M-ANNHEIM classification system in combination with presence of abdominal pain symptoms in combination with flare type symptoms [12]. CAP was defined as pancreas-type pain as judged by the treating physician, but without a biochemically or radiologically confirmed diagnosis of either acute or chronic pancreatitis [13, 14]. Patients with a pancreatic malignancy were excluded from the study, as well as those who underwent a previous endoscopic intervention of the pancreatic duct. This study was conducted according to the guidelines in the Helsinki Declaration and was approved by the ethics committee of the Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Data collection

Each individual patient record was systematically reviewed. Data were collected on demographical factors (e. g. age, sex), clinical factors (e. g. medication use, alcohol and nicotine consumption, symptoms and number of episodes of pancreatitis prior to ERCP), findings on imaging studies (e. g. pancreatic duct strictures or dilatation), and ERCP characteristics (e. g. use of secretin, performance of sphincterotomy and stent placement). Patient records were reviewed for the number of episodes of AP, flares of CP or CAP symptoms after treatment and procedure-related adverse events (AEs). Minor papilla sphincterotomy was performed with a pull-type sphincterotome or needle-knife precut in case of failed cannulation. Plastic stents used were 5 or 7 cm in length and had a diameter of 5 or 7 Fr. Reasons for straight stent placement were presence of concomitant ductal strictures, presence of obstructive pancreatic stones, or inability to perform a safe sphincterotomy. In these patients, a sphincterotomy over the stent was considered at repeat ERCP. Secretin was administered when the minor papilla could not be identified and/or cannulation failed by decision of the endoscopist. For all patients, the maximum follow-up time was based on data availability in individual medical records after ERCP.

Study outcomes

The primary outcome of the study was clinical success of endoscopic treatment, which was defined as either no recurrent episode of AP for RAP patients, no flare of CP for CP patients, or absence of abdominal pain for patients with CAP, at 3 months after technically successful ERCP. Long-term success was defined as sustained clinical response for a period of 12 months after ERCP. Secondary study outcomes were technical success, defined as performance of minor papilla sphincterotomy and/or deployment of a stent in the dorsal duct, short-term and long-term complications, and predictors for either success or relapse after technically successful endoscopic treatment.

▶ **Table 1** Baseline patient characteristics.

Characteristics	Symptomatic PDiv (N = 81)
Sex – no. (%)	
▪ Female	45 (55.6 %)
▪ Male	36 (44.4 %)
Age (year) (mean ± SD)[1]	51.4 ± 17.4
Medical history – no. (%)	
▪ Cholecystectomy	26 (32.1 %)
▪ Hypertension	12 (14.8 %)
▪ DM II	8 (9.9 %)
Alcohol – no. (%)	
▪ Former alcohol abuse	4 (4.9 %)
▪ Current alcohol abuse	3 (3.7 %)
Smoking – no. (%)	
▪ Former smoker	20 (24.7 %)
▪ Current smoker	8 (9.9 %)
PDiv type – no. (%)	
▪ Complete	69 (85.2 %)
▪ Incomplete	12 (14.8 %)
PDiv diagnosis by – no. (%)	
▪ EUS	12 (14.8 %)
▪ MRCP	49 (60.5 %)
▪ MRCP + secretin	8 (9.9 %)
▪ MRI	8 (9.9 %)
▪ CT	2 (2.5 %)
▪ Unknown	2 (2.5 %)
PDiv presentation – no. (%)	
▪ RAP	66 (81.5 %)
▪ CP	12 (14.8 %)
▪ CAP	3 (3.7 %)
Number of AP episodes before treatment (absolute) (median) (range)	4.0 (2–40)
No AP episodes (per year) (median (range)	2.96 (0.19–22.14)[2]
Pancreatic duct dilatation – mm[3]	
▪ Head (median (range)	3.0 (1–8.5)
▪ Corpus (median (range)	2.8 (1–8.6)
▪ Prior imaging:	
– CT	8
– EUS	1
– MRCP	40
– SS-MRCP	18
– MRI	12

PDiv, pancreas divisum; DM II, type 2 diabetes mellitus; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; CAP, chronic, abdominal, pancreatic-type pain; AP, acute pancreatitis; CT, computed tomography; SS-MRCP, secretin-stimulated magnetic resonance cholangiopancreatography.
[1] Age at first endoscopic treatment.
[2] Calculated as the number of AP episodes per year from first AP to first intervention.
[3] Measurable in 55 patients at imaging.

Statistical analysis

Descriptive statistics were used for continuous and categorical variables. Continuous variables were described using mean and standard deviation for normally distributed variables or using median and range for non-normally distributed variables. Categorical variables were described using frequencies and percentages. The Shapiro-Wilk test was used to check the normality of the variables. The Student's t-test, Wilcoxon test or the Mann-Whitney U test were used to analyze continuous variables. The Chi-square test or Fisher's Exact test were used for categorical and dichotomous variables. A 2-sided $P<0.05$ was considered statistically significant. The statistical analyses were performed using R Version 3.6.2.

Results

During the study period, a total of 81 patients underwent ERCP for symptomatic PDiv. Forty-five patients (56 %) were female. The mean age was 51.4 years (SD ± 17 years). The majority of patients referred for ERCP presented with RAP (n = 66 [82 %]). In these patients, the median number of AP episodes in total prior to ERCP was four (range, 2–40). The median number of AP episodes per year was three (range, 0.2–22). Baseline characteristics of the included patients are shown in ▶ **Table 1**.

Technical success

Cannulation of the minor papilla was successful in 61 of 81 patients (75 %), after a median of two ERCPs per patient (range, 1–4). Of these 61 patients, 48 (79 %) had successful cannulation at first intervention and 11 (18 %) at second intervention. In 13 of 81 patients, secretin was administered, which resulted in successful cannulation in six of them (46 %). In six patients, an endoscopic ultrasonography-guided rendezvous technique was attempted, which resulted in successful retrograde cannulation in one.

Of the 61 patients in whom cannulation was successful, 60 (48 RAP, 9 CP, 3 CAP) underwent a technically successful intervention (98 %), defined as completion of minor papilla sphincterotomy and/or deployment of a stent in the dorsal pancreatic duct. A minor papilla sphincterotomy was performed in 53 of 60 patients (88 %). In six patients (10 %) a straight plastic stent without sphincterotomy was deployed as final treatment, and balloon dilatation of the minor papilla without sphincterotomy was performed in one patient (2 %). Median stent length was 5 cm (range, 5–7) and median stent diameter was 5 Fr (range, 5–7). The stents were left indwelling for a median of 65 days

(range, 48–153). After this period all stents were removed and no stents were replaced.

In 40 of 61 ERCPs (66 %) with cannulation of the minor papilla, short-term prophylactic pancreatic drainage by deployment of a 5 or 7 Fr single pigtail stent was performed. Follow-up data were available for all 60 patients with a median of 26.5 months (range, 1–213).

Clinical success

Efficacy in PDiv patients with RAP

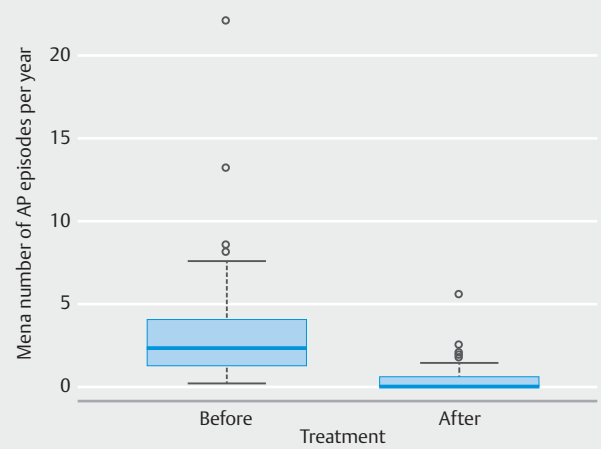
Clinical success was achieved in 23 of 48 RAP patients (48 %). For patients with at least 3 months of follow-up, 20 of 45 patients (44.4 %) had clinical success and for patients with at least 12 months of follow-up, 17 of 37 patients (46 %) had sustained clinical success. In total, 22 patients (46 %) had a RAP episode after technical successful intervention. For patients with an acute pancreatitis episode after technical successful intervention, the mean number of pancreatitis episodes per year before and after endoscopic treatment decreased from 3.5 (SD 3.1) to 1.13 (SD: 1.2) ($P = 0.0003$), respectively (▶ **Fig. 1**). Subsequently, the mean number of days between pancreatitis episodes before and after successful minor intervention increased from 278 (SD 424) to 690 (SD 623) ($P = 0.0003$), respectively (▶ **Fig. 2**). The median duct diameter was 3 mm (range, 1.0–8.4). Only five patients had a dilated dorsal pancreatic duct ≥ 5 mm (10.4 %). In those patients, clinical success was achieved in four patients (80 %). Of the 43 patients without dilatation, 19 patients achieved clinical success (44.2 %). This was not significantly different ($P = 0.18$). In total, 10 patients underwent MRCP with secretin prior to endoscopic treatment. Only four patients (40 %) had a pathological increase of duct diameter after secretin administration. Clinical success was achieved in two patients (50 %). In the patients with a normal SS-MRCP, clinical success was achieved in three patients (50 %).

Of the 25 patients without clinical success, five patients underwent surgery. Two patients underwent pancreatoduodenectomy and pancreatic tail resection, respectively. Two other patients underwent a pancreatojejunostomy. They did not have an episode of pancreatitis after surgery. Progression from RAP to CP was diagnosed in a total of nine patients (18.8 %) with RAP. Progression to CP was diagnosed by computed tomography in four of nine patients, magnetic resonance imaging in two of nine, and endoscopic ultrasonography in three of nine. Genetic mutations playing a role for CP development were not routinely assessed. However, in two patients, the CFTR gene was detected prior to endoscopic treatment. One patient developed a symptomatic CP, for which he underwent a pancreatic head resection. Afterwards, he was opioid dependent.

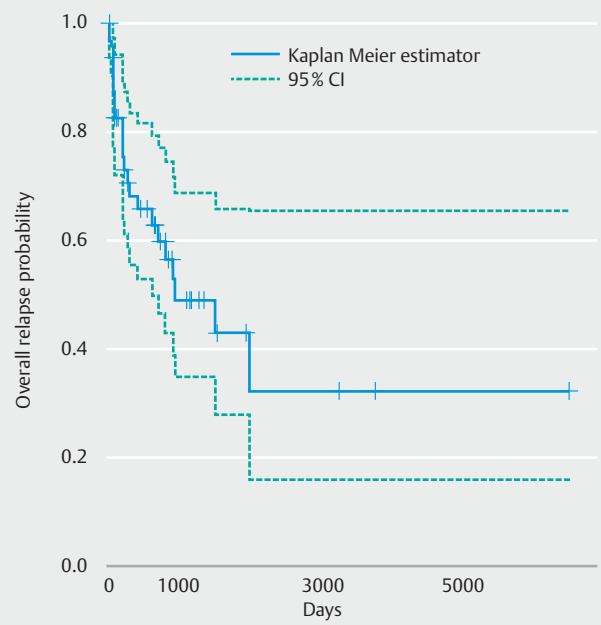
Efficacy in PDiv patients with CP

Clinical success was achieved in five of nine patients (56 %). However, three patients had a follow-up shorter than 3 months. For these patients, no flare of CP was reported in the available follow-up period.

Two of the six patients (33.3 %) with follow-up > 3 months achieved clinical success. Out of five patients with at least 12 months of follow-up, one patient (20 %) reported no flares of CP. Overall, four patients underwent surgery after ERCP. Three patients underwent a pancreatojejunostomy after endoscopic treatment, and in one patient this was combined with an additional tail resection after 1 year. In another patient a pancreatic head resection was performed. Three patients remained opioid-dependent after surgery.



▶ **Fig. 1** Box plot for mean number of AP episodes per year for RAP, before, and after treatment for patients with ≥ 3 months of follow-up.



▶ **Fig. 2** Kaplan-Meier curve for overall relapse probability for RAP until the first date a relapse occurred. This includes all patients, regardless of follow-up and surgeries performed.

Efficacy in PDiv patients with CAP

Clinical success was achieved in one of three (33.3 %) CAP patients, who did not experience a relapse of abdominal pain within a total follow-up period of 11 months. The remaining two patients still had complaints of abdominal pain after endoscopic treatment.

Predictive factors for clinical successful minor intervention

Univariate logistic regression analysis was performed to analyze potential predictive factors for clinical success (▶ **Table 2**). Male sex was significantly associated with a lower chance of clinical success (OR = 0.25, *P* = 0.02). No other associations were identified.

Post-procedure adverse events

AEs were reported in in 26 of 81 patients (32.1 %). Post-ERCP pancreatitis was diagnosed in 18 patients (22.2 %), of whom 17 had a mild and one a moderate course, according to the Revised Atlanta Classification [15]. Based on the total number of procedures, the prevalence of post-ERCP pancreatitis was 18 of 148 (12.2 %). Post-sphincterotomy delayed bleeding was reported in one patient (1.2 %). One patient developed a pancreatic fluid collection shortly after ERCP (1.2 %). In patients in whom a straight stent was placed as treatment (n = 6), distal stent migration occurred in 2 (33 %) and occlusion in one patient (16.7 %). All stents could easily be removed and no additional treatment was necessary.

▶ **Table 2** Results of univariate analysis of potential predictive factors for clinical success (> 3 months) after technically successful minor intervention.

Univariate analysis	OR	CI	*P* value
Sex (male = 1)	0.25	0.07 – 0.79	0.02
Age	1.02	0.99 – 1.05	0.296
Stent vs sphincterotomy	2.18	0.33 – 17.67	0.417
Incomplete PDiv	0.64	0.08 – 3.62	0.629
PDiv presentation			
▪ RAP	1.6	0.05 – 29.8	1.000
▪ CP	1.0	0.14 – 35.9	0.709
Number of AP episodes (absolute)	1.06	0.86 – 1.32	0.587
Pancreatic duct diameter head (mm)	1.07	0.74 – 1.56	0.698
Minor stenosis	1.21	0.33 – 4.28	0.766

PDiv, pancreas divisum; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; AP, acute pancreatitis.

Discussion

Although symptomatic PDiv is generally considered a suitable indication for ERCP, the efficacy of endoscopic treatment to relieve symptoms is unclear. In the present study, we report the technical and clinical success of ERCP in a multicenter cohort of symptomatic PDiv patients who were treated in tertiary referral centers. In this cohort with a median follow-up of 26.5 months, ERCP with minor papilla sphincterotomy or dorsal duct stent placement benefits approximately half of patients in whom cannulation of the PD was achieved. Overall success of endoscopic treatment was however limited by moderate initial pancreatic duct cannulation rate at first ERCP and a relatively rate of post-ERCP pancreatitis. The clinical success is highest for the subgroup of patients with RAP, as compared to CP and CAP, which is further illustrated by a significant decrease in AP episodes after ERCP compared to before the ERCP in the RAP population.

Another important finding in our series is that nearly 20 % of patients with RAP progressed to CP during follow-up despite endoscopic therapy. Of note, in our clinical practice, evolution to CP is not routinely assessed and additional imaging studies are only performed in patients presenting with clinical signs of CP. The view of the theory of progression from RAP to CP can provide a rationale for early endoscopic treatment of RAP in symptomatic PDiv patients to halt progression into CP. In patients with CP the etiology of pain is more likely to be multifactorial, with not only ductal hypertension necessarily as the sole cause, but also neuropathy of intra-pancreatic nerves and central sensitization. Therefore, endoscopic therapy may be less clinically successful in this subgroup of patients.

The clinical efficacy of ERCP for PDiv in our cohort is lower as compared to previous reports. An important explanation is that we only included patients in which symptomatic PDiv had been confirmed prior to ERCP on consultation at the outpatient clinic and after exclusion of other causes of pancreatitis with a standardized diagnostic work-up. Patients in which an incomplete PDiv was detected during ERCP performed for other reasons, such as trans-papillary drainage of pseudocysts, were excluded. In addition, we used stringent and objective definitions for treatment outcome instead of subjective patient-reported outcomes. Tringali et al. reported a clinical success rate of 72 % after a mean follow-up of 9.7 years in PDiv patients with RAP (n = 48) [16]. An important explanation for this higher efficacy of endoscopic treatment may be the selection of a favorable group of patients who answered the questionnaire after long-term follow-up, as the study design suggests exclusion of patients who were lost to follow-up, deceased, or developed CP. Another cohort study from the United States showed similar differences between the subgroups as our study. In 62 RAP, 22 CP, and 29 CAP patients, reported success rates were 53.2 %, 18.2 %, and 41.4 %, respectively. However, this study was limited by the subjective nature of primary outcome measures, i. e. better or cured on a Likert scale, without needing narcotics, after one ERCP procedure [13]. A meta-analysis by Michailidis et al. reported an overall clinical success rate of 67 % after endoscopic treatment for PDiv [11]. Success rates were reported to be 76 %, 52 %, and 48 % for patients with RAP, CP and CAP, respectively. Important to note is that if strict objective outcome measures were used, instead of subjective measurements like self-reported pain or opioid usage, a smaller per-

centage of the patients reached clinical success in this review [17], which is in line with the outcome of our current study.

Overall, a high rate of post-ERCP pancreatitis was observed in our study, which ran a mild course in the majority of patients. These results are consistent with literature, and confirm that the risk of post-ERCP pancreatitis is higher in PDiv patients, as compared to other indications for ERCP [18, 19]. This complication risk influences the risk-benefit ratio of endoscopic treatment in patients with PDiv, and underlines the importance to identify predictors of clinical success. Additional univariate regression analysis revealed that male sex was significantly associated with a lower chance of clinical success (OR = 0.25, P = 0.02). However, due to the low number of cases, multivariate regression analysis could not be performed to test for an independent association between male gender and clinical success after endotherapy. The model was at potential risk of multiple testing and finding a false-positive association. Therefore, this finding should be interpreted with caution. Michailidis et al. found in the pooled analysis that male sex seemed to predict better response rates, although this was not significant [11]. To the best of our knowledge, there is no other study available describing the relationship between male sex and the effect of endotherapy, irrespective of PDiv. A larger cohort study should be performed to reliably test for the association between male sex and the effect of endotherapy in patients with PDiv. Although a dilated pancreatic duct is often presumed to be a potential predictor, dilatation of the Santorini duct as measured at imaging studies prior to ERCP was not significantly associated with clinical success. This finding calls into question whether increased ductal outflow is the main pathogenetic mechanism for symptoms in PDiv patients. However, it might well be that a relative stenosis of the minor papilla or Santorini duct is hard to identify on regular non-dynamic MRCP. Dynamic secretin-stimulated MRCP (SS-MRCP) can be helpful in revealing relative ductal abnormalities otherwise not detected on MRCP alone, with increase in the distention of the upstream portion of the duct and/or decreased pancreatic duct compliance after secretin stimulation. In our patients, SS-MRCP was not routinely performed at baseline prior to ERCP. Dorsal duct stenting was the only significant predictor of success in the meta-analysis by Michailidis et al., but given the significant heterogeneity among included studies, those results should be interpreted with caution [11]. In our study, dorsal duct stent placement did not result in significantly greater treatment success as compared to minor papilla sphincterotomy alone.

Although a major strength of our study is its multicenter design with inclusion of a large number of patients, it also has some limitations, which should be considered when interpreting our results. First, data were collected retrospectively and follow-up was not standardized. This resulted in a range of follow-up time points. Despite this shortcoming, follow-up data of at least 12 months was available for 70 % of the patients. The follow-up was relatively complete and systematically documented as standard follow-up intervals after endoscopic treatment were adhered to in clinical practice. Second, the sample size of our cohort may have been too small to allow for identification of predictors of clinical success in logistic regression analysis. Also, the subgroup of patients with CP and CAP was relatively small compared to RAP. Therefore, the clinical success rate in these two subgroups could be overestimated and should be interpreted with caution.

Conclusions

In conclusion, endoscopic treatment is effective to relieve symptoms in PDiv patients in half of patients after technically successful ERCP, and should be considered, in particular, for patients with RAP. Clinical decisions may benefit from more data pertaining to the appropriate selection of patients for ERCP to weigh risk and benefits, because the risk of post-ERCP pancreatitis in PDiv is considerable. Multicenter, preferably randomized, clinical trials in which minor papilla sphincterotomy is compared to sham treatment in PDiv patients are needed to optimize the selection of PDiv patients and to identify potential risk factors for relapse after ERCP.

Competing interests

Dr. Poley receives consultancy, travel, and speaker fees from Boston Scientific, Cook Endoscopy, and Pentax Medical. Dr. Fockens serves as a consultant for Cook Endoscopy and Olympus and receives research support from Boston Scientific. Dr. Voermans is a consultant for and receives grants for investigator-initiated studies from Boston Scientific. Dr. Bruno serves as a consultant and receives support for industry and investigator-initiated studies from Boston Scientific and Cook Medical and receives support for investigator-initiated studies from Pentax Medical, 3M, Interscope, and Mylan.

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