Clinical outcomes and nonendoscopic interventions after minor papilla endotherapy in patients with symptomatic pancreas divisum

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Background: Long-term outcomes of minor papilla endotherapy (MPE) in pancreas divisum are limited.

Objective: To determine the efficacy of MPE in symptomatic pancreas divisum subgroups.

Design: This was a retrospective study of patients from an endoscopy database. The data collection instrument included preprocedure and postprocedure pain score, narcotic use, acute pancreatitis episodes, emergency department visits, and hospitalizations. A follow-up was obtained by chart review and telephone contact with a questionnaire.

Setting: A tertiary-referral center.

Main Outcome Measurements: (1) Clinical improvement defined as a ≥50% reduction in the evaluated data points and (2) non-MPE interventions for pain.

Results: Between January 2000 and April 2006, 57 patients were identified. Indications were recurrent acute pancreatitis (RAP) (n = 27 [47%]), abdominal pain and chronic pancreatitis (CP) (n = 20 [35%]), abdominal pain alone (n = 8 [14%]), other (n = 2 [4%]). Successful MPE occurred in 49 of 57 patients (86%). Initial MPE entailed minor papilla sphincterotomy (n = 46), stenting without sphincterotomy (n = 2), and tamponade of bleeding (n = 1). Follow-up was obtained in 56 of 57 patients (98%) for a median of 20 months (interquartile range 12-39 months); 28 of 48 patients (58%) with successful MPE had clinical improvement: 16 of 21 (76%) with RAP, 8 of 19 (42%) with CP, and 2 of 6 (33%) with pain alone (RAP vs non-RAP; P = .019). Two patients had resolution of a dorsal-duct leak and bleeding, respectively. Twelve of 57 patients (21%) underwent 16 additional interventions for incomplete response: celiac plexus block (4), intrathecal narcotic pump (2), sphincteroplasty (7), bilateral thoracic splanchnicectomy (2), and Puestow procedure (1); 7 of 12 patients (58%) clinically improved.

Limitation: This was a retrospective study.

Conclusions: (1) MPE is most effective in patients with pancreas divisum and with RAP with or without pancreatic ductal changes, (2) although patients with chronic pain and pancreas divisum respond poorly to MPE, the majority will have clinical improvement after additional nonendoscopic interventions for pain management. (Gastrointest Endosc 2008;68:667-73.)

The rationale for endoscopic therapy in patients with symptomatic pancreas divisum is based on the theory that minor papilla outflow obstruction exists and causes an increase in ductal pressure.1-4 In general, patients have been divided into the following subcategories: recurrent acute pancreatitis (RAP), chronic pancreatitis (CP), and chronic abdominal pain with normal pancreatic duct (CAP).5-11 Most published series on minor papilla endotherapy (MPE) are retrospective and involve a small number of patients.5-7,10,11 In patients who do not respond to MPE, pain management options are considered. These include celiac plexus block, intrathecal narcotic pumps, splanchnecotomy, and lateral pancreaticojejunostomy (Puestow procedure). However, studies that assessed these treatment options in patients with pancreas divisum are limited to surgical intervention.15-18

Abbreviations: CAP, chronic abdominal pain with normal pancreatic duct; CP, chronic pancreatitis; IQR, interquartile range; MPE, minor papilla endotherapy; RAP, recurrent acute pancreatitis.

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The objectives of our study were to assess the clinical outcomes of MPE in subgroups of patients with symptomatic pancreas divisum and to determine the clinical outcomes of additional non-MPE treatments in patients who did not respond.

PATIENTS AND METHODS

Patients
All patients with pancreas divisum who underwent an attempted MPE were identified by a search of the endoscopy database of the University of Colorado at Denver and Health Sciences Center. Institutional review board approval was obtained for the retrospective collection of data and to obtain clinical follow-up. The procedure reports and medical records of the patients generated by this search were reviewed. Patients identified as having incomplete pancreas divisum were included. Patients with MPE who did not have predominantly dorsal-duct anatomy (ie, obstructing pancreatic stone upstream of the major papilla that necessitated minor papilla access), patients who were asymptomatic, and those patients in whom MPE was not attempted were excluded.

For data analysis, patients were categorized by clinical presentation at the time of index attempt at MPE into 3 subgroups: (1) RAP and pain-free intervals with or without radiographic changes of CP (RAP) (Fig. 1), (2) CAP, with radiographic evidence of CP, and (3) chronic abdominal pain without radiographic evidence of CP or pancreatic enzyme elevation (CAP). RAP was defined as two or more episodes of documented pancreatitis (lipase or amylase ≥3 times the upper limit of normal), with pain-free intervals. CP was based on ductal dilatation, strictures, stones, irregularity, and/or prominent side-branch abnormalities identified by dorsal ductography. If suboptimal dorsal pancreateography was noted at an ERCP, then results of other imaging modalities (eg, CT, MRCP, EUS) were used to subgroup patients with CP.

Procedures
MPE was performed by 2 experienced pancreatic endoscopists (Y.K.C., R.J.S.). Each patient underwent an ERCP, with attempted cannulation of the minor papilla by using a tapered cannula and a guidewire. Secretin was used at the discretion of the endoscopist. Pancreateography findings were recorded based on both the endoscopist’s and radiologist’s interpretations. Minor papillotomy was performed either in a pull-type fashion by using a monofilament short-tip traction sphincterotome or a monofilament needle-knife over a pancreatic stent by using the ERBE generator (ICC 200; ERBE USA Inc, Marietta, Ga) at an Endocut setting of 200 W. For prophylactic pancreatic stents, patients typically had an abdominal radiograph performed 7 to 14 days after stent placement to assure spontaneous passage. Retained stents were removed by endoscopy by using a snare or a stent-retrieval forceps. For the treatment of ductal strictures associated with upstream dilatation, single or multiple stents that ranged in size from 5F to 10F were used.

Outcome measures and clinical follow-up
During the study period, it was customary to evaluate all patients in an outpatient visit before considering pancreatic endotherapy. This included a review for laboratory evidence of pancreatitis, narcotic doses, and pain scores (1-10 linear scale). Clinical follow-up was based on the review of medical records and telephone contact by using a standardized questionnaire and a data collection sheet for each subgroup of patients. The questionnaire was administered by one of the investigators (L.N.C.) not involved in the clinical care of the study patients. The duration of follow-up was calculated from the time of the index MPE. Technical success was noted when the intended endotherapy was completed.
improvement in patients with RAP was defined as a ≥50% reduction in annual episodes of acute pancreatitis, emergency department visits, or hospitalizations. For patients with CP or CAP, pain scores and narcotic dosages available from preprocedure assessment were used as a reference during the follow-up telephone interview and/or subsequent visits. On the data collection sheet, preprocedure narcotic use was recorded and compared with the average narcotic use after the procedure. Preprocedure pain assessment was from the onset of pain to the time before an MPE. Post-MPE pain assessment was from the date of an MPE to the date of the last clinic follow-up or telephone interview. Clinical improvement was defined as a ≥50% reduction in the pain score, use of narcotic analgesia, annual emergency department visits, or hospitalizations. In the setting of symptom recurrence after an MPE, the need to extend a previous sphincterotomy was based on endoscopic appearance and/or the ability to accommodate a tapered tip (5F-4F-3F) cannula.

Statistical analysis
Categorical variables were reported in standard fashion. Statistical analysis was performed by using JMP 6.0 (SAS Institute Inc, Cary, NC) and Prism 5.01 (Graph Pad Software, San Diego, Calif). A comparison of outcomes among the 3 groups of patients with symptomatic pancreas divisum was made by using a 2-tailed Fisher exact test. A P value <.05 was considered statistically significant.

RESULTS
Between January 2000 and April 2006, 57 consecutive patients (40 women and 17 men) with symptomatic pancreas divisum had an MPE at the University of Colorado Hospital: 27 (47%) had RAP, 20 (35%) had CP, 8 (14%) had CAP, and 2 (4%) had other indications for MPE (1 for hemosuccus pancreaticus and 1 for suspected dorsal-duct leak). Three patients had incomplete pancreas divisum. Forty-four of 57 patients (77%) had abdominal pain that necessitated hospitalization before an MPE. The median age was 47 years (interquartile range [IQR] 33-56 years), and the median duration of symptoms before referral to our center was 24 months (IQR 11-80 months). Patient characteristics are summarized in Table 1. Of the 27 patients with RAP, 15 (56%) had normal pancreatograms and 12 (44%) had pancreatography changes: 9 had ductal dilatation alone, two had a dorsal-duct stricture with upstream dilatation, and one had a dorsal-duct stricture alone. Of the 20 patients in the CP subgroup, 15 had ductal dilatation alone, 4 had a stricture with upstream dilation, and one had a dorsal-duct stricture alone. By definition, all patients with CAP had normal dorsal ductograms.

Endotherapy
The median number of ERCPs per patient before attempted MPE was 1 (IQR 0-2). Thirty-one patients (54%) had a prior cholecystectomy. Six patients (11%) had undergone a prior endoscopic or surgical intervention of the minor papilla, primarily at outside facilities before our study period. A total of 204 ERCPs (including ERCPs performed at our institution and at outside facilities) were performed on the 57 patients, with a median of 3 ERCPs per patient (IQR 2-4). Twenty patients (35%) also underwent 26 EUS. Technical success was achieved in 49 of 57 patients (86%). The number of attempts to achieve technical success was 1 (n = 41), 2 (n = 7), and 3 (n = 1). MPE interventions are summarized in Table 2. Of the 8 patients in whom MPE failed, 6 had a native minor papilla, one had a prior successful MPE, and one had a prior surgical sphincteroplasty that had stenosed. Secretin injection was used in 10% of the procedures to facilitate dorsal-duct cannulation. The sphincterotomy cut was 3 to 10 mm in length, and the transpapillary pancreatic stent diameter was 3F to 10F, depending on the pancreatic-duct diameter.

Clinical response
Follow-up was successful in 56 of 57 patients (98%), with a median of 19.8 months (IQR 11.9–39.3 months) and entailed record review only in 8 patients (14%) and record review with a telephone interview in 48 patients (86%). The clinical response is summarized in Figure 2. Among the 48 patients who had a successful MPE, clinical improvement was seen in 16 of 21 patients (76%) with RAP, 8 of 19 patients (42%) with CP, and 2 of 6 patients (33%) with CAP (RAP vs CP, P = .052; RAP vs CAP, P = .118; RAP vs non-RAP patients, P = .019). Among subgroups, the following clinical parameters improved: for RAP, the annual frequency of hospitalizations

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<tr>
<td>Median age (y)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>No. men (%)</td>
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<td>No. women (%)</td>
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<td>Median symptom duration (mo)</td>
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Outcomes of patients with symptomatic pancreas divisum

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Non-MPE interventions after an MPE

Twelve (3 in the RAP group, 9 in the chronic pain or CP group) of the 57 patients (21%) had additional interventions for pain management during the study period (Table 3). Four of these 12 patients had a failed attempt at MPE, whereas the other 8 patients had persistent symptoms, despite technically successful MPE. Four of these 8 patients had clinical improvement: 2 initially after an MPE, but, subsequently, they required surgical sphincteroplasty for refractory restenosis, and 2 only after additional interventions (1 with intrathecal pump, 1 with surgical sphincteroplasty). Overall, 7 of 12 patients (58%) reported clinical improvement after these additional interventions: the CP or CAP subgroup (4/9 [44%]) and RAP (3/3 [100%]).

Complications

Procedural complications were defined according to previously published consensus criteria.20 Complications occurred in 12 of 103 procedures (11.7%) and included 11 cases of pancreatitis (8 mild, 3 moderate) and 1 case of perforation (moderate).

DISCUSSION

This is one of the largest series that evaluated the clinical outcomes of MPE in patients with symptomatic pancreas divisum. In our hands, MPE was technically successful in 86%, with mild-to-moderate complications occurring in 12%. At nearly 2 years of follow-up, subgroup analyses indicated that patients with RAP, irrespective of pancreatic-duct changes, were more likely to benefit from MPE (76%) than patients with chronic pain with or without pancreatic-duct changes (40%) (P 4 .019). Our results also suggest a sex difference in clinical outcomes in favor of men. Prior studies either subgrouped patients with CP similarly14 or classified patients based on the presence of pancreatic-ductal changes only,5,6 whereas others have not distinguished subgroups15 or included all pancreatitis patients in a single group.11 As a result, because of differences in patient subgroup definitions and/or outcome measures, a comparison of response rates between patients with chronic pain, CP, and RAP is difficult.

Only one small randomized-controlled trial that included 19 patients with RAP was published.8 Ninety percent of the patients in the treatment arm reported >50% clinical improvement, compared with 11% in the control arm (P < .05). In considering studies that included subgroups of patients, most showed benefit in those patients with relapsing episodes of pancreatitis and, in general, showed lower response rates to MPE for patients with chronic pain or CP and pain.5,7,13,14 Although Coleman et al8 reported clinical improvement in 60% of patients with CP, it was unclear if they included patients with intermittent symptoms in this subgroup. Further, if the CP and chronic pain without pancreatitis groups are combined, 41% of patients would have clinical improvement that is similar to our series. An additional study, by Boerma et al,12 reported that 11 of 16 patients (69%) with CP had clinical improvement between 14 and 45 months of follow-up; however, 11 of 16 patients (69%) had relapsing episodes of pancreatitis with pain-free intervals. Preliminary results of a randomized, controlled study by Sherman et al9 included 33 patients with chronic abdominal pain alone who underwent minor papilla sphincterotomy and prophylactic stent placement. The overall response was poor, because only 44% of the treated patients had benefit compared with 24% in the control group (P 4 not significant).

In a retrospective study of 52 patients with pancreas divisum who were undergoing minor papilla sphincterotomy, Lehman et al5 found that a significantly higher proportion of patients with RAP had improved pain scores at 1.7 years of follow-up compared with patients who had CP or chronic abdominal pain alone (76.5% vs 27.3% vs 26.1%, respectively; P 4 .01 for RAP vs CP group and P 4 .002 for RAP vs chronic pain). Patients with any ductal abnormalities were included in the CP subgroup. Interestingly, 7 of 11 patients (64%) in the CP subgroup had

### TABLE 2. Index MPE

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<th>No. patients</th>
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<tr>
<td><strong>Sphincterotomy</strong></td>
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<tr>
<td>Needle-knife</td>
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*Eight patients had dilation of stenoses. †Tamponade for hemosuccus pancreaticus.
recurrent pancreatitis episodes, without chronic pain, 3 of whom had clinical improvement after MPE. In contrast, the 4 patients with chronic pain and pancreatitis did not improve with MPE. In another retrospective series that included only patients with RAP, 20 of 24 patients (83%) actually had chronic pain. MPE reduced the frequency of RAP episodes at 39 months of follow-up but did not improve chronic pain.

Gerke et al published a large retrospective series of 89 patients with pancreas divisum, and subgroups were based on clinical presentation similar to our study. Patients with pancreatic-duct changes were included in the RAP subgroup, and 73% had short-term relief of symptoms compared with patients with chronic pain ($P = .036$). However, only 44% had longer-term benefit at 29 months of follow-up. This is lower than our RAP group and may be related to variation in defining clinical improvement. Their results, however, are limited by the low 60% rate of follow-up. One uncontrolled, single-investigator, prospective series treated 25 patients with RAP with minor papilla dilation and stenting, without minor papillotomy. Although the patients lacked ductal dilatation, it is uncertain whether other ductal changes, such as strictures or irregularities, were considered. Stents were exchanged over 2-month to 3-month intervals, and, although 3 of 4 patients remained symptom free at 2 years of follow-up, stent-related dorsal-duct changes were noted in a high percentage of patients (84%). At our center, we prefer to perform a minor papillotomy by using short-term stenting, primarily to reduce the risk of postprocedure pancreatitis and reserve intermediate or long-term stenting for those patients with dilated ducts who declined surgical decompression. Whether patients with an initial response to MPE should be referred to surgery for recurrent symptoms remains controversial. We consider surgery for patients with technically unsuccessful MPE, repeated restenosis of the minor papilla sphincterotomy, or recurrent symptoms after completion of a stent trial in the setting of a dilated duct.

When assessing the effect of pancreatic-duct changes in our RAP subgroup, clinical improvement was observed in 76% of patients; there was no difference in the response between the patients with RAP and ductal changes (75%) and those patients with normal ducts (71%). In contrast, only 42% of the patients in the CP subgroup had a response to MPE; the difference did not reach statistical significance ($P = .052$), likely because of the relatively small number of patients. Nevertheless, the results of this analysis suggest that the pain pattern (chronic pain vs discreet episodes of pain), rather than the presence or absence of pancreatic-ductal changes, is more predictive of a clinical response to MPE. Thus, we advocate including patients with pancreas
divisum in with RAP episodes and pancreatic ductal changes in the RAP subgroup, because their response to endotherapy is more consistent with this group than with patients who have chronic pain. It is possible that, with additional years of follow-up, the patients with pain-free intervals may progress to chronic pain; this issue remains a limitation of the published literature.

One hypothesis as to why patients with CP are less likely to respond to MPE has been that the irreversible duct changes in these patients do not allow for adequate drainage, despite sphincterotomy and/or stent placement. In this study, most patients with RAP and with ductal changes, despite sphincterotomy and/or stent placement, are more likely to respond to MPE has been that the irreversible duct changes in these patients do not allow for adequate drainage, despite sphincterotomy and/or stent placement. However, many patients with chronic pain without evidence of pancreatitis likely do not have pancreatic ductal or sphincter pain mechanisms, because they are least likely to benefit from MPE (33%).

We further describe the intensive endotherapy and additional interventions required to treat patients with symptomatic pancreas divisum. The median duration of symptoms before referral to our center was 2 years. Overall, our patients had a median of 3 ERCPs, and a third of patients had at least 1 EUS to evaluate for pancreatic cancer or CP. Despite 86% of patients having technically successful MPE, 1 in 5 required additional surgical and interventional procedures for pain management, and slightly more than half of these patients reported clinical improvement on follow-up. Our results further suggest that the majority of patients with RAP, regardless of the presence of pancreatic-duct changes, would be expected to respond. When considering the lower rates of improvement (40%) in patients with chronic pain with and without CP and that a third required additional non-MPE interventions, endoscopic treatment should only be offered after patients have been informed about all pain management options.

Although endoscopic intervention of the minor papilla is challenging and often requires sequential ERCPs, we conclude that it is a reasonable first step in patients with symptomatic pancreas divisum. Patients with CP and/or chronic abdominal pain should be counseled that only a minority with their symptom presentation respond to endoscopic treatment and, despite technically successful MPE, additional non-ERCP interventions may be required to obtain a sustained clinical benefit. Despite pancreatography changes of CP, patients with a clinical pattern of recurrent pancreatitis and pain-free intervals will have similar clinical benefit to patients with recurrent pancreatitis that lack pancreatic ductal changes.

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DISCLOSURE

The authors report that there are no disclosures relevant to this publication.

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