Natural Course of Abdominal Pain in Chronic Pancreatitis with Intermittent (Type A) Pain after Conservative Treatment

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Background: *Abdominal pain in chronic pancreatitis (CP) is difficult to treat and appropriate choice of treatment is controversial. It has been suggested that patients with CP, particularly from alcohol (ACP) with intermittent attack of abdominal pain (type A pain) should be managed conservatively because pain relief will be achieved in most cases. However, data of the efficacy of this strategy is scanty and conflicting and whether this strategy is effective or feasible in idiopathic CP (ICP) is unclear.*

Material and Method: *Data of all patients with CP with type A pain, who were followed-up and managed conservatively during 2004-2008 were analyzed. Pain relief was defined by the absence of abdominal pain for more than 1 year.*

Results: *Twenty-two patients were followed-up with a median duration of 31 months (range 5-96 months). The etiology of CP was alcoholic (ACP) in 12 (56%), early-onset idiopathic (E-ICP) in 5 (22%) and late-onset idiopathic (L-ICP) in 5 (22%). Alcohol abstinence was successful in every ACP patient. Overall, 18 patients (82%) had pain relief with a median duration of 39 months (range 16-167 months) from the onset of pain or 14 months (range 11-57 months) from the time of diagnosis of CP. Pain relief was achieved at a higher level mainly in ACP (100%) and L-ICP (80%) but was only 40% in E-ICP. Median duration from onset until pain relief were 28 months (range 16-167 months) for ACP, 36 months (range 16-39 months) for L-ICP and 120 months (range 42-120 months) for E-ICP. The difference was statistically significant between L-ICP and E-ICP ($p = 0.036$), but not between ACP and E-ICP ($p = 0.13$) and between ACP and L-ICP ($p = 0.80$). Median duration from the time of diagnosis of CP until pain relief was only 14 months for ACP, 13 months for L-ICP, but was 52 months for E-ICP. None of the patients required narcotics, endoscopic therapy or surgery.*

Conclusion: *Conservative management was feasible and effective in most patients with CP and type A pain, particularly ACP after alcohol abstinence, and L-ICP. Conservative treatment was not effective in E-ICP.*

Keywords: *Abdominal pain, Chronic disease, Pain measurement, Pancreatitis*

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Chronic pancreatitis (CP) is a chronic inflammatory disorder of the pancreas resulting in chronic abdominal pain, pancreatic calcification and finally, exocrine and endocrine insufficiency. Among these, treatment of abdominal pain in CP is the most difficult, challenging and controversial issue for physicians. Only one guideline on the management of abdominal pain in CP exists[1], thus making practices vary widely among centers and countries. The main reasons are the yet not understood pathogenesis of the abdominal pain, the diversity of natural course of this pain either among different etiologies or among different types of pain.

Many pathogenetic mechanisms of abdominal pain in CP have been proposed including ductal hypertension, parenchymal hypertension, pancreatic ischemia from the compartment syndrome, alterations of pancreatic nerves, neuroimmune interaction and most recently, the cortical (brain) sensitization. It is

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widely agreed that no single mechanism can explain pain in all patients.

Natural course of CP is greatly diverse. Although most studies on natural course of CP similarly showed that abdominal pain usually declined progressively over time and, finally, pain relief is usually achieved[2-7], however, the duration of pain before pain relief may vary markedly among studies, countries and etiologies of CP[2-7]. The pain relief may be accompanied by the presence of calcification, exocrine and endocrine insufficiency (burn-out of the pancreas) as proposed by Ammann et al[3,7,8], however, some investigators did not agree[5,9]. The fact of the existence of spontaneous pain relief in CP is very important, particularly when interpreting the efficacy of any treatment option for pain in CP because it must be compared with the natural and spontaneous relief of pain[10].

The type or characteristic of pain is also an important factor in determining the natural course of pain in CP. A landmark study by Ammann et al[8] demonstrated that ACP patients with intermittent pain (type A pain) almost always achieved pain relief with only conservative treatment. In contrast, ACP patients with continuous pain (type B pain) usually associated with complications *i.e* pseudocyst, biliary stricture, duodenal obstruction or severe pancreatic ductal hypertension (demonstrated by the pancreatic duct dilatation), were not helped by conservative treatment, hence surgery (or endoscopic therapy) is usually required because such conservative treatment in patients with type B pain may put patients at risk of narcotic addiction. The strategy of choosing treatment options based on type of pain has also been advocated by some experts[8,10,11]. However, most of the published studies on the treatments of pain in CP, particularly on endoscopic therapy, failed to recognize or classify patients by the type of pain, thus making the interpretation of the results of these studies very difficult[10]. Importantly, surgical and endoscopic treatments of CP required expertise and carry significant high morbidity and mortality[12]. Therefore, the need for correct information to identify patients who can be conservatively managed and those who will receive most benefits from aggressive endoscopic therapy or surgery is critical.

For the above reasons, accurate information regarding the natural course of abdominal pain in CP in Thailand is very important to help physician deciding appropriate treatment for each patient. However, the information in Thailand is lacking. The authors observed that patients with CP in the authors' institution, particularly those with type A pain could successfully be treated with conservative treatments in most cases, and pain relief was usually achieved in a short time. Thus, the objective of the present study is to demonstrate the natural course of abdominal pain in CP with intermittent (type A) pain after conservative treatment and to determine the feasibility and efficacy of conservative treatment in this group of patients.

Material and Method

Data of all patients with CP who were managed and followed up in the Gastrointestinal Clinic, Siriraj Hospital during January 2004 to July 2008 were retrospectively reviewed and analyzed. Only patients presenting with intermittent (type A) abdominal pain were included in the analysis.

Diagnosis of CP and etiology of CP

CP was diagnosed by clinical data combined with one or more of the following imaging studies: plain abdominal x-ray showing pancreatic calcifications; computed tomography (CT); magnetic resonance cholangiopancreatography (MRCP); endoscopic retrograde cholangiopancreatography (ERCP); endoscopic ultrasonography showing $\geq$ 5 criteria of CP.

Exocrine insufficiency was presumptively diagnosed by any of the following: visible steatorrhea, positive Sudan III stain of stool, unexplained weight loss, or diarrhea responding to pancreatic enzyme supplementation. Diabetes was diagnosed by fasting plasma glucose $\geq$ 126 mg/dl, for 2 times.

Etiology of CP was classified to alcoholic (ACP), early-onset idiopathic CP (E-ICP) and late-onset idiopathic CP (L-ICP). ACP was diagnosed when patients consumed alcohol more than 80 g/day for more than 5 years[3,7]. E-ICP and L-ICP were divided by the age of onset before or after the age of 35 years[4].

Definition of type A pain

Type A pain was defined by short episodes of pain, usually less than 10 days' duration, separated by pain free intervals of months to years according to study by Ammann et al[8].

Definition of pain relief

Pain relief was defined by the absence of abdominal pain for more than 1 year.

Statistical analysis

Demographic data were analyzed by standard

descriptive statistics and presented in mean, standard deviation and per cent. Pain relief was analyzed by Kaplan-Meier analysis and presented in per cent, median time and range.

The present study was approved by Siriraj Ethics Committee.

Results

Overall, there were 32 patients with CP who had been followed up regularly. The etiologies were ACP in 15 patients (47%), L-ICP in 10 patients (31%) and E-ICP in 7 patients (22%). Twenty-seven patients had pain as a presentation, of which 22 (81%) were type A and 5 (19%) were type B. Therefore, twenty-two patients were finally included for the analysis.

Of the 22 patients (12 ACP, 5 L-ICP, 5 E-ICP) with type A pain, the median duration of follow-up was 31 months (range 5-96 months). The demographic data of patients in each etiologic subgroup is shown in Table 1. Alcohol abstinence was successful in every ACP patient.

Overall, 18 patients (82%) had pain relief with a median duration of 39 months from the onset of pain (range 16-167 months) or 14 months (range 11-57 months) from the time of diagnosis of CP. Frequency, median time of pain relief after onset and after diagnosis according to each etiology of CP were shown in Table 2 and Fig. 1. There was a statistically significant difference between pain relief in L-ICP and E-ICP ($p = 0.036$). None of the patients required regular opioid narcotics, endoscopic therapy or surgery.

Discussion

In the present study, the authors demonstrated the natural course of type A abdominal pain in CP after conservative treatment. Results of the study showed that conservative treatment was feasible and effective in most (>80%) of patients with type A pain, particularly ACP (100%) and L-ICP (80%) but not in E-ICP (40%). Patients could be conservatively treated until spontaneous pain relief was achieved which were usually within a median time of 2-3 years after the

Table 1. Demographic data of 22 patients with CP and type A pain according to etiology

	Etiology of CP		
	ACP (n = 12)	Late-onset ICP (n = 5)	Early-onset ICP (n = 5)
Age of onset, mean ± SD (range)	40 ± 9 (28-58)	52 ± 10 (43-65)	15 ± 6 (18-25)
Male, n (%)	11 (92)	2 (40)	3 (60)
Type of CP according to the size of pancreatic duct, n (%)			
Small duct	5 (42)	3 (60)	5 (100)
Large duct	7 (58)	2 (40)	0
Pancreatic calcifications, n (%)	9 (75)	5 (100)	2 (40)
Exocrine insufficiency, n (%)	6 (50)	3 (60)	0
Diabetes, n (%)	5 (42)	3 (60)	0

Table 2. Details of pain relief of 22 patients with CP and type A pain according to etiology

	Etiology of CP		
	ACP (n = 12)	Late-onset ICP (n = 5)	Early-onset ICP (n = 5)
Number with pain relief, n (%)	12 (100)	4 (80)	2 (40)
Time from onset to pain relief in month, median (range)	28 (16-167)	36 (16-39)	120 (42-120)
Time from diagnosis to pain relief in month, median (range)	14 (11-57)	13 (12-14)	52 (12-52)
Regular opioid narcotics, n (%)	0	0	0
Endoscopic therapy, n (%)	0	0	0
Surgery, n (%)	0	0	0

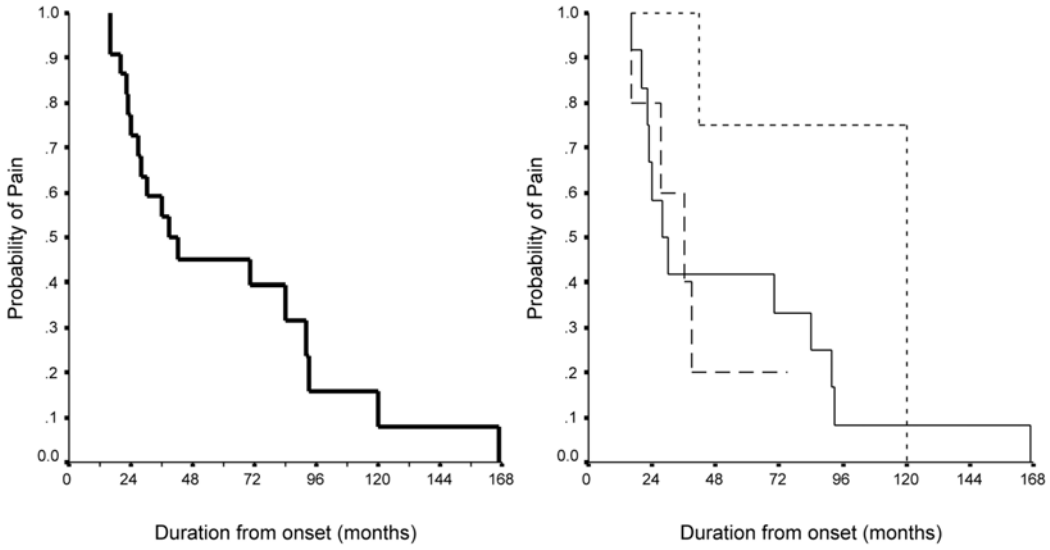

Fig. 1 Left: Probability of remaining pain over time in all patients with CP and type A pain. Right: Probability of remaining pain over time in patients with ACP (solid line), L-ICP (long hatch line) and E-ICP (short hatch line). There was a significant difference between pain relief in L-ICP and E-ICP (p = 0.036), but not between ACP and E-ICP (p = 0.13) and between ACP and L-ICP (p = 0.80)

onset of pain or approximately 1 year after the diagnosis of CP. Furthermore, opioids addiction, endoscopic therapy and surgery could be avoided in all patients. Results of the present study supported and emphasized the strategy proposed by Ammann et al[8] that patients with type A pain should be conservatively treated since pain relief will be achieved without the need of putting patients at risk for endoscopic therapy or surgery. This strategy was also recommended by some other authorities[10,11]; however, it is still not widely recognized. The results of the present study did not imply that conservative treatment was better than endoscopic therapy or surgery, but it provides the baseline information concerning the normal, natural course for any treatment of type A pain CP (*i.e* pharmacologic, endoscopic or surgical therapy) to which their results may be compared.

The present study showed that Thai patients with CP and type A pain had spontaneous pain relief much earlier than indicated in most studies in the literature (Table 3) but was close to that indicated in Ammann's study[8] which so far remains the series showing earliest pain relief in the literature. The precise reason is unclear, although one obvious conjecture is that the present study included only patients with type A, while most studies included all patients without classifying patients according to the type of pain. Another plausible reason, which has been believed by most investigators, is that most patients in Ammann's study did not use narcotics and most of them did stop drinking. These reasons may similarly explain the results of the present study.

The present study, although it was small, had many strengths because patients were carefully followed-up by a single investigator (S.P) and details of the etiology, type of pain and onset of pain relief were assessed and recorded systematically and consistently. Although selection bias of the study population could not be excluded, the authors tried conscientiously to include all patients that had been followed-up or consulted. However, a larger study, particularly on more patients with E-ICP and L-ICP, is still required to confirm or add more information concerning the natural course of pain in CP in Thailand.

In conclusion, conservative management was feasible and effective in most patients with CP and type A pain, particularly ACP after alcohol abstinence, and L-ICP. Conservative treatment was not effective in E-ICP.

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Table 3. Published studies on the natural course of pain in CP and the present study

Author, year	Country	No. of patients	Follow-up, median (years)	ACP (%)	Type of pain	Median time from onset to pain relief (years)	Definition of pain relief
Miyake, 1987[2]	Japan	125	6	62	NA	5	Relief or improvement
Lankisch, 1993[5]	Germany	335	10	73	NA	10	Pain free ≥ 1 year
Layer, 1994[4]	USA	315	15	79	NA	12 (ACP) 13 (L-ICP) 25 (E-ICP)	Pain decreased or pain free
Cavallini, 1998[6]	Italy	715	10	75	NA	8	Pain free ≥ 1 year
Ammann, 1999[8]	Switzerland	207	17	100*	A and B	6	Pain free ≥ 2 years
Mullhaupt, 2005[7]	Switzerland	304	NA	83*	A and B	4 (ACP) 1 (L-ICP) 5 (E-ICP)	Pain free ≥ 2 years
Present study, 2008	Thailand	22	2.5	55	A	2.3 (ACP) 3 (L-ICP) 10 (E-ICP)	Pain free ≥1 year

NA, not available
* Majorities of ACP in both studies were same group of patients

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การดำเนินโรคของอาการปวดท้องในผู้ป่วยตับอ่อนอักเสบเรื้อรังที่มีการปวดเป็นครั้งคราว (แบบ A) หลังการรักษาแบบประคับประคอง

สุพจน์ พงศ์ประสบชัย, สถาพร มานัสสถิตย์

ภูมิหลัง: *อาการปวดท้องในผู้ป่วยตับอ่อนอักเสบเรื้อรังเป็นปัญหาที่ยากในการรักษา และทางเลือกของการรักษาที่เหมาะสมก็ยังสับสนไม่ชัดเจน มีคำแนะนำว่าผู้ป่วยตับอ่อนอักเสบเรื้อรัง โดยเฉพาะจากแอลกอฮอล์ที่มีอาการปวดเป็นครั้งคราว (แบบ A) ควรให้การรักษาแบบประคับประคองเนื่องจากอาการทุเลาปวดมักเกิดได้เองในที่สุด แต่ข้อมูลประสิทธิภาพของการรักษาด้วยวิธีดังกล่าวยังมีน้อยและไม่ชัดเจน รวมทั้งข้อมูลในผู้ป่วยตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุยังไม่ชัดเจน*

วัสดุและวิธีการ: *ทำการวิเคราะห์ข้อมูลแบบย้อนหลังของผู้ป่วยตับอ่อนอักเสบเรื้อรังที่มีอาการปวดท้องแบบ A ที่ได้รับการรักษาแบบประคับประคองตั้งแต่ปี พ.ศ. 2547-2551 การทุเลาปวดหมายถึงไม่มีอาการปวดเป็นเวลา 1 ปี*

ผลการศึกษา: *ผู้ป่วย 22 รายได้รับการรักษาและติดตามเป็นเวลาเฉลี่ย 31 เดือน (พิสัย 5-96 เดือน) สาเหตุเกิดจากแอลกอฮอล์ 12 ราย (ร้อยละ 56), ตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุในคนอายุน้อย 5 ราย (ร้อยละ 22) และตับอ่อนอักเสบเรื้อรังชนิดไม่ทราบสาเหตุในคนอายุมาก 5 ราย (ร้อยละ 22) ผู้ป่วยตับอ่อนอักเสบเรื้อรังจากแอลกอฮอล์สามารถหยุดแอลกอฮอล์ได้ทุกราย โดยรวม ผู้ป่วย 18 ราย (ร้อยละ 82) มีการทุเลาปวด โดยมีค่ามัธยฐานของระยะเวลานับจากเริ่มปวดครั้งแรก 39 เดือน (พิสัย 16-167 เดือน) หรือ 14 เดือน (พิสัย 14-57 เดือน) นับจากได้รับการวินิจฉัยตับอ่อนอักเสบเรื้อรัง การทุเลาปวดพบได้ร้อยละ 100 ของตับอ่อนอักเสบเรื้อรังจากแอลกอฮอล์ โดยมีค่ามัธยฐาน 28 เดือน (พิสัย 16-167 เดือน), พบได้ร้อยละ 80 ของตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุในคนอายุมาก (ค่ามัธยฐาน 36 เดือน, พิสัย 16-39 เดือน) แต่พบเพียงร้อยละ 40 ของตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุในคนอายุน้อย (ค่ามัธยฐาน 120 เดือน, พิสัย 42-120 เดือน) โดยมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ระหว่างอาการทุเลาปวดในตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุในคนอายุมากกับในคนอายุน้อย ($p = 0.036$) แต่ไม่แตกต่างอย่างมีนัยสำคัญระหว่างตับอ่อนอักเสบเรื้อรังจากแอลกอฮอล์กับตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุใน คนอายุมาก ($p = 0.80$) หรือ ระหว่างตับอ่อนอักเสบเรื้อรังจากแอลกอฮอล์กับตับอ่อนอักเสบเรื้อรังที่ไม่ทราบ สาเหตุในคนอายุน้อย ($p = 0.13$) แต่ระยะเวลาตั้งแต่ได้รับการวินิจฉัยตับอ่อนอักเสบเรื้อรังจนเกิดทุเลา ปวดมีค่ามัธยฐานเพียง 14 เดือน, 13 เดือน และ 52 เดือนในผู้ป่วยตับอ่อนอักเสบเรื้อรังจากแอลกอฮอล์ ตับอ่อน อักเสบเรื้อรังไม่ทราบสาเหตุในคนอายุมากและอายุน้อย ตามลำดับ ไม่มีผู้ป่วยรายใดติดยาแก้ปวดกลุ่มมอร์ฟีน หรือ ต้องได้รับการรักษาโดยการส่องกล้อง หรือผ่าตัด*

สรุป: *การรักษาแบบประคับประคองในผู้ป่วยตับอ่อนอักเสบเรื้อรังที่มีอาการปวดท้องแบบ A สามารถทำได้ และมีประสิทธิภาพ โดยเฉพาะในผู้ป่วยตับอ่อนอักเสบเรื้อรังจากแอลกอฮอล์ที่หยุดดื่มแอลกอฮอล์ได้ และตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุในคนอายุมาก แต่ได้ผลไม่ดีในตับอ่อนอักเสบเรื้อรังที่ไม่ทราบสาเหตุในคนอายุน้อย*