Clinics in Surgery

Research Article
Published: 15 Sep, 2016

Extracorporeal Shock Wave Lithotripsy in Combination with Endoscopic Retrograde Cholangiopancreatography for Treatment of Initial Endotherapy-Failed Pancreatic Ductal Stones: A Retrospective Clinical Study

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Abstract

Objective: To evaluate the efficacy and safety of extracorporeal shock wave lithotripsy (ESWL) in combination with Endoscopic Retrograde Cholangiopancreatography (ERCP) for treatment of initial Endotherapy failed Pancreatic Ductal Stones (PDSs).

Methods: The clinical data of patients with initial Endotherapy failed PDSs treated by ESWL in combination with ERCP in our hospital were analyzed retrospectively. Radiographic assessments are performed for these patients before treatment. These patients underwent ESWL for stone fragmentation and post-ESWL therapeutic ERCP for endoscopic clearance of stone fragments. Patients' outcomes including successful stones clearance, pain relief, complications, mortality and stone recurrence were followed-up and observed, respectively.

Results: A total of 12 patients with initial Endotherapy failed PDSs received our treatment. Abdominal pain, episodes of pancreatitis, associated diabetes mellitus, concomitant alcohol abuse, malnutrition and idiopathic were observed in 100%, 83.3%, 83.3%, 66.7%, 16.7% and 8.3% of patients, respectively. The causes of the initial Endotherapy failure included: multiple, radiopaque stones with a mean size of >6.33±2.06 mm; concomitant pancreatic duct stricture with upstream main pancreatic duct dilation; and endoscopic pancreatic sphinterotomy inadequacy; in particular, no combination with ESWL. By following-up of a median period of 21 (range 4~60) months, a high rate of effective clearance of PDSs (75.0% complete clearance, 16.7% partial clearance) and a high rate of pain relief (75.0% complete pain relief and 16.7% partial pain relief) were achieved in 91.6% of patients, respectively. No procedure-related major complication and mortality occurred.

Conclusion: ESWL in combination with ERCP is an effective and safe treatment procedure for initial Endotherapy failed PDSs.

Keywords: Extracorporeal shock wave lithotripsy (ESWL); Endoscopic therapy; Endoscopic retrograde cholangiopancreatography (ERCP); Pancreatic ductal stone; Treatment

Introduction

Pancreatic ductal stone (PDS) i.e. pancreatolithiasis is a main complication of chronic pancreatitis (CP). PDSs develop during the natural course of longstanding CP and are observed in 50% ~ 90% of patients during long-term follow-up [1-3]. These PDSs contribute to ductal hypertension by impeding pancreatic juice outflow and obstructing pancreatic duct, ischemia from increased parenchymal pressure and destruction of the pancreatic parenchyma and ductal structures, and thus leading to continual abdominal pain [1-5]. Therefore, the main aim of calcific CP treatment is to decompress the main pancreatic duct (MPD) by pancreatic stone removal and pancreatic duct dilation in order to alleviate pain and improve outcome of the patients with PDSs [1,4-7].

Surgical removal, endoscopic therapy (Endotherapy) and extracorporeal shock wave lithotripsy (ESWL) are options for treatment of PDSs in the multidisciplinary plans [1-7]. A variety of treatment modalities have been described in clinical research of PDSs, although lingering controversies have hindered a consensus recommendation. The most common surgical treatment

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Received Date: *03 Aug 2016*
Accepted Date: *30 Aug 2016*
Published Date: *15 Sep 2016*

Citation:
Zhang J-T, Lu X-S, Gui Y-P, Fan Y-Z. Extracorporeal Shock Wave Lithotripsy in Combination with Endoscopic Retrograde Cholangiopancreatography for Treatment of Initial Endotherapy-Failed Pancreatic Ductal Stones: A Retrospective Clinical Study. Clin Surg. 2016; 1: 1120.

for painful obstructing main PDSs is a lateral pancreaticojejunostomy (Puestow procedure) and its modified procedure [8,9]. This operation is best suited for patients with stones in a dilated MPD (preferred ≥8 mm), which permits mucosa to mucosa anastomosis. Over the last 30 years, endoscopic procedures are developed to manage main PDSs and pancreatic duct strictures in CP patients. Endotherapy for PDSs is at present considered because of its minimally invasive and its aim to decompress the MPD by performing complete stone clearance and ductal drainage, thus relieving the obstruction and pain [6]. ESWL has lately been used in treatment of PDSs [1,4,6,10-14]. A significant advancement in PDS removal has been achieved by using ESWL for fragmentation with the aid of endoscopic retrograde cholangiopancreatography (ERCP) techniques [12-14]. But, ESWL in combination with ERCP for treatment of initial Endotherapy failed PDSs has rarely been reported.

In this study, we retrospectively analyzed the clinical data of 12 patients with initial Endotherapy failed PDSs received ESWL in combination with ERCP in our hospital to evaluate the efficacy, safety and outcome of ESWL in combination with ERCP for treatment of Endotherapy failed PDSs.

Material and Methods

Patients

This was a retrospectively clinical study for patients with PDSs from January 2008 to December 2012 in our hospital. All patients were transferred from other hospital, in which initial Endotherapy for PDSs was unsuccessful and in them pancreatic duct stent was still placed; in order to treat symptomatic Endotherapy failed PDSs in our treatment center. These patients provided informed consent for treatment and review of their records; the study was carried out according to the official recommendations of Chinese Community Guidelines and was approved by the Ethics Committee and the Institutional Review Board at the Tongji Hospital.

These initial Endotherapy-failed patients underwent radiographic assessments before ESWL in combination with ERCP for treatment of their PDSs. Radiographic assessments included plain radiography, abdominal enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or diagnostic ERCP to confirm the diagnosis of chronic calculi pancreatitis, to determine the location, number, size of stones, the morphology of the pancreatic duct and its anomalies such as strictures or dilatation, and to find out the causes of the failure of initial Endotherapy for PDSs.

Treatments

ESWL: In this study, all of symptomatic patients with PDSs are firstly considered for ESWL, especially those who have stones that are >5 mm in size. The objective of ESWL is to fragment the stones successfully until they are < 3 mm in size, or to completely pulverize the stones until they are almost a granular powder form, so that they can be removed by subsequent ERCP *via* a successful stone clearance.

ESWL were performed with an electromagnetic lithotripter (Shenhang Co, Shanghai, China) with fluoroscopic focusing system, power setting at 9~10EKV, and 1000~1500 shock waves were delivered in one ESWL session. The shockwave energy settings were adapted to the individual patient's tolerance and comfort. If the patients can't tolerate the treatment, the power and the number of shock waves would be adjusted or treatment paused. Successful fragmentation was determined based on the change of density and volume of stones. Repeat ESWL sessions are carried out on successive days until the stone fragments are < 3 mm in diameter, or almost a granular powder form.

ERCP: After successful fragmentation by ESWL, therapeutic ERCP for endoscopic clearance of stone fragments is performed in all patients by endoscopic pancreatic sphinterotomy(EPS), balloon dilation, stone extraction and pancreatic duct stent, depending on the conditions of the patients and the causes of the initial Endotherapy failure such as more, larger or compacted stones, EPS inadequacy and dominant pancreatic stricture.

This therapeutic ERCP is performed with duodenoscope (JF-240 or TJF-240, Olympus Optical Co, Tokyo, Japan), which begins with cannulation of the pancreatic orifice and contrast instillation to delineate the ductal anatomy and assess the pancreatic ductal morphology (stricture or dilation) and the number, size and location of the stone fragments. Subsequently, a standard EPS was performed with a pull-type sphincterotome (Clevercut, Olympus Optical Co) passed over a guide wire or with a needle-knife incision over a guiding pancreatic stent *via* irrigation of the pancreatic duct with saline solution. In patients with pancreas divisum, ductal access *via* the minor papilla is followed by minor papilla sphinterotomy (MPS). Extraction balloon or basket trawling is performed for removing of residual fragmented stones of the pancreatic duct. When pancreatic duct strictures are present, stricture dilation may be required to facilitate stone removal by using radial expansion balloon (10~12 mm), dilator catheters or stent placement. A plastic stent (5~7Fr) is inserted in patients with pancreatic duct strictures after stone extraction, or when residual stones cannot be removed completely to guarantee an unobstructed flow of pancreatic juice. Pancreatic duct stricture is often densely fibrotic and is a main factor of stone recurrence, balloon dilation alone generally do not result in satisfactory long-term resolution, thus pancreatic duct stents are placed through the strictures even in patients with complete stone clearance for about three months to prevent the recurrence of stricture and stone.

Follow-up and outcome measures

Follow-up data were recorded from the patient's medical records and completed by a telephone survey, routine visit record and address. Clinical outcome was followed from the date of treatment or until the end of December 30, 2012.

The primary outcome measures were performed and defined as follows [11]: 1. Complete clearance: fragmentation of PDS to < 3 mm in size with clearance of 90%~100% of stone fragments; 2. partial clearance: clearance of 50%~90% of stone fragments; 4. unsuccessful or fail clearance: presence of PDS >3 mm in size or clearance of < 50% of stone. The secondary outcome measures included pain relief at the end of follow-up, complications and mortality, and stone recurrence. Pain relief at the end of follow-up was classified as complete (Izbicki pain score, ≤ 10) or partial (Izbicki pain score, >10 after a decrease of >50%) [15]. Complications of ESWL in combination with ERCP included ESWL complications and ERCP complications. The complications from ESWL such as skin or duodenal contusions, pancreatitis, asymptomatic hyperamylasemia, right renal subcapsular hematoma, and collateral spleen damage [6,16] and the complications from ERCP such as acute pancreatitis, bleeding, perforations, and soon on [17] were observed. Treatment was considered to have failed in patients whose treatment was converted from ESWL in combination with ERCP to surgery. Stone recurrence of patients is observed by radiographic assessments such as CT scan and/or MRI.

Table 1: Demographics and clinical manifestation and causes of initial Endotherapy failure of 12 patients with PDS.

S.N of patients	Demographics			Clinical manifestation			Main causes of initial endotherapy failure					
	Sex (M/F)	Age (y)	Abdominal pain	Diabetes mellitus	Alcohol abuse	Mal-nutrition	EPS inadequacy	Pancreatic stricture	PDS			
									Location	Number	Size(mm)	Nature
1	F	12	Yes	No	No	Yes	Yes	Yes	Head	3	> 5	Radiopaque
2	F	40	Yes	Yes	No	No	Yes	No	Head-body	3	> 5	Radiopaque
3	F	56	Yes	Yes	No	No	Yes	Yes	Full	Many	> 5	Radiopaque
4	M	17	Yes	No	Yes	Yes	No	Yes	Head-body	3	> 5	Radiopaque
5	M	42	Yes	Yes	Yes	No	No	Yes	Head	2	> 5	Radiopaque
6	M	49	Yes	Yes	Yes	No	Yes	Yes	Head	1	> 10	Radiopaque
7	M	52	Yes	Yes	Yes	No	Yes	Yes	Body-tail	Many	> 5	Radiopaque
8	M	57	Yes	Yes	Yes	No	No	Yes	Head	2	> 5	Radiopaque
9	M	60	Yes	Yes	Yes	No	No	Yes	Head-body	2	> 5	Radiopaque
10	M	62	Yes	Yes	Yes	No	Yes	No	Head	1	> 10	Radiopaque
11	M	64	Yes	Yes	Yes	No	Yes	Yes	Head-body	3	> 8	Radiopaque
12	M	67	Yes	Yes	Yes	No	Yes	No	Head	2	> 8	Radiopaque

EPS: Endoscopic Pancreatic Sphincterotomy; Pancreatic Stricture: Pancreatic Stricture with Upstream Main Pancreatic Duct Dilation; PDS: Pancreatic Ductal Stone; Full: both main and accessory pancreatic duct were fully filled with stones; many: number of PDS >3

Table 2: Treatment procedures and outcomes of 12 patients with PDS.

S.N. of patients	Procedures					Outcomes				
	ESWL	Therapeutic ERCP				Stone clearance	Pain relief	Complications		Other
		EPS	Balloon	Basket	Stent			Pancreatitis	Hyper-M	
1	1	Yes	Yes	Yes	Yes	Complete	Complete	No	No	No
2	2	Yes	No	Yes	Yes	Complete	Complete	No	No	No
3	3	Yes	Yes	Yes	Yes	Fail	Fail	Mild	Yes	Surgery
4	1	No	Yes	Yes	Yes	Complete	Complete	No	No	No
5	1	No	Yes	Yes	Yes	Complete	Complete	No	No	No
6	1	Yes	Yes	Yes	Yes	Complete	Complete	No	No	Recurrence
7	2	Yes	Yes	Yes	Yes	Partial	Partial	Mild	Yes	No
8	1	No	Yes	Yes	Yes	Complete	Complete	No	No	No
9	1	No	Yes	Yes	Yes	Complete	Complete	No	No	No
10	1	Yes	No	Yes	Yes	Complete	Complete	No	No	No
11	2	MPS	Yes	Yes	Yes	Partial	Partial	No	No	No
12	1	Yes	No	Yes	Yes	Complete	Complete	No	No	No

PDS: Pancreatic Ductal Stone; ESWL: Number of Extracorporeal Shock Wave Lithotripsy Sessions; ERCP: Endoscopic Retrograde Cholangiopancreatography; EPS: Endoscopic Pancreatic Sphincterotomy; MPS: Minor Papilla Sphincterotomy + EPS; Balloon: Ductal Dilation and Stone Extraction by Extraction Balloon; Basket: Stone Removal by Basket Trawling; Stent: Plastic Stent Placement for Treatment of Pancreatic Duct Strictures after Stone Extraction, or for Removal of Residual Stones to Guarantee an Unobstructed Flow of Pancreatic Juice; Hyper-M: Hyperamylasemia

Results

Patient cohort

A total of 12 patients with initial Endotherapy-failed PDSs were treated in our hospital. These patients consisted of 9 men (75%) and 3 women (25%) with a mean age of 48.17 ± 17.78 years (mean ± SD, range 12~67 years). The mean duration of PDS was 5.6 ± 3.2 years (mean ± SD, range 1.4 years~32 years) with 83.3% (10/12) of patients reporting prior episodes of pancreatitis. Of these, all patients had upper abdominal pain radiating to the back; 83.3% (10/12) of patients had associated diabetes mellitus; two-thirds (66.7%) of patients (only male) had concomitant alcohol abuse; malnutrition and idiopathic were noted in 16.7% and 8.3% of patients, respectively (Table 1).

Imaging findings

Imaging findings according to plain radiography, CT scan, MRI and/or diagnostic ERCP in this study were presented in Table 1. Overall, frequent findings included PDSs, concomitant pancreatic duct stricture with upstream main pancreatic duct dilation, and EPS inadequacy, which were present 66.7%, 100%, and 75.0% of patients, respectively. Of these PDSs, multiple stones were present in 83.3% of patients, of whom 100% had stones in the pancreatic head, while in patients with stones in the head, 50% had associated stones in the body and/or tail, 8.3% of stones scattered throughout both main and accessory pancreatic duct. And for all patients, 100% of stones were radio-opaque with hardness and irregular natures underlying duct stricture, and a mean size of >6.33 ± 2.06 mm (mean ± SD, range>5~10 mm). Characteristics of these imaging findings, in particular, no combination with effective lithotripsy modalities such as ESWL could be the main causes of the failure of initial Endotherapy for patients with PDSs.

Treatments and outcomes

Overall, all the patients received ESWL in combination with ERCP for PDSs. A total of 19 ESWL sessions with a mean session of 1.58 ± 0.79 (mean ± SD, range 1~3 sessions) were performed for adequate fragmentation: 58.3% of patients required a single session, 25.0% required two sessions and 16.7% required three sessions. Post-ESWL therapeutic ERCP procedures included EPS, extraction balloon, basket trawling, and plastic stent which were present 66.7%, 75.0%, 100%, and 100% of patients, respectively; of them, 8.3% of patients received EPS and MPS simultaneously.

All the patients were followed up, with median follow-up period of 21 (range, 4~60) months. The primary and secondary outcomes are summarized in Table 2. Complete clearance of PDSs was achieved in 75.0% of patients; partial clearance was achieved in 16.7% patients, thus a high rate of effective clearance of PDSs or MPD decompression was achieved in 91.6% patients. It was showed as Figure 1~2, the pulverized stones with less dense and spread along the duct were observed in ESWL procedure on fluoroscopy (Figure 1); the patient underwent post-ESWL therapeutic ERCP including balloon dilation and stone extraction in whose loosened or fragmented stones were observed in MPD and were extracted easily (Figure 2). But, unsuccessful or fail clearance was observed in 8.3% patients due to extensive stones in the head, body and tail of the pancreas with multiple stricture of the pancreatic duct.

A high rate of effective pain relief was achieved in 91.6% of patients (75.0% complete reliefs of pain and 16.7% partial reliefs of pain, respectively); only 8.36% (1/12) of patients with pain relief was failed owing to extensive stones and multiple strictures, subsequently received surgery. Per-procedural ESWL and ERCP related complications occurred in 8.36% (1/12) and 16.7 (2/12) of patients, respectively. These complications included mile pancreatitis and asymptomatic hyperamylasemia, which could be cured by observation or conservative medical treatment. Other complications such as skin or duodenal contusions, right renal subcapsular hematoma, and collateral spleen damage from ESWL, and severer pancreatitis, bleeding, perforations from ERCP were not observed. There were no severe or life-threatening complications in procedures. Stone recurrence is observed in one patient, who has concomitant alcohol abuse, 18 months after treatment.

Discussion

As a main complication of CP, PDSs have been brought to the patient suffering and trouble, and their pathogenesis remains unknown. Most studies have revealed that there was a tight relation between formation of PDSs and CP. PDSs are generally considered to be consequence of CP and almost occur in 50% to 90% of patients with long-stand disease [1-3]. These stones tend to cause further obstruction of outflow from pancreas, pancreatic duct hypertension, worsen pathologic changes of pancreatic parenchyma, pancreatic inflammation and continual abdominal pain, and even result in inflammatory masses or carcinoma [1-5]. Another factor associated with PDSs is alcohol abuse. Inui et al. [18] reported that alcohol drinkers make up 76.6% of PDS patients. Some studies have demonstrated a direct correlation between stone formation and long-term alcohol abuse. Other factors including biliary disease, hyperparathyroidism, and malnutrition, hereditary or idiopathic factors are also related to PDS formation. Abdominal pain is the predominant symptom in patients with PDSs and has affected the patient's life. In this study, all of patients with initial Endotherapy-failed PDSs had upper abdominal pain radiating to the back; 83.3% of patients had clinical presentation of CP and associated diabetes mellitus; two-thirds (66.7%) of patients (only male) had concomitant

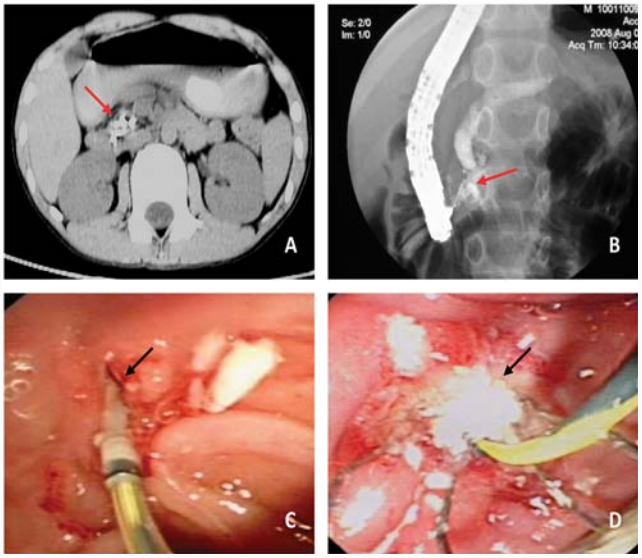

Figure 1: Endoscopic clearance of pancreatic duct stones after extracorporeal shock wave lithotripsy. (A) Abdominal computed tomography scan shows multiple calcified stones (*red arrow*) in pancreatic head. (B) After two sessions of ESWL, endoscopic retrograde cholangiopancreatography displays multiple small filling defects (*red arrow*) and stricture in the main pancreatic duct at the pancreatic genu, with upstream dilation of the main duct. (C) Endoscopic pancreatic sphincterotomy. A papillotome (*black arrow*) is inserted into the orifice of the pancreatic duct. Stone was visualized intraluminally. (D) Many fragmented stones (*black arrow*) were removed with a basket.

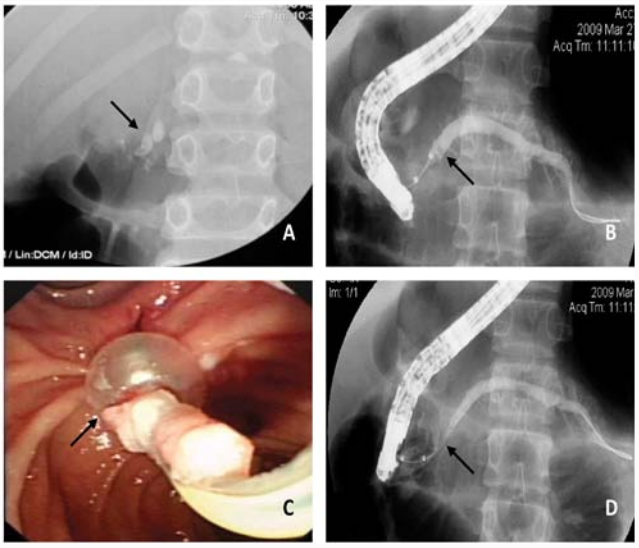

Figure 2: Endoscopic clearance of pancreatic duct stones after extracorporeal shock wave lithotripsy. (A) Plain radiography shows multiple radioopaque stones with a stone of 8 mm in size (*black arrow*) in the main pancreatic duct. (B) After one session of ESWL, endoscopic retrograde cholangiopancreatography displays multiple small filling defects (*black arrow*) and stricture in the main pancreatic duct opening, with upstream dilation of the main duct. (C) Many fragmented stones (*black arrow*) were removed with an extraction balloon after sphincterotomy followed by endoscopic balloon dilation of the pancreatic orifice. (D) No filling defect (*black arrow*) but smaller duct diameter was synchronously observed in the main pancreatic duct after complete stone removal.

alcohol abuse; malnutrition was noted in 16.7% of patients (Table 1). The results showed that a correlation between the formation of PDSs and CP, alcohol abuse as well as malnutrition.

Abdominal pain is the predominant clinical symptom requiring therapy in most patients with calculi CP, due to obstruction and hypertension of the pancreatic duct either by stones or stricture with increasing intraductal pressure and parenchymal ischemia [6,7]. Therefore, the main aim of treatment for PDSs is to decompress the MPD by performing complete stone clearance and ductal drainage [4,6,7]. Multiple series have demonstrated that removing obstructing stones from the MPD improves symptoms in the majority of CP patients. Prior to the introduction of ESWL by Sauerbruch in 1987 [19], surgery and endoscopic therapy were the main options for clearance of PDSs.

With advancement in noninvasive technology and improvement in accessory, therapeutic ERCP as a less invasive treatment had popularly been used for treatment of patients with PDSs. The current American Society for Gastrointestinal Endoscopy (ASGE) suggests endoscopic therapy as the first-line treatment of CP and PDSs because of its lower degree of invasiveness [20]. Endoscopic techniques for stone removal include EPS, stone retrieval using balloons, baskets, or rat tooth forceps, stent placement, mechanical lithotripsy, and endoscopic balloon dilation of the pancreatic orifice after sphincterotomy [1]. But successful clearance of PDSs *via* therapeutic ERCP greatly depends on the location, size, number of stones as well as the morphological change of pancreatic duct. Selection of the proper candidates is crucial because endoscopic treatment cannot be used for all patients. It was reported that the indications for endoscopic treatment of PDSs or factors favoring successful stone clearance by Endotherapy were ≤ 3 stones, location of stones at the pancreatic head and/or body, absence of stricture downstream to the stone, stone diameter ≤ 10 mm, and absence of impacted stone(s) [5,21]. The best candidates for endoscopic removal are MPD stones of the head or body with upstream MPD dilation [6]. If a PDS is situated at the MPD and is small, removal is more likely to be successful. In contrast, patients with many stones with hardness, impacting natures underlying duct stricture, or PDSs scattered throughout the pancreatic duct or stones at the side branch duct without MPD dilatation are poor candidates for endoscopic removal of PDSs [1,21,22]. In a large series of 1,000 CP patients who were treated endoscopically with long-term follow-up, 65% of patients with strictures and/or stones showed pain improvement after Endotherapy [23]. But, large stones, presence of strictures, stones impacted behind strictures, stuck to the ductal epithelium or sited predominantly in the pancreatic tail do not usually respond well to endoscopic therapy. Complete clearance of PDSs with standard endoscopic techniques alone was approximately 40~50% [6,17, 21,24,25]. Even in a retrospective series of 125 patients, less than 10% of them had successful endoscopic ductal clearance without prior ESWL [26]. In this study, all of patients with PDSs had received Endotherapy at the other hospital, but initial Endotherapy for PDSs was unsuccessful, these patients still had continual abdominal pain. Main causes of the failure of initial Endotherapy for the patients with PDSs according to imaging findings by CT scan, MRI and/or diagnostic ERCP could be included as follows: 1) multiple stones (83.3%); 2) the presence of concomitant pancreatic duct stricture with upstream MPD dilation (75.0%); 3) radio-opaque stones (100%), with hardness and irregular natures underlying duct stricture; 4) a large stone burden, with a mean size of >6.33 ± 2.06 mm (mean ± SD, range >5~10 mm); 5) EPS inadequacy (66.7%) in initial Endotherapy. These factors eventually lead to the failure of initial Endotherapy for PDSs. Therefore, it is necessary to combine therapeutic ERCP with other effective modalities for treatment of these initial Endotherapy-failed PDSs.

It is necessarily emphasized that surgery is an older treatment method than Endotherapy. Surgery, as a more invasive treatment and almost 25% of patients experience pain recurrence, and considerable procedure-related morbidity and mortality, is often considered second-line therapy for patients in whom endoscopic therapy fails, [6]. Surgery should be option in patients in whom Endotherapy for PDSs has failed or in those with stone recurrence or presence of other complications such as a pancreatic mass with suspicion of malignancy, and/or duodenal stenosis [7,17,26,27]. In two prospective randomized controlled trials (RCTs) that compared Endotherapy with surgery for patients with PDSs, surgery was more effective and better clinical outcomes than endoscopic therapy [7,17,27,28-30]. But, it is worth noting that in Díte et al. trial [28], patients in the Endotherapy group did not receive ESWL, and the protocol also excluded cumulative stenting or repeat sessions for recurrent symptoms; that Cahen DL' trial [29] was limited by a lower than usual overall technical success (53%) in the Endotherapy group, perhaps due to a very high proportion of pancreatic duct strictures (84%), and these patients were probably treated with inadequate short-term stenting (median, 27 weeks); thus reducing the maximum potential of Endotherapy to provide good clinical outcome [4]. So, it should be considered that some forms of lithotripsy rather than surgery are used for treatment of the larger and impacted PDSs before stone removal by therapeutic ERCP.

ESWL seems to be the best technique for pulverizing PDSs. As PDSs consist of radiopaque calcium salts with carbonate and phosphate, these stones in about 90% of patients can be effectively fragmented by ESWL, which works by concentrating focused shock waves on stones under fluoroscopy. By pulverizing the stones and reducing the stone burden, ESWL overcomes the problem of stone size, an obstacle of endoscopic therapy, thus facilitating the endoscopic clearance of stones of the duct [5,12-14]. ESWL is safe, effective, and noninvasive because broken pieces can be removed out of the pancreatic duct once they are reduced in size. Endoscopic therapy, combined with ESWL, can remove stones in the MPD, even as well as those in the accessory pancreatic duct [1,31,32]. In a randomized study that compared ESWL alone to ESWL with endoscopic therapy, ESWL alone was safer and more effective [33]. Therefore, ESWL can be used as a primary treatment, in addition to its compensatory role in endoscopic therapy [33,34]. The European Society of Gastrointestinal Endoscopy (ESGE) regarding therapeutic intervention in CP patients [33,35] recommends ESWL and ERCP as the first-line treatment method; ESWL as a first step in treating patients with radiopaque PDSs ≥5 mm obstructing the MPD, immediately followed by endoscopic extraction of stone fragments. In CP patients with a MPD stricture, the ESGE recommends placement of a single 10-Fr plastic stent [33,35]. For fewer stones that are < 5 mm and located between the pancreatic head and body, the ESGE recommends endoscopy [35]. Both ASGE guideline and ESGE guideline recommend endoscopic treatment as the first-line treatment for such stones, rather than surgery, but the ESGE guideline emphasizes the role of ESWL more than the ASGE guideline [20,35]. In Japan, ESWL is predominant with endoscopic treatment used adjunctively [36,37]. Surgery is indicated for patients who do not meet these indications or for whom nonsurgical treatment has failed [1], while ESWL was decided upon if stone volume was

deemed too high for successful endoscopic therapy or if therapeutic endoscopy was unsuccessful [11]. According to literatures, successful stone fragmentation was achieved by ESWL in a very high percentage [1,36,37], and ESWL is necessary to fragment the stones prior to endoscopic extraction in 36%~68% of patients with CP and PDSs [26,31], while attempts at endoscopic removal without fragmentation have unsatisfactory results [39]. Approximately 50% of PDSs can be removed by alone Endotherapy, the addition of ESWL increased the success rate to 60% to 90% as ESWL can fragment large stones to lessen the burden [1]. Long-term follow-up studies have shown that ESWL combined with endoscopic therapy relieves pain and may avoid the need for surgery in approximately two-thirds of patients [34]. ESWL can assist in long-term pain relief, when it is combined with endoscopic therapy to treat PDSs under the proper indications [1]. Therefore in this study, ESWL in combination with ERCP rather than surgery is considered for treatment of initial Endotherapy- failed PDSs.

With regard to the standard of successful PDS fragmentation, most authors believed that the production of stone fragments ≤ 3 mm was associated with the successful removal of stones. Previously reported predictors of successful PDS fragmentation and duct clearance included single PD stone, absence of PD stricture and PD stone location in the head of the pancreas [26,35]. As multiple, large stones may prevent complete endoscopic removal; particularly, Stones >5 mm in diameter are often impacted in the MPD and require fragmentation to facilitate their expulsion [40,41]. Solitary PDSs and location in the head of the pancreas and stone attenuation have been associated with successful ESWL and complete duct clearance [26,35,42]. ESWL is indicated in all patients of chronic calcific pancreatitis with large PDS (>5 mm) that are not amenable to routine Endotherapy - where pain is the predominant symptom. The aim is to break the calculi to fragments of ≤ 3 mm, so that they can be removed by subsequent ERCP. And, over 95% of patients with PDSs require three sessions or fewer of ESWL for adequate fragmentation [16]. Repeat sessions are carried out on successive days until the stone fragments are < 3 mm in diameter. Recently, Lapp RT et al. [43] reported that PDS diameter of < 9 mm, number of PDSs of < 2, MPD diameter of < 7 mm, and need for only 1 ESWL session were predictive of successful fragmentation; that pre-ESWL pancreatic Endotherapy appears to have no affect on the success of PDS fragmentation by ESWL; that patients with PDSs of < 12 mm and MPD diameter of < 8 mm may benefit from early referral to ESWL without pancreatic duct stent placement as initial intervention regardless if a pancreatic duct stricture is present. However, ESWL is not indicated in patients with extensive calculi in the head, body and tail of the pancreas, or in patients with isolated calculi in the tail area because of increased chance of collateral damage to the spleen are high [16]. In addition, patients with pancreatic duct >12 mm in diameter and PDSs >12 mm are associated with ESWL and endoscopic failure and may benefit from early referral to surgery [43].

In this study, 100% of patients' PDSs were located in the pancreatic head, accompanied by 50% in the body and/or tail and 8.3% throughout both main and accessory pancreatic duct, a mean size of stone >6.3 ± 2.1 mm (mean ± SD, range >5~10 mm) and 100% of radiopaque stones; and 75.0% of concomitant pancreatic duct stricture with upstream MPD dilation and 66.7% of EPS inadequacy. All patients received ESWL and subsequent therapeutic ERCP. A total of 19 ESWL sessions with a mean session of 1.58 ± 0.79 (mean ± SD, range 1~3 sessions) were performed for adequate fragmentation. Post-ESWL therapeutic ERCP procedures including EPS, extraction balloon, basket trawling, and plastic stent were used for clearance of PDSs. By following-up 21 (range, 4~60) months, complete clearance of PDSs was achieved in 75.0% patients; partial clearance was achieved in 16.7% (2/12) patients, one of them whose PDSs located predominantly in the pancreatic tail, and another one whose stones partially located in the accessory pancreatic duct where stones could not reached by extraction basket; thus total effective clearance of PDSs was achieved in 91.6% patients. Complete and partial reliefs of pain were observed in 75.0% and 16.7% of patients, respectively. And, there were no severe or life-threatening complications in procedures. But clearance of PDSs and pain relief were failed in 8.3% (1/12) of patients in whom both main and accessory pancreatic duct were filled with stones. In this patient, successful fragmentation was achieved but the stone extraction basket could not open in pancreatic duct, leading to failed extraction, subsequently to surgery. Stone recurrence is observed in one patient (8.3%). The stone recurrence rate was lower than 22% reported by Inui K et al. [36]. Serial studies have showed that pre-Endotherapy ESWL could confer a higher rate of successful Endotherapy to achieve effective clearance of PDSs; ESWL fragmentation of PDSs in conjunction with endoscopic clearance of the MPD is associated with significant improvement in clinical outcomes in most patients with CP; ESWL followed by Endotherapy is the accepted initial step for most patients with stones larger than 5 mm in the MPD [1,23,34,44,45]. Thus, this study showed that the proper ESWL for adequate fragmentation and the subsequent effective therapeutic ERCP for stone clearance help to treat initial Endotherapy-failed PDSs.

There are several limitations in this study. Firstly, this study is a retrospective analysis at a single treatment center. Such retrospective studies can overestimate clinical success and underestimate complications. Secondly, the sample size of the study is less, which is not conducive to the evaluation of the curative effect. Thirdly, our patients are transferred from other different hospital in which initial Endotherapy for PDSs is failed, thus an accurate comparison with ESWL followed by ERCP studies remains difficult. Finally, the cohort presented here likely suffers from referral bias as patients who have more symptomatic or complex disease are more likely to be referred to a treatment center.

Conclusion

The clearance of multiple main PDSs in patients with initial Endotherapy-failure is effectively, safely performed *via* the nonsurgical methods of ESWL in combination with ERCP. If in patients with the appropriate indications or who are at high risk for surgery, ESWL in combination with ERCP can be considered a first-line treatment for patients with initial Endotherapy failure. Of course, large sample, prospective, multicenter studies for treatment of patients with initial Endotherapy failed PDSs will be needed. We expect that the development of advanced endoscopic and ESWL techniques and equipments will expand the role of nonsurgical treatments i.e. ESWL in combination with ERCP in complete clearance of initial Endotherapy failed PDSs.

References

1. Kim YH, Jang SIII, Rhee K, Lee DK. Endoscopic Treatment of Pancreatic Calculi. Clin Endosc. 2014; 47: 227-235.

2. Maydeo A, Soehendra N, Reddy N, Bhandari S. Endotherapy for chronic pancreatitis with intracanalar stones. Endoscopy. 2007; 39: 653-658.

3. Hirota M, Shimosegawa T, Masamune A, Kikuta K, Kume K, Hamada S, et al. The sixth nationwide epidemiological survey of chronic pancreatitis in Japan. Pancreatology. 2012; 12: 79-84.

4. Kwek AB, Ang TL, Maydeo A. Current status of endotherapy for chronic pancreatitis. Singapore Med J. 2014; 55: 613-620.

5. Liu BN, Zhang TP, Zhao YP, Liao Q, Dai MH, Zhan HX. Pancreatic duct stones in patients with chronic pancreatitis: surgical outcomes. Hepatobiliary Pancreat Dis Int. 2010; 9: 423-427.

6. Choi EK, Lehman GA. Update on endoscopic management of main pancreatic duct stones in chronic calcific pancreatitis. Korean J Intern Med. 2012; 27: 20-29.

7. Jabłońska B. Is endoscopic therapy the treatment of choice in all patients with chronic pancreatitis? World J Gastroenterol. 2013; 19: 12-16.

8. Haggard WD, Kirtley JA. Pancreatic calculi: a review of sixty-five operative and one hundred thirty-nine non-operative cases. Ann Surg. 1939; 109: 809-826.

9. Fragulidis GP, Vezakis A, Dellaportas D, Sotirova I, Koutoulidis V, Kontis E, et al. Puestow modified procedure in the era of advanced endoscopic interventions for the management of chronic lithiasic pancreatitis. A two cases report. Int J Surg Case Rep. 2015; 15: 85-88.

10. Ohara H, Hoshino M, Hayakawa T, Kamiya Y, Miyaji M, Takeuchi T, et al. Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones. Am J Gastroenterol. 1996; 91: 1388-1394.

11. Ong WC, Tandan M, Reddy V, Rao GV, Reddy N. Multiple main pancreatic duct stones in tropical pancreatitis: Safe clearance with extracorporeal shockwave lithotripsy. J Gastroenterol Hepatol. 2006; 21: 1514–1518.

12. Delhaye M, Arvanitakis M, Bali M, Matos C, Deviere J. Endoscopic therapy for chronic pancreatitis. Scand J Surg. 2005; 94: 143-153.

13. Parsi MA, Stevens T, Lopez R, Vargo JJ. Extracorporeal shock wave lithotripsy for prevention of recurrent pancreatitis caused by obstructive pancreatic stones. Pancreas. 2010; 39: 153-155.

14. Guda NM, Partington S, Freeman ML. Extracorporeal shock wave lithotripsy in the management of chronic calcific pancreatitis: a meta-analysis. JOP. 2005; 6: 6-12.

15. Cahen DL, Gouma DJ, Nio Y, Rauws EAJ, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007; 356: 676-684.

16. Tandan M, Reddy DN. Extracorporeal shock wave lithotripsy for pancreatic and large common bile duct stones. World J Gastroenterol. 2011; 17: 4365-4371.

17. Clarke B, Slivka A, Tomizawa Y, Sanders M, Papachristou G, Whitcomb DC, et al. Endoscopic therapy is effective for patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2012; 10: 795-802.

18. Inui K, Tazuma S, Yamaguchi T, Ohara H, Tsuji T, Miyagawa H, et al. Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: result of a multicenter survey. Pancreas. 2005; 30: 26-30.

19. Sauerbruch T, Holl J, Sackmann M, Werner R, Wotzka R, Paumgartner G. Disintegration of a pancreatic duct stone with extracorporeal shock waves in a patient with chronic pancreatitis. Endoscopy. 1987; 19: 207–208.

20. Adler DG, Lichtenstein D, Baron TH, Davila R, Egan JV, Gan SL, et al. The role of endoscopy in patients with chronic pancreatitis. Gastrointest Endosc. 2006; 63: 933-937.

21. Sherman S, Lehman GA, Hawes RH, Ponich T, Miller LS, Cohen LB, et al. Pancreatic ductal stones frequency of successful endoscopic removal and improvement in symptoms. Gastrointest Endosc. 1991; 37: 511-517.

22. Tringali A, Boskoski I, Costamagna G. The role of endoscopy in the therapy of chronic pancreatitis. Best Pract Res Clin Gastroenterol. 2008; 22: 145-165.

23. Rösch T, Daniel S, Scholz M, Huibregtse K, Smits M, Schneider T, et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy. 2002; 34: 765-771.

24. Heyries L, Sahel J. Endoscopic treatment of chronic pancreatitis. World J Gastroenterol. 2007; 13: 6127-6133.

25. Smits ME, Rauws EA, Tytgat GN, Huibregtse K. Endoscopic treatment of pancreatic stones in patients with chronic pancreatitis. Gastrointest Endosc. 1996; 43: 556-560.

26. Farnbacher MJ, Schoen C, Rabenstein T, Benninger J, Hahn EG, Schneider HT. Pancreatic duct stones in chronic pancreatitis: criteria for treatment intensity and success. Gastrointest Endosc. 2002; 56: 501-506.

27. Fragulidis GP, Vezakis A, Dellaportas D, Sotirova I, Koutoulidis V, Kontis E, et al. Puestow modified procedure in the era of advanced endoscopic interventions for the management of chronic lithiasic pancreatitis: A two cases report. Int J Surg Case Rep. 2015; 15: 85-88.

28. Díte P, Ruzicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy. 2003; 35: 553-558.

29. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007; 356: 676-684.

30. Cahen DL, Gouma DJ, Laramée P, Nio Y, Rauws EA, Boermeester MA, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology. 2011; 141: 1690-1695.

31. Brand B, Kahl M, Sidhu S, Nam VC, Sriram PV, Jaeckle S, et al. Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic calcific pancreatitis. Am J Gastroenterol. 2000; 95: 3428- 3438.

32. Ohara H, Hoshino M, Hayakawa T, Kamiya Y, Miyaji M, Takeuchi T, et al. Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones. Am J Gastroenterol. 1996; 91: 1388-1394.

33. Dumonceau JM, Costamagna G, Tringali A, Vahedi K, Delhaye M, Hittelet A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomized controlled trial. Gut. 2007; 56: 545-552.

34. Kozarek RA, Brandabur JJ, Ball TJ, Gluck M, Patterson DJ, France R, et al. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc. 2002; 56: 496-500.

35. Dumonceau JM, Delhaye M, Tringali A, Dominguez-Munoz JE, Poley JW, Arvanitaki M, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2012; 44: 784-800.

36. Inui K, Tazuma S, Yamaguchi T, Ohara H, Tsuji T, Miyagawa H, et al. Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: results of a multicenter survey. Pancreas. 2005; 30: 26–30.

37. Inui K, Yoshino J, Miyoshi H, Yamamoto S, Kobayashi T. New developments in diagnosis and non-surgical treatment of chronic pancreatitis. J Gastroenterol Hepatol. 2013; 28: 108–112.

38. Dumonceau JM, Devière J, Le Moine O, Delhaye M, Vandermeeren A, Baize M, et al. Endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones: long-term results. Gastrointest Endosc. 1996; 43: 547–555.

39. Luetmer PH, Stephens DH, Ward EM. Chronic pancreatitis: reassessment with current CT. Radiology. 1989; 171: 353-357.

40. Maydeo A, Soehendra N, Reddy N, Bhandari S. Endotherapy for chronic pancreatitis with intracanalar stones. Endoscopy. 2007; 39: 653–658.

41. Maydeo A, Soehendra N, Reddy N, Lehman GA. Role of ERCP and other endoscopic modalities in chronic pancreatitis. Gastrointest Endosc. 2002; 56: S237-S240.

42. Ohyama H, Mikata R, Ishihara T, Tsuyuguchi T, Sakai Y, Sugiyama H, et al. Efficacy of stone density on noncontrast computed tomography in predicting the outcome of extracorporeal shock wave lithotripsy for patients with pancreatic stones. Pancreas. 2015; 44: 422–428.

43. Lapp RT, Wolf JS Jr, Faerber GJ, Roberts WW, McCarthy ST, Anderson MA, et al. Duct diameter and size of stones predict successful extracorporeal shock wave lithotripsy and endoscopic clearance in patients with chronic pancreatitis and pancreaticolithiasis. Pancreas. 2016; 45: 1208-1211.

44. Tandan M, Reddy DN, Santosh D, Vinod K, Ramchandani M, Rajesh G, et al. Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi: a large single center experience. Indian J Gastroenterol. 2010; 29: 143-148.

45. Tandan M, Reddy DN, Talukdar R, Vinod K, Santosh D, Lakhtakia S, et al. Long-term clinical outcomes of extracorporeal shockwave lithotripsy in painful chronic pancreatitis. Gastrointest Endosc. 2013; 78: 726-733.