The role of extracorporeal shock wave lithotripsy in the treatment of chronic pancreatitis

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Abstract

Pain is the most frequent symptom in chronic pancreatitis (CP) and has an important impact on quality of life. One of its major pathophysiological mechanisms is ductal hypertension, caused by main pancreatic duct stones and/or strictures. In this article, we focus on extracorporeal shock wave lithotripsy (ESWL) as a treatment for main pancreatic duct stones, which have been reported in >50% of CP patients. ESWL uses acoustic pulses to generate compressive stress on the stones, resulting in their gradual fragmentation. In patients with radiopaque obstructive main pancreatic duct (MPD) stones larger than 5 mm, located in the pancreas head or body, ESWL improves ductal clearance, thereby relieving pain and improving quality of life. In case of insufficient ductal clearance or the presence of an MPD stricture, ESWL can be followed by endoscopic retrograde cholangiopancreatography (ERCP) to increase success rate. Alternatively, direct pancreaticoscopy with intracorporeal lithotripsy or surgery can be performed (Acta gastroenterol. belg., **2021,** 84**, 620-626**).

Keywords: calcifications, chronic pancreatitis, pain, lithotripsy, ESWL.

Introduction

Chronic pancreatitis (CP) is a progressive, inflammatory disorder resulting in structural damage and fibrosis, which can ultimately lead to pancreatic exocrine and endocrine dysfunction (1,2).

Alcohol is considered the most common etiologic factor, accounting for 44-65% of the cases. Other risk factors for chronic pancreatitis are included in the TIGAR-O classification: **t**oxic-metabolic, **i**diopathic, **g**enetic, **a**utoimmune, **r**ecurrent and severe acute pancreatitis and **o**bstructive etiologic factors, such as pancreas divisum or rarely a bifurcation of the pancreatic duct (3-6).

Abdominal pain, which might be constant in nature or occur in flares (7), is the most disabling symptom of chronic pancreatitis, especially in patients with alcoholic etiology (8-10). The complex underlying pathophysiological pain mechanisms can be devided into three components (1,9). First, multiple neuropathic alterations take place, including an increase in size and number of intrapancreatic nerves, perineural inflammation and visceral and central sensitisation (11,12). Second, pancreas tissue inflammation, fibrosis and calcifications result in parenchymal hypertension and ischaemia (1). The third and probably easiest mechanism to target is ductal hypertension, which is caused by the formation of stones and/or strictures in the main pancreatic duct (13,14).

The general management of chronic pancreatitis includes life style changes such as abstinence from smoking and alcohol, analgesics using the "pain relief ladder" and treatment of pancreatic exocrine and endocrine insufficiency (3,8). However, one of the cornerstones in the treatment of pain in CP is relieving ductal hypertension, which can be achieved by ESWL, endoscopic (ERCP) or surgical methods (15-17).

In this article we review ESWL as a treatment for pancreatic ductal stones, its indications, efficacy and the rationale for combination therapy with ERCP.

Pancreatic ductal stones

Pancreatic stones are common, direct sequelae of chronic pancreatitis. The vast majority appears as calcified stones, but they can also project as radiolucent protein plugs. The latter may or may not become calcified during the further course of disease (18). Pancreatic calculi are estimated to occur in about 50% of patients, particularly in those with alcohol-induced CP (15,18). Their prevalence even increases with time and reaches up to approximately 100% at 14 years after disease onset (16,18).

Calcifications in CP are due to a supersaturation of the pancreatic fluid with calcium carbonate, which deposits in multiple layers over an amorphous inner nidus (1,17).

Pancreatic calculi are classified based upon type (radiopaque, radiolucent or mixed) and number (single or multiple stones). Furthermore, the location in relation to the duct (main pancreatic duct, side branches or pancreatic parenchyma) and the region of the pancreas (head, body or tail) are relevant in their therapeutic approach (17).

Treatment of pancreatic ductal stones – who to select for ESWL?

ERCP is recommended as first line therapy for small (<5 mm) or radiolucent main pancreatic duct stones, using pancreatic sphincterotomy with basket or balloon

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extraction, and for ductal stenting in the presence of a dominant main pancreatic duct stricture (8,18).

In uncomplicated CP with large (> 5 mm) MPD calculi, ESWL is considered the gold standard treatment. Patients with few radiopaque obstructive calcifications, wich are ideally located in the head or body of the pancreas, and secondary upstream ductal dilation are the best candidates (3,8,17). The use of ESWL is not recommended in patients with multifocal strictures, extensive calculi and/or pancreatic tail calculi, the last due to the risk of collateral damage to the spleen. Other contra-indications to ESWL include pregnancy, coagulopathy and the presence of a head mass under evaluation. In case of difficult visualisation, especially with radiolucent stones, prior endoscopic placement of a pancreatic duct stent or naso-pancreatic tube for the instillation of contrast may help target the shock waves at the time of the ESWL procedure (16,17).

Surgical options consist of drainage (in ductal obstruction), resection (in inflammatory masses or CP restricted to one part of the pancreas) or combined procedures. A detailed discussion of the surgical techniques, however, is beyond the scope of this article. Current evidence suggests that early surgical intervention within the first 2-3 years after diagnosis or symptom onset, may result in better pain control (8, 15,19). Several randomised controlled trials compared the effects of surgical and endoscopic interventions in the management of painful obstructive CP (20-23). All suggested superiority of surgery in treating pain, though most of these studies had important shortcomings, both in terms of methodology and the endoscopic techniques used. Endotherapy and surgery should probably be considered as complimentary rather than competitive strategies. Patients with few uncomplicated pancreatic duct stones or strictures, limited to the head of the pancreas, will benefit from endoscopy/ESWL as first line therapy. For patients with an inflammatory head mass or multiple strictures or calculi, surgery might be a better option (17,19). In any case, short-term follow-up after endoscopy and, if indicated, early referral to surgery is essential (23).

The ESWL procedure

ESWL was first introduced in 1980 for the desintegration of renal calculi (24), whereas the earliest description of its use in calcified chronic pancreatitis dates from 1987 (25).

In ESWL shock waves are focussed on ductal stones, which generates compressive stress on their outer surface, resulting in a gradual fragmentation. All lithotripters share four basic components: a shock wave generator, a focusing system, a coupling mechanism and a stone localization unit. There are three sources available for *generating shock waves,* where each has its own *focusing system*. The original method is electrohydraulic, meaning that the shock wave is produced by an electric spark-gap located at the base of a water-filled container, which directs the acoustic wave from an ellipsoidal reflector towards the stone at the focal point (26,27). Second, piezoelectric shock waves are generated by the stimulation of ceramics via high-frequency, high-voltage energy pulses. The motion of these piezoceramic elements, which are arranged within a hemispherical disc, creates ultrasonic vibrations, resulting in the production of a shock wave directed to the focal point (26,27). Finally, in electromagnetic devices, a high voltage is applied to an electromagnetic coil, which induces high-frequency vibration in an adjacent metallic membrane. This high-pressure wave is transformed into a shock wave and focused by an acoustic lens (26,27). At interfaces with different densities, such as the skin surface, a shock wave loses energy. Therefore water is used as a *coupling system*, as this has a density similar to that of soft tissue. In the first lithotripters the patient was placed in a water bath, whereas second and third generation machines use an enclosed water cushion to provide air-free contact with the patient's skin (27,28). Finally, *imaging systems* are used to localize the stone as well as to track the progress of treatment and consist of either fluoroscopy or ultrasonography (26,27,29). The use of the former results in the best fragmentation of pancreatic stones (26). Ultrasonography has the advantage of preventing exposure to ionizing radiation, however it may have low precision due to interposed air-filled bowels. Some third generation lithotripters combine both imaging systems in the same machine (26).

Shock waves generated by piezoelectric or electromagnetic systems generally have a smaller high-intensity focal zone compared with electrohydraulic lithotripters. Although this results in less tissue damage and less pain during the procedure, respiration may cause the stone to move out of the target zone, thereby leading to higher retreatment rates (26). There were no significant differences between electromagnetic and electrohydraulic systems regarding clearance of endoscopically unretrieveble pancreatic duct stones, however a lower number of shock waves per patient was administered in the electrohydraulic group, due to a greater power (26).

The optimal frequency of shock wave administration seems to be 90 shock waves per minute. Faster rates are associated with lower succes rates of ESWL in urolithiasis, especially in large stones (greater than 10 mm), whereas slower rates obviously increase the total procedure time (30).

If there is insufficient fragmentation, the procedure can be repeated, with the total number of ESWL sessions per patient ranging from 1 to 12 in reported series (31-35). In more than half of these patients only one ESWL procedure was performed (55-60%) but the mean number of sessions varied around 2-3 (13,31-37) (Table 1). How the technical success of ESWL was determined and whether there was a predefined maximum number of sessions varied greatly between the studies, highlighting

Table 1. — **Number of ESWL sessions**

Author, year	Study design	Patients, n (m/f)	Minimum ESWL sessions	Maximum ESWL sessions	Median/Mean ESWL sessions
Korpela et al, 2016 (31)	Retrospective	83 (59/24)	1	4	mean: 1
Li et al, 2016 (32)	Prospective	849 (603/246), PPC: 59 (51/8), Non-PPC: 790 (552/238)	1	PPC: 5, Non-PPC: 12	median: 2
Tandan et al, 2010 (33)	Prospective	1006 (663/343)	1	6	NR
Dumonceau et al, 2007 (34)	RCT	55 (43/12), ESWL alone: 26 (22/4), ESWL and endoscopy: 29 (21/8)	1	ESWL alone: 3, ESWL and endoscopy: 4	mean: 2
Tadenuma et al, 2005 (37)	Retrospective	117 (85/32)	NR	NR	mean: 5.8
Delhaye et al, 2004 (36)	Prospective	56 (46/10)	NR	NR	Clinical success group: mean 0.7, Clinical failure group: mean 1.5
Farnbacher et al, 2002 (13)	Retrospective	114 (NR)	NR	NR	mean: 2,5
Karasawa et al, 2002 (35)	Retrospective	24 (19/5)	1	12	mean: 3.6

ESWL, extracorporeal shock wave lithotripsy; NR, not reported; PPC, pancreatic pseudocyst; RCT, randomised controlled trial

Table 2. — **Comparative results**

Author, year	Study design	Patients, n (m/f)	Post-ESWL ERCP, n/N (%)	Complete ductal clearance, n/N (%)	Outcome in terms of pain relief, n/N (%)
Korpela et al, 2016 (31)	Retrospective	83 (59/24)	83/83 (100%)	69/83 (83%)	Complete or partial pain relief: 74/83 (89%)
Li et al, 2016 (32)	Prospective	849 (603/246), PPC: 59 (51/8), Non-PPC: 790 (552/238)	PPC: 58/59 (98%), Non-PPC: NR	696/849 (82%), PPC: 39/58 (67%), Non-PPC: 657/790 (83%)	Complete pain relief in PPC: 35/55 (64%), Partial pain relief in PPC: 14/55 (26%)
Vaysse et al, 2016 (54)	Retrospective	146 (96/50)	91/132 (69%)	75/132 (57%)	Clinical success[1]: 100/132 (76%)
Suzuki et al, 2013 (52)	Retrospective	479 (NR)	255/479 (53%)	356/479 (74%)	Pain relief: 435/479 (91%)
Milovic et al, 2011 (48)	Prospective	32 (24/8)	32/32 (100%)	13/32 (41%)	Complete pain relief: 17/32 (53%)
Merrill et al, 2011 (57)	Retrospective	30 (20/10)	30/30 (100%)	27/30 (90%)	NR
Tandan et al, 2010 (33)	Prospective	1006 (663/343)	1006/1006 (100%)	762/1006 (76%)	Significant relief of pain with decrease in analgesic use: 711/846 (84%)
Dumonceau et al, 2007 (34)	RCT	55 (43/12), ESWL alone: 26 (22/4), ESWL and endoscopy: 29 (21/8)	29/55 (53%)	NR	Pain relapse at 2 year follow up in ESWL alone: 10/26 (38%), in ESWL and endoscopy: 13/29 (45%)
Tadenuma et al, 2005 (37)	Retrospective	117 (85/32)	65/115 (56%)	65/115 (56%)	Significant relief of pain at 1 year follow up: 49/70 (70%)
Inui et al, 2005 (51)	Retrospective	555 (465/90)	237/555 (43%)	403/555 (73%)	Pain relief: 428/470 (91%)
Delhaye et al, 2004 (36)	Prospective	56 (46/10)	56/56 (100%)	27/56 (48%)	NR
Farnbacher et al, 2002 (13)	Retrospective	114 (NR)	NR	39/114 (34%)	NR
Karasawa et al, 2002 (35)	Retrospective	24 (19/5)	14/24 (58%)	13/24 (54%)	Relief of abdominal symptoms at 1 year follow up: 11/24 (46%)
Brand et al, 2000 (50)	Prospective	48 (35/13)	48/48 (100%)	21/48 (44%)	Complete pain relief: 17/38 (45%), Partial pain relief: 14/38 (37%)

ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; NR, not reported; PPC, pancreatic pseudocyst; RCT, randomised controlled trial. [1] Resolution of pain, no analgesic treatment, no acute pancreatitis and no surgical treatment for chronic pancreatitis 6 months after the ESWL.

the need for a standardised method to evaluate the efficacy of each ESWL session. In clinical practice, ESWL is often combined with ERCP and the ability to extract MPD stones is hereby used to assess the efficacy of ESWL. Alternatively, evaluation of fragmentation by CT scan or assesment of the reduction of MPD dilation could be markers of sufficient drainage.

ESWL for pancreas lithiasis is mostly performed by urologists. Jaben et al showed that a transition to gastroenterologist-directed ESWL resulted in a higher

mean number of shocks per ESWL session and improved ductal clearance, with more patients undergoing same-session ERCP (38).

ESWL can be carried out under moderate sedation, epidural anesthesia or general anesthesia. Epidural anesthesia seems to provide better patient tolerance than moderate sedation and by reducing patient movements, it facilitates targeting and fragmentation of the stones (39,40). In patients undergoing ESWL and ERCP consecutively, general anesthesia can be used (26).

Finally, data on post-ESWL pancreatitis prophylaxis are lacking because in most studies ESWL and ERCP were consistently combined.

Efficacy and complications of ESWL

Three meta-analyses studied the efficacy of ESWL in the treatment of calcified CP (41-43). In one meta-analysis by Moole et al, comprising data of 27 studies including 3189 patients, a complete pain relief and an improved quality of life were reported in 52,7% and 88,2% of pooled patients, respectively. Ductal clearance, defined as >90% clearance of the MPD stones, was complete in 70,7% of pooled patients (41). The most recent meta-analysis, by Van Huijgevoort et al, reported similar results with a complete ductal clearance in 69,8% and a complete pain relief in 64,2% of pooled patients (43). No conclusions were drawn about the effect of ESWL on exocrine and endocrine dysfunction, due to the heterogeneity of the different studies (41,43). In addition, several trials reported a long-term clinical succes of ESWL, both in terms of sustained pain relief as well as avoidance of surgery (31,36,37,44).

Comparative results of reported series are listed in Table 2. Factors associated with a higher rate of ductal clearance after ESWL are solitary stones, stones located in the pancreatic head, pancreatic stenting prior to ESWL and administration of secretin during ESWL (13,18,31,45).

ESWL is generally considered a safe procedure. In a prospective study with 634 patients major complications were classified into five groups, including post-ESWL pancreatitis, bleeding, infection, steinstrasse (acute stone incarceration in the papilla) and perforation (46). These complications and transient adverse events, such as skin erythema, mild tenderness of the region in contact with the shockwave head, asymptomatic hyperamylasemia, hematuria and gastrointestinal mucosal injury, were detected in 6,7% and 21,2% of the procedures, respectively (46). Other rare complications that have been described following ESWL include splenic rupture, pancreatico-biliary fistula, pancreatic fluid collections, perirenal hematoma, biliary obstruction, bowel perforation and liver trauma (17,41,43,46). Complication frequencies are listed in Table 3. Given that ESWL is complicated with post-procedural pancreatitis in around 4% of the patients (41), one could argue that adequate intravenous hydration and NSAID prophylaxis may be beneficial, analogous to post-ERCP pancreatitis prophylaxis.

Table 3. — **Complication frequencies**

Complication	Frequency (43, 46)
Pancreatitis	4%
Infection	1.4%
Bleeding	0.3%
Steinstrasse	0.4%
Perforation	0.3%
Pancreatico-biliary fistula	0.1%
Other: splenic rupture, pancreatic fluid collection, perirenal hematoma, biliary obstruction, bowel perforation, liver trauma	Case reports

Combination of ESWL and ERCP

As mentioned before, in most clinical studies it was common practice to perform an ERCP, with stone extraction and pancreatic stenting when indicated, after ESWL (13,31,36,37,44,47-50). In terms of ductal clearance, small studies showed a benefit of a complementary ERCP procedure, although to a varying degree (51,52). Since a complete ductal clearance results in better pain relief, both on the short and the long term, combination therapy might be the preferred strategy (13,37).

By contrast, Ohara et al suggested that ESWL alone is sufficient to treat MPD calculi (53). Only two studies, one randomised controlled trial and one retrospective clinical study, provided a head-to-head comparison between ESWL alone and a combination of ESWL and ERCP (33,54). Both showed that ESWL is a safe and effective treatment for patients with painful calcified CP. However, systematic combination with therapeutic ERCP added to the cost of patient care without any additional benefit in pain control.

A large cohort of patients with CP and pain showed that ductal hypertension was due to calcifications in 18%, strictures in 47% and a combination of both in 32% (55). The presence of an MPD stricture is associated with a higher risk of long-term pain relapse (37) and requires interventional ERCP with ductal stenting (8,18,56). Therefore, in clinical practice, the combined presence of strictures and calculi often necessitates the use of both ERCP and ESWL. This is also reflected in the current European Society of Gastrointestinal Endoscopy (ESGE) guidelines, which recommend restricting the use of endoscopic therapy after ESWL to patients without spontaneous clearance of pancreatic stones after adequate fragmentation by ESWL and to patients with MPD strictures (18). A flowchart for the choice of therapy is given in Figure 1.

Another matter of debate is the timing of ERCP after ESWL. Some data suggest that if additional ERCP is needed, it should be performed at least two days after ESWL, because of the possible presence of reactive edema in the MPD or surrouding tissues (57). Remarkably, in the randomised trial studying ESWL *versus* ESWL with ERCP, the endoscopic procedure was done immediately after the last ESWL session (33).

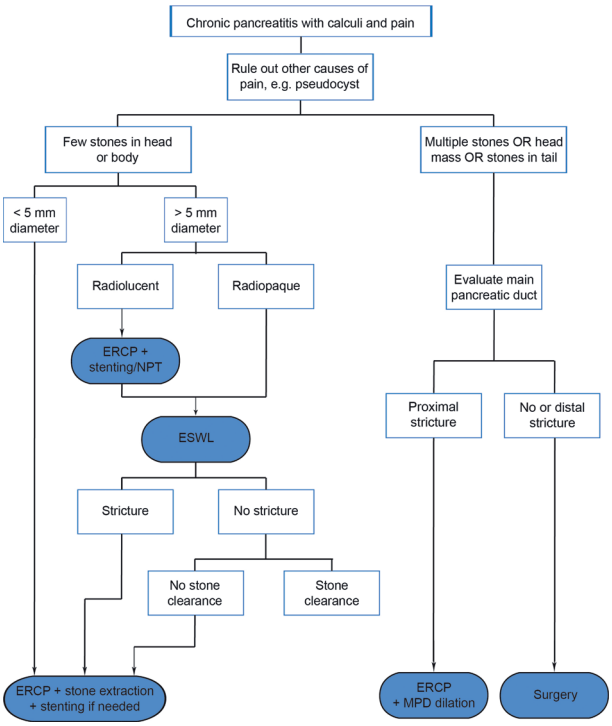

Figure 1. — Flowchart choice of therapy
ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; MPD, main pancreatic duct; NPT, naso-pancreatic tube.

Conclusion and future prospects

The current rationale for treating pain in chronic calcified pancreatitis is the relief of ductal hypertension. In this article, we focussed on ESWL as a treatment for MPD stones. Studies show that ESWL is an effective therapy in CP patients with large ductal stones in the pancreatic head and neck. In case of insufficient ductal clearance or strictures, additional ERCP improves outcome. In contrast, surgery is mostly reserved for patients failing endoscopic therapy or patients with suspected malignancy, although there are increasing data that early surgical interventions may lead to better pain control. To establish the position of early surgery as well as the position and timing of combination therapy (ESWL and ERCP) in the treatment of painful pancreatic duct calculi, we are in need of more prospective, randomised and controlled studies. Furthermore, the assessment of the efficacy of ESWL should be standardised.

Other strategies have been proposed to improve pain management and ductal clearance. First, the quality of peroral pancreaticoscopy has improved substantially. Data of its use with intracorporeal (electrohydraulic or laser) lithotripsy are sparse, but the first available results are promissing in terms of pain relief and ductal clearance (58). For now, this technique could provide a solution for stones that were not fragmented after adequately performed ESWL (17,18). However, the main pancreatic duct must be sufficiently dilated to allow passage of the pancreaticoscope.

Another approach to optimise ductal clearance is intravenous administration of secretin during ESWL, as suggested by Choi et al (45). Analogous to the use of diuretics in ESWL for ureteral stones, secretin stimulates pancreatic fluid secretion and results in a distention of the pancreatic duct. This creates a fluid-filled space around the stones, which enhances the efficacy of the shock waves. In addition, it might expedite flushing out stone fragments. Unfortunately, complication rates were not reported in this study.

Finally, the current treatments do not take into account our advances in the understanding of pain mechanisms in chronic pancreatitis (19). In particular, the neuroplastic changes and the mechanism of central sensitisation could serve as therapeutic targets in the near future.

Conflict of interest

None

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