Management of Pancreatic Duct Stones: Extracorporeal Approach

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KEYWORDS

• Extracorporeal shock wave lithotripsy • Chronic pancreatitis • Pancreatic calculi
• Endoscopic retrograde cholangiopancreatography

KEY POINTS

- Extracorporeal shock wave lithotripsy (ESWL) is a safe and effective procedure for large pancreatic calculi in the head and body not extractable by standard endoscopic retrograde cholangiopancreatography techniques as an alternative to surgery.
- ESWL in properly selected patients can lead to long-term pain relief in two-thirds of patients with a need for re-intervention in less than half on long-term follow-up.

INTRODUCTION

Chronic pancreatitis (CP), a disease of diverse etiology, is associated with progressive and irreversible changes leading to the destruction of functional pancreatic tissue with resulting loss of exocrine and endocrine function. Of the many etiologies, alcohol and smoking are the commonest in most industrialized nations. In India, an idiopathic variety of CP is prevalent in young adults who do not consume any alcohol.[1,2] Predisposition due to genetic mutation is a likely major contributing factor in these patients with idiopathic CP.[3,4] Irrespective of the etiology, pancreatic calculi (PC) are common sequelae of this disease. They are seen in over 50% of patients.[1,5] The incidence of calculi increases with time and may even reach 100% at 14 years.[6,7] These calculi eventually obstruct the main pancreatic duct (MPD) resulting in upstream ductal hypertension with subsequent development of parenchymal hypertension. This ductal hypertension is responsible for the recurring pain, often excruciating, which is a dominant symptom in patients with CP.

As CP is an irreversible disease, the aim of all therapies, both endoscopic and surgical is to remove the calculi and reduce the ductal hypertension with a resultant

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decrease in the pain.[2] Pain in CP is, however, multifactorial and can be secondary to tissue and neural ischemia, neural entrapment, nociception, or visceral and central sensitization.[8] These multiple mechanisms of pain explain the persistence of pain in some patients despite complete clearance of the MPD.[2,8] Pancreatic stone extraction can be done endoscopically with or without the use of lithotripsy or by surgical methods. Lithotripsy can be extracorporeal shock wave lithotripsy (ESWL) or intraductal lithotripsy using a pancreatoscope. For intraductal lithotripsy either electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) is used to fragment the calculi. In this article, we will discuss in detail the extracorporeal approach to clear the stones from the MPD in patients with CP.

CLASSIFICATION OF PANCREATIC CALCULI

PC are classified based on type, density, numbers, and location.

1. PC may be radio opaque, radiolucent, or mixed type. The majority of PC are radio opaque. In our experience with over 5000 patients, 79.2% of calculi were radio opaque, 16% were radiolucent while the rest (4.7%) were of the mixed type.[2] Radio opaque calculi were seen in 62% of patients in a multi-center survey of 879 patients. Stones were more frequent in men who were heavy alcohol consumers (>80 g/day) and heavy smokers (>20 cig/day).[9]
2. PC may be single or multiple. In the above-mentioned study of over 5000 patients, 75.1% of PC were single while the rest were multiple (**Table 1**).[2]
3. Stones were also classified based on their location, that is, in the head, body, or tail. In 51.5% of patients in our study, PC were located in the head region, 21.4% in the body, and 7.4% in the tail area; 15.9% were extensive and located in multiple areas, that is, head, body, and tail regions (see **Table 1**).[2]
4. PC may be intraductal, either MPD, in secondary branches, or in the parenchyma.

PC > 5 mm in size, located in the MPD are difficult to extract by the standard procedure of endoscopic retrograde cholangiopancreatography (ERCP) and pancreatic sphincterotomy. Balloon trawl or baskets are used to clear the pancreatic duct (PD) of calculi. PC, especially those in idiopathic CP are dense, spiculated, and adherent to the ductal mucosa. This makes their extraction challenging. Besides, the relatively thin diameter of the MPD, as well as its tortuosity, makes the passage of endoscopic accessories difficult. The European Society of Gastrointestinal Endoscopy (ESGE) in its clinical guidelines states that for uncomplicated and painful CP with calculi >5 mm in MPD, ESWL should be performed, followed by subsequent ERCP to clear the duct.[10,11] These guidelines were not changed over 7 years, despite advances in technology and technique indicating that ESWL is an established therapy and the standard of care in managing large PC in the MPD.

PATHOGENESIS OF STONE FORMATION AND ITS COMPOSITION

PC consists of a central nidus over which layers of calcium carbonate are deposited. The nidus is amorphous and consists of small quantities of trace elements such as nickel, chromium, and iron. This nidus can be identified and located on scanning electron microscopy and energy dispersive x-ray fluorescence.[12] Over this central nidus, calcium carbonate or calcite is deposited in layers and forms the typical PC.

Precipitation of calcium carbonates in the pancreatic juice is the initial event and dependent on the concentration of the pancreatic stone protein (PSP). Various factors including genetic variants cause reduction in the PSP. This reduction results in supersaturation of calcium carbonate in the pancreatic juice and its eventual deposition in layers

Table 1
Characteristics of patients and extracorporeal shock wave lithotripsy features in 5124 patients

		Number	%
Age	<40 years	3541	69.1
	41–60 years	1035	20.1
	>60 years	548	10.6
Female		*1655*	*32.3*
Etiology	*Alcohol and/or Smoking*	*495*	*9.6*
	Idiopathic	*4629*	*90.4*
Stone characteristics	Single	3851	75.1
	Multiple	1273	24.8
	Radio opaque	4063	79.2
	Radiolucent	820	16.0
	Mixed	241	4.7
Stone location	Head	2824	51.1
	Body	1099	21.4
	Tail	384	7.4
	Head/Body/Tail	817	15.9
Associated stricture		1153	22.5
ESWL sessions	≤4	4920	96
	>5 (maximum 8)	204	4
Fragmentation	Complete	3722	72.6
	Partial	886	17.3
	Unsuccessful	516	10

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over the inner nidus.[13] Irrespective of the etiology of CP, the stricture and composition of the PC are similar indicating a common pathway for pancreatolithiasis.[13]

TECHNIQUES OF PANCREATIC DUCTAL STONE EXTRACTION

1. Various endoscopic options exist for the extraction of stones from the MPD. For small calculi, the standard procedure of ERCP and pancreatic sphincterotomy followed by either a balloon trawl or extraction with a basket is recommended. However, the success rate at ERCP and stone extraction are not high in patients with CP. A few studies have revealed clearance rate of 9% in 1041 patients, and 14% in 1834 patients.[14–16] Mechanical lithotripsy for PC is not a procedure of choice because of poor results in extraction and unacceptably high incidence of adverse effects.[17] A retrospective analysis of over 700 patients revealed a complication rate thrice as high as for biliary mechanical lithotripsy.[17] This, as mentioned earlier, is because of the thin diameter of the MPD as well as its tortuosity, as compared to the common bile duct. Manipulation of large accessories in the main MPD is technically challenging and often not very efficient, resulting in many adverse effects.[2] Factors associated with poor results include stones > 10 mm in size, diffuse distribution of calculi, stone impaction in MPD, and a stricture proximal to the calculi.[15,18]

2. Lithotripsy of PC can be performed extracorporeally using ESWL or intraductally using a per oral pancreatoscope with either EHL or LL. These techniques are specifically meant for large and dense calculi which cannot be extracted by the above-mentioned standard ERCP. ESWL has been shown to clear over 80% of PC after an initially failed endotherapy.[14]
3. Chemical dissolution of the stones using an anti-epileptic compound Trimethadione was first reported around four decades ago.[19] The same group has recently published a case series of 13 patients where the compound was used successfully.[20] These results need to be validated by multi-center trials before their acceptance for widespread use. Limitations exist in the form of long duration of therapy required to achieve dissolution. These compounds are seldom used routinely in present-day practice of management of PC.
4. Surgical procedures either in the form of drainage or resection or their combination are well-accepted modes of managing PC. These were the standards of care before the advent of advanced endoscopic procedures. Detailed comparison of pros and cons of ERCP/ESWL and surgery are beyond the scope of this article. Briefly, two earlier studies showed the surgery was superior to endotherapy. In one of these, after a 5-year follow-up, pain was absent in 15% of the endoscopy group versus 34% in the surgery group.[21] This indicated that neither method gave satisfactory results. The other study had only 39 patients and there was selection bias in the two arms of the study that had been highlighted by several experts.[22] A randomized controlled trial revealed that ESWL was effective in providing pain relief in 62% of patients on a 4-year follow-up.[23] Results of ESWL versus surgery were analyzed in a retrospective study of 81 patients with CP. Similar pain relief was reported on follow-up of over 5 years. However, surgery reported more morbidity and higher cost.[24] The issue is not to compare surgery with ESWL but to decide which patient should go for surgery and which for ESWL. ESGE guidelines suggest that early referral for surgery should be advised in case of failure of endotherapy.[11] Both these modalities are complimentary and not competitive.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

ESWL was first introduced in the 1980s for managing urinary tract calculi.[25] However, its indications were quickly expanded to include the gastrointestinal tract and has since been used regularly for fragmenting biliary and pancreatic calculi.[26] Today, it is accepted as the standard of care in the management of large PC in the MPD.[1,2,5,11,27–29]

PRINCIPLES OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

ESWL is based on the principle of shock wave energy. The present-day lithotripters used for fragmenting PC have an electromagnetic device for generating these shock waves. The activated electromagnetic device releases high-energy waves in an enclosed space. These high-energy waves are directed through a cone enclosing water onto the patient's abdominal wall, focusing on the PC. When these waves pass through substances of different acoustic impedance, a compressive stress is produced at the interphase of the two densities. These stresses overcome the inherent tensile strength of the target, which in this case is the PC. Fragmentation of the margin occurs. The shock waves travel through the calculus and are reflected from the posterior surface of the stone resulting in further fragmentation.[30] Presently, at our institute, a third-generation electromagnetic dual-focus lithotripter is used for ESWL. This lithotripter

has the facilities for focusing on the calculi either by ultrasound or by fluoroscopy. From our earlier experience, a shock wave rate of 90/minute at a voltage of 16 kv is ideal for fragmenting calculi.[30] Shockwaves at a higher frequency have a tendency to reflect from the calculi and interfere with the efficacy of oncoming shockwaves.[30]

INDICATIONS AND CONTRAINDICATIONS

ESWL is indicated in all patients with painful uncomplicated CP and large radio opaque or radiolucent PC which are not amenable to extraction by the standard procedure of ERCP.[1,2,10,11,27,28,31,32] ESWL should be avoided in patients with extensive calculi involving the head, body, and tail regions. Patients with multiple strictures (chain of lake appearance), as well as suspicious head mass, presence of moderate to severe ascites, should not be taken up for ESWL. Calculi in the pancreatic tail are not targeted at ESWL because of the risk of injury to the spleen.[33] Cholangitis or coagulopathy secondary to biliary obstruction and sepsis should be first controlled and patient subjected to ESWL subsequently.[1,11,32] The aim of ESWL is to achieve fragmentation of the PC to <3 mm in size or demonstrate a decrease in density heterogeneity of the stone mass.[1,11,12,32] Small fragmented calculi either pass off spontaneously or are easily extracted at a subsequent ERCP.

Protocol of Extracorporeal Shock Wave Lithotripsy in Radio Opaque and Radiolucent Pancreatic Calculi

A standard protocol has been devised at our center for performing ESWL (**Fig. 1**).[1,2,32] The presence and size of calculi are confirmed by cross-sectional imaging (MRCP/CT), in those patients who are candidates for ESWL and have large radio opaque PC in the head and body[1,2,32] At our center, fluoroscopic guidance is the preferred method for localizing radio opaque calculi. We carry out the procedure predominantly in a supine position under epidural anesthesia and sedation.[34] Total intravenous analgesia and general anesthesia have occasionally been used for the procedure in a few of our patients as well as at other centers.[2,34]

Between 5000 and 6000 shocks are delivered per session, at a rate of 90/minute and energy level of 16 kv. ESWL is performed on successive days till adequate fragmentation is achieved. An ERCP and pancreatic sphincterotomy is performed subsequently and fragments are cleared. A single pigtail plastic is placed in MPD in those patients who have achieved partial fragmentation as well as in the presence of associated stricture. These stents are removed at a subsequent follow-up between 3 and 6 months after the index procedure, once the MPD is free of any obstructive pathology. A few centers used IV secretin before ESWL as this creates a fluid stone interphase similar to ureteric calculi and results in successful fragmentation.[35] The successful use of a small, mobile, lithotripter has been reported in a small series of patients.[36]

For large radiolucent calculi not extracted at ERCP, a nasopancreatic tube (NPT) is placed in the MPD. This facilitates the use of contrast to localize the PC. The presence of the fluid around the PC also facilitates good fragmentation.[1,2,32] The rest of the protocol is similar to what has been detailed for the radio opaque calculi. An alternative for fragmenting radio lucent calculi would be the use of ultrasound for focusing on the PC, instead of placement of a NPT.

TECHNICAL AND CLINICAL SUCCESS

The following criteria are employed to assess the MPD clearance following ESWL.[1,2,32,37,38]

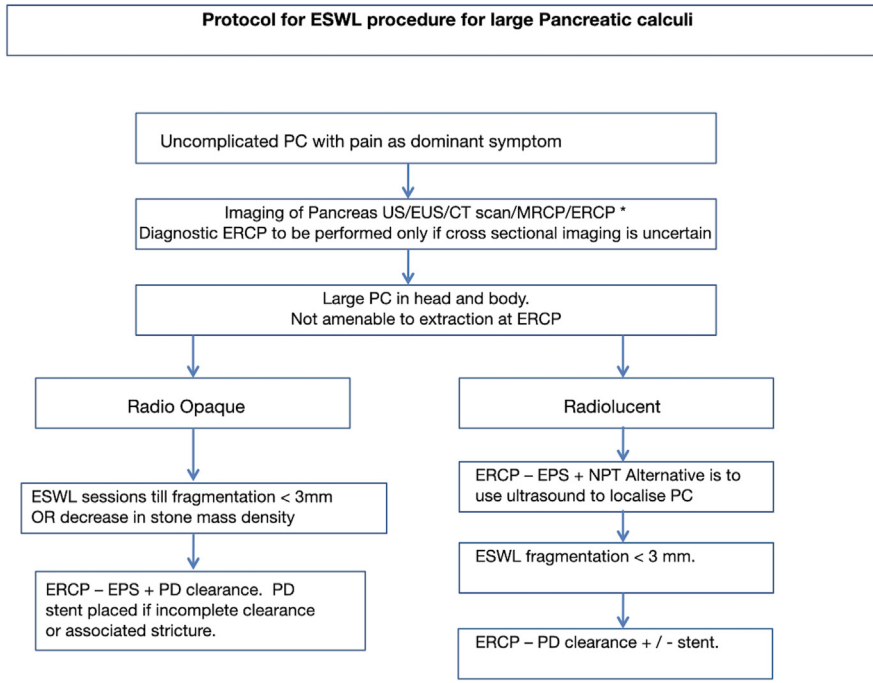

Fig. 1. Protocol followed at Asian Institute of Gastroenterology for extracorporeal shock wave lithotripsy of large PC (* if adequate information is not available with a single imaging technique, then a second imaging procedure was performed). CT, computed tomography; EPS, endoscopic pancreatic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; NPT, nasopancreatic tube; PD, pancreatic duct; US, ultrasound. (*Data from* Refs.[1,2])

1. Complete clearance—clearance of >90% of stone volume.
2. Partial clearance—clearance between 50% and 90% of stone volume.
3. Unsuccessful clearance—clearance < 50% of stone volume.

Clinical success is usually assessed based on pain relief, reduction in number of analgesics used, reduction in number and days of hospitalization, and overall improvement in quality of life.

In our experience of over 5000 patients who have undergone ESWL, complete stone clearance was seen in 3722 out of 5124 patients (72.6%), partial clearance in 17.3%, and clearance was unsuccessful in the rest.[2] Significant pain relief was seen in 82.6% on 6 months follow-up (see **Table 1**) (**Figs. 2–4**).

An associated stricture was present in 1153 (22.5%) patients. More than 84% of the patients required three or lesser sessions of ESWL while 3.9% required five sessions or more (maximum of eight sessions) to achieve fragmentation (see **Table 1**).[2] Strictures have been reported approximately in 50% of patients with calculi in the head.[11]

Pain relief was evaluated in a meta-analysis of 27 studies with 3181 patients. ESWL achieved complete clearance in 70% and partial in 22% of patients.[38] On a 2-year follow-up, pain was absent in 52.7% and mild to moderate in 33.4%. Quality of life improved in 88.2% of patients.[38] Other studies have revealed that patients who have no pain relapse at 2 years, rarely have significant pain at a later period. This

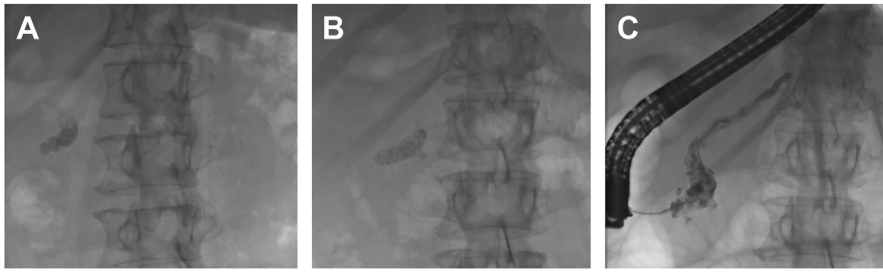

Fig. 2. ESWL procedure for radio opaque PC in the head. (*A*) Pre-ESWL dense radio opaque calculi in the head. (*B*). Post-ESWL reduction in stone density. (*C*) Pancreatic duct calculi fragments cleared during ERCP.

indicates that a good relief from pain in the first 2 years following ESWL is likely to be sustained for a longer period.[23,39] Complete stone clearance was seen in most of these patients with pain relief.

ESWL is established as a standard of care for the management of large PC in centers all over the world.[1,2,27,40–42] ESGE guidelines state that all patients with painful PC > 5 mm especially in the head region should undergo ESWL and subsequent ERCP to clear the MPD.[10,11] An earlier meta-analysis of 17 studies with 489 patients revealed ductal clearance rates between 37% and 100%.[43] A systemic review of over 1000 patients showed successful clearance in 89%.[44]

As CP, especially in our country, is a disease of the young, the long-term effects of ESWL on pain relief following stone clearance are important. Our own experience of 8 years of follow-up has revealed satisfactory pain relief in 60% of patients.[45] This follow-up has now extended to 18 years with similar results. Pain recurrence was present in a few patients even after complete ductal clearance indicating that other mechanisms of pain are also responsible for the pathogenesis.[8,32] Other studies revealed pain relapse between 30% and 50% of patients on follow-up of up to 14 years and 6.9% of these patients required surgery.[11] Similar long-term pain relief and avoidance of surgery have been reported elsewhere.[5,41,46,47] A retrospective long-term follow-up study of 120 patients showed complete pain relief in 50% of patients with avoidance of narcotic use. Partial relief was seen in up to 84% of patients.[48] Higher pain relief has been reported in our patients following treatment as compared to the West because of a higher incidence of alcohol, smoking, and use of opioids in the West.[49,50] It is also a possibility that our patients are more tolerant of pain.[2]

Fig. 3. ESWL procedure for radio opaque PC in head and body. (*A*) Pre-ESWL dense radio opaque calculi in head and proximal body. (*B*) Post-ESWL, majority of stones cleared. (*C*) Pancreatic duct calculi cleared during ERCP.

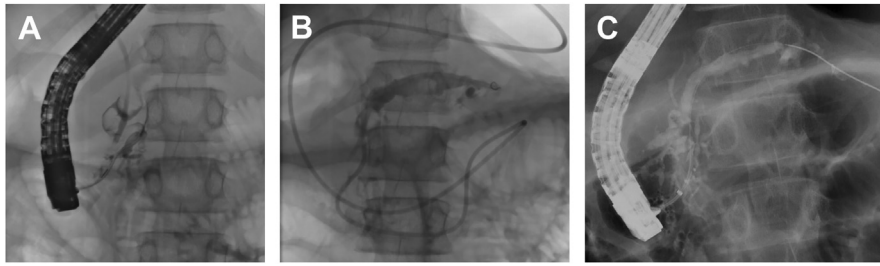

Fig. 4. ESWL procedure for radiolucent pancreatic stones. (*A*) Pre-ESWL multiple large radiolucent calculi in head. (*B*) NPT in situ to localize the calculi. (*C*) Post-ESWL fragmented calculi cleared at ERCP.

A recurrence rate of 22.8% has been reported in patients who had complete MPD clearance, over long-term follow-up.[1,2,47] However, pain recurrence was seen in much lesser numbers. The conclusion is that patients with asymptomatic recurrence of calculi need not undergo repeated endoscopic procedures. A comparison of results of ESWL from different centers is shown in **Table 2**.

COMPLICATIONS OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

ESWL is a safe procedure in large volume centers with very few serious adverse effects or mortality being reported. Our series of over 5000 patients had mild and self-limiting complications in 22% of patients.[2] These included pain at the site of contact of the water cushion in 13.5%, ecchymosis of skin at the site of contact in 19%, and mild pancreatitis in 3.5%.[1,2] Severe post-ESWL and post-ERCP pancreatitis were seen in 0.5% of patients. The incidence of pancreatitis is not higher in ESWL followed by ERCP as compared to ERCP alone. There was no mortality in the study.[2] A meta-analysis of over 1800 patients including 1000 from our center reported a complication rate of 5.8% with a single mortality (0.05%).[10] Another study reported an adverse event rate of 6.7% in over 1470 ESWL procedures.[51] Accurate focusing of the shock-waves on the PC is easier with third-generation lithotripters. This combined with restriction of patient movement with efficient anesthesia help in reducing collateral tissue damage and minimizing complication.[1,31,32,34] A number of rare complications

Table 2
Studies showing efficacy of extracorporeal shock wave lithotripsy for pancreatic calculi

Author	No. of Patients	Complete Clearance (%)	Pain Relief (%)	Follow-up (mo)
Tandan et al,[2] 2019	5124	72.9	82	6
Farnbacher et al,[14] 2002	125	64	48	29
Dumonaceau et al,[23] 2007	29	-	55	51
Delhaye et al,[27] 1992	123	59	85	14
Costamagna et al,[28] 1997	35	74	72	27
Tandan et al,[32] 2010	1006	76	84	6
Kozarek et al,[42] 2002	40	-	80	30
Tandan et al,[45] 2013	272	76	60	96
Adamek et al,[46] 1999	80	-	76	40

have been reported following ESWL. These include hepatic sub-capsular hematoma, biliary obstruction, splenic abscess and rupture, bowel perforation, necrotizing pancreatitis, and liver trauma.[33,52–54] Most of these have been reported in anecdotal case reports. Steinstrasse (street of stones) occurs due to acute stone incarceration at the papilla and may requires early ERCP and pancreatic sphincterotomy to reduce the pain.[11] As technology and techniques improve the incidence of these complications is likely to reduce further.

LIMITATIONS OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

Despite being the standard of care and widely used as the first-line therapy for the large PC, ESWL has limitations too.

1. Failure of fragmentation in approximately 10% of patients has been reported.[1,2] If such patients could be identified before ESWL, they could be subjected to an alternative procedure. Calculi with a density of over 820.5 HU on non-contrast CT (NCCT) have reduced fragmentation rates.[55] Use of NCCT for renal calculi has been reported earlier.[56,57] Another study reported better fragmentation when mean stone density was <375.4 HU on NCCT.[58] A validation of the cut-off value on NCCT could help avoid ESWL in those patients who have high stone density and are poor candidates for this procedure.
2. Recurrence of calculi has been reported in 23% of long-term follow-up.[1,2] Pharmacological agents such as Trimethadone have been successfully used on limited patients in Japan.[19,20] Development of such compounds which can dissolve recurring calculi can minimize repeated endoscopic interventions.
3. Effect of ESWL on the development of exocrine and endocrine insufficiency has not been clarified. Our own study reported improvement in diabetes in a few patients.[32] The numbers are, however, too small to draw any significant conclusion. A few studies reported improvement in both exocrine and endocrine functions, while others have failed to do so.[46,59,60] A recent long-term follow-up study from our center demonstrated that early ductal intervention in CP may delay the onset of diabetes.[61] It is possible that early intervention can alter the course of the disease and its various sequelae.
4. ESWL and its role in preventing the development of pancreatic carcinoma have not yet been evaluated.
5. Limitation in efficacy and success of fragmentation at ESWL has been reported in low-volume centers.[15,16]
6. Special precautions are needed in patients with implanted pacemakers and defibrillators.[62]

A topic of debate has been the use of ERCP after successful and complete fragmentation by ESWL. Two uncontrolled studies revealed that if ESWL is performed adequately, the fragments could spontaneously clear obviating the need for ERCP.[60,63] A randomized trial compared ESWL alone and ESWL followed by ERCP demonstrated equal efficacy between the two arms, but the cost of the procedure is higher in the patient who underwent both procedures.[23] In our experience, the calculi in idiopathic CP, commonly seen at our centers are denser and adherent, and as a practice, we perform ERCP after successful fragmentation.[1,2,32]

COMPARISON WITH OTHER MODALITIES OF TREATMENT OF PANCREATIC CALCULI

Single-operator pancreatoscopy with intraductal lithotripsy (SOPIL), either using EHL or LL is a technique in evolution, and a detailed discussion on comparison with ESWL

as well as the pros and cons of surgical removal of PC is beyond the scope of this article. A study comparing 240 patients who underwent ESWL with 19 who underwent SOPIL concluded that both are safe and effective and SOPIL may require lesser sessions for complete fragmentation.[64] SOPIL is emerging as an attractive alternative to ESWL. ESGE guidelines, however, recommend that pancreatoscope guided lithotripsy be used when ESWL is not available or PC are not fragmented after an adequately performed ESWL.[11]

A recent study comparing early surgery versus endoscopy first approach on relief of pain in patients with CP reported that lower pain scores were seen in patients who underwent early surgery. This was a randomized clinical trial with 44 patients in each arm and authors have suggested that further studies are needed to replicate these findings.[65]

SUMMARY

ESWL is a safe and effective procedure for large PC not extracted by the standard technique at ERCP. In properly selected patients, it should be offered as the first line of therapy. Stone clearance as well as short- and long-term pain relief have been well established with this relatively safe procedure. At present, it is considered the standard of care in the management of large PC.

CLINICS CARE POINTS

- ESWL is a very effective technique for large radio opaque or radiolucent PC in uncomplicated painful CP as an alternative to surgery
- ESWL should be avoided in patients with extensive calculi, multiple pancreatic duct strictures, suspected head mass, and isolated pancreatic tail calculi
- ESWL can lead to complete stone clearance in three-fourths of patients.
- Long-term pain relief is achieved in nearly two-thirds of patients after ESWL
- Less than half of the patients require re-intervention after stone clearance with ESWL
- Future prospective studies need to compare this approach with intraductal lithotripsy

DISCLOSURE

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