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Success of extracorporeal shock wave lithotripsy and ERCP in symptomatic pancreatic duct stones: a systematic review and meta-analysis

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Authors

Nadine C.M. van Huijgevoort*,[1], Joyce V. Veld*,[1], Paul Fockens[1], Marc G. Besselink[2], Marja A. Boermeester[2], Marianna Arvanitakis[3], Jeanin E. van Hooft[1]

Institutions

1 Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, location AMC, Amsterdam, The Netherlands
2 Department of Surgery, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, location AMC, Amsterdam, The Netherlands
3 Department of Gastroenterology and Hepatology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

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Corresponding author
Jeanin E. van Hooft, MD, PhD, MBA, Amsterdam Gastroenterology and Metabolism, Dept. of Gastroenterology and Hepatology, C2-115, Amsterdam UMC, location AMC, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Fax: +31206917033
j.e.vanhooft@amsterdamumc.nl

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ABSTRACT

Background and study aims Pain is the most frequent and dominant symptom of chronic pancreatitis. Currently, these patients are treated using a step-up approach, including analgesics and lifestyle adjustments, endoscopic, and eventually surgical treatment. Extracorporeal shock wave lithotripsy (ESWL) is indicated after failure of the first step in patients with symptomatic intraductal stones larger than 5 mm in the head or body of the pancreas. To assess the complete ductal clearance rate and pain relief after ESWL in patients with symptomatic chronic pancreatitis with pancreatic duct stones, a systematic review and meta-analysis was performed.

Patients and methods A systematic literature search from January 2000 to December 2018 was performed in PubMed, the Cochrane Library, and EMBASE for studies on ductal clearance rate of ESWL in patients with symptomatic chronic pancreatitis with pancreatic duct stones.

Results After screening 486 studies, 22 studies with 3868 patients with chronic pancreatitis undergoing ESWL for pancreatic duct stones were included. The pooled proportion of patients with complete ductal clearance was 69.8% (95% CI 63.8–75.5). The pooled proportion of complete absence of pain during follow-up was 64.2% (95% CI 57.5–70.6). Complete stone fragmentation was 86.3% (95% CI 76.0–94.0). Post-procedural pancreatitis and cholangitis occurred in 4.0% (95% CI 2.5–5.8) and 0.5% (95% CI 0.2–0.9), respectively.

Conclusion Treatment with ESWL results in complete ductal clearance rate in a majority of patients, resulting in absence of pain during follow up in over half of patients with symptomatic chronic pancreatitis caused by obstructing pancreatic duct stones.

Introduction

Chronic pancreatitis is an inflammatory condition of the pancreas, in which development of fibrosis and loss of pancreatic parenchyma may lead to impaired endocrine and exocrine pancreatic function. Chronic pancreatitis is most frequently caused by alcohol and smoking, with idiopathic, genetic predisposition and autoimmunity as less frequent causes [1–3].

Pain is the most frequent and dominant symptom and has a highly variable clinical presentation, differing in chronicity and severity [4]. Pathogenesis of pain in chronic pancreatitis is mul-

* Drs. Van Huijgevoort and Veld: These authors contributed equally.

tifactorial, but poorly understood. Intraductal stones and/or strictures may lead to pancreatic ductal and pancreatic parenchymal hypertension, causing pain [5]. More recently, activation of intrapancreatic nociceptors, hypertrophy, and inflammation of intrapancreatic nerves and abnormal pain processing in the central nervous system have also been implicated [6].

For management of pain in chronic pancreatitis, a step-wise treatment is advocated, starting with lifestyle modifications, analgesics, plus, in selected patients, endoscopic therapy and/or extracorporeal shock wave lithotripsy (ESWL) [7–9] with surgical decompression of the pancreatic duct as a last step (**Supplementary Fig. 1**). Endoscopic therapy and/or ESWL is indicated in patients with painful chronic pancreatitis with an obstructed main pancreatic duct (PD) in the head/body of the pancreas [8–10] (**Supplementary Fig. 2, Supplementary Fig. 3**, ▶**Video 1**, ▶**Video 2**). Hypothetically, (endoscopic) PD drainage causes decompression of the duct, with a decrease in intraductal pressure and subsequent relief of pain as a result. For clearance of one or multiple radiopaque obstructive intraductal stones ≥ 5 mm located in the head/body of the pancreas, patients should be treated with ESWL, whereas endoscopic retrograde cholangiopancreatography (ERCP) is indicated for stones that are radiolucent or smaller than 5 mm. Use of endoscopic therapy after ESWL has to be restricted to patients with PD strictures and no spontaneous clearance of the intraductal stones after adequate fragmentation by ESWL [8, 11]. Clinical response to endoscopic therapy and/or ESWL should be evaluated 6 to 8 weeks after the procedure. If insufficient, surgical options have to be considered [9].

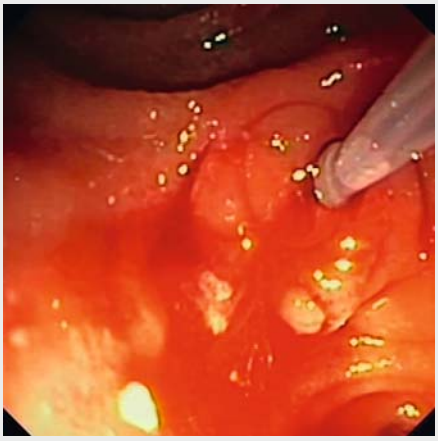
Recently, retrospective and prospective cohort studies have been published evaluating the efficacy and safety of ESWL in patients with symptomatic chronic pancreatitis. Therefore, the aim of this systematic review was to evaluate the efficacy of ductal clearance and pain relief from ESWL in treatment of patients with chronic pancreatitis with obstructing PD stones.

Patients and methods

Study selection

PRISMA guidelines reporting on meta-analyses and systematic reviews of observation studies were applied. A systematic literature search from January 2000 to December 2018 was performed in PubMed, the Cochrane Library, and EMBASE for studies on ductal clearance rate of ESWL in patients with symptomatic chronic pancreatitis with PD stones. Only full-text articles written in English were considered eligible. Search terms used were “lithotripsy,” “extracorporeal shock wave lithotripsy,” “stones,” “pancreas,” and “chronic pancreatitis” restricted to title, abstract, and keywords. Independent reviewers (NvH and JV) screened each title and abstract for eligibility. Duplicate references were excluded. Discrepancies were solved through discussion and consensus, and in case of any doubt resolved with the senior author (JvH). Next, the eligibility of full text articles was assessed similarly. References of included articles were checked manually for studies that had not been identified in the primary search. Inclusion criteria were consecutive series of patients with chronic pancreatitis undergoing ESWL for symptomatic PD stones, reporting of complete ductal clearance, and availability of a full article written in English. Exclusion criteria were studies with fewer than five patients and reviews, editorials, abstracts, letters, animal studies, or studies in children. The cut-off for minimum cohort size was arbitrarily chosen.

Video 1 A 50 year-old male patient with chronic calcifying pancreatitis and continuous pain had previously undergone ESWL with stone fragmentation. ERCP followed with pancreatic sphincterotomy and fragmented stone extraction is shown with a standard balloon catheter.



Video 2 A 60 year-old woman with chronic calcifying pancreatitis and continuous pain had previously undergone ESWL with partial stone fragmentation. The patient had already a previous pancreatic sphincterotomy and stone extraction was performed with a basket catheter, introduced along the guidewire, in the pancreatic duct. The catheter is flushed with saline during manipulation to facilitate fragment evacuation.

Data extraction

The following variables were extracted, when available: study design, publication year, country of origin, number of patients undergoing ESWL, stone size (mean), complete stone fragmentation rate, complete stone fragmentation rate after first session, complete ductal clearance, complete ductal clearance after first session, number of session required for complete ductal clearance (mean), complications, follow-up time, pain relief, complete pain relief, partial pain relief, quality of life, exocrine insufficiency, and endocrine insufficiency.

Outcomes

Our primary outcome was complete ductal clearance rate. Complete ductal clearance was defined as the ability to retrieve at least 90 % of all pancreatic duct stones with ESWL, including additional ERCP when applied. Secondary outcomes were patients being completely pain free after ESWL, complete ductal clearance after the first ESWL session, stone fragmentation rate, stone fragmentation rate after the first ESWL session, post-procedural pancreatitis rate, post-procedural cholangitis rate, and exocrine and endocrine insufficiency. Stone fragmentation was defined as the rupture of stones by ESWL.

Methodological quality assessment

All included studies were assessed for quality using The Oxford Centre for Evidence-Based Medicine Levels of Evidence checklist. The Newcastle–Ottawa Quality Assessment Scale for cohort studies was used to evaluate any risk of bias [12]. Any doubt regarding the methodological quality assessment was discussed by two independent reviewers (NvH and JV).

Statistical analysis

Normally distributed variables were reported as means ± standard deviation (SD), non-normally distributed variables as medians and interquartile range (IQR). Categorical data were reported as proportions. Heterogeneity among studies was assessed using the I^2 statistic (I^2 value of ≥ 50 % represented significant heterogeneity) [13]. Considering the variability of methods and populations in the included studies, a random effects model was used for analyses. Pooled proportions were calculated and presented as percentages with 95 % confidence intervals (95 % CI). Funnel plots of complete ductal clearance as our primary outcome were created to identify possible publication bias. Sensitivity analysis was performed by excluding retrospective studies and by excluding all studies in which post-ESWL ERCP was not performed. Analyses were performed with MedCalc version 18.5 (MedCalc Software).

Results

Study selection

The initial search contained 486 articles (**Supplementary Fig. 4**). After removal of 109 duplicates, 377 studies remained of which 342 were excluded based on title and abstract. After full text review, 22 eligible articles with 3868 patients undergoing ESWL for pancreatic duct stones were included. Cross-reference did not reveal any studies missed with the initial search. No studies were excluded as a result of inadequate methodological quality (**Supplemental Table 1**). An overview of study characteristics can be found in ▶ **Table 1**.

Complete ductal clearance

All studies reported on complete ductal clearance (▶ **Table 2**). Meta-analysis of pooled proportions revealed complete ductal clearance in 69.8 % (95 % CI 63.8–75.5), as shown in ▶ **Fig. 1a**. However, the test for heterogeneity did reveal a $P < 0.001$ with a corresponding I^2 of 92.6 % (95 % CI 90.1 to 94.5). ▶ **Fig. 1b** represents publication bias for complete ductal clearance. As only two studies assessed complete ductal clearance after first ESWL session [14, 15], pooled analysis was not performed. Reported proportions of patients with complete ductal clearance after the first ESWL session were 60.2 % [14] and 68 % [15].

Pain relief

Pain intensity was heterogeneously reported among the respective studies (▶ **Table 2**). Pain intensity was measured using the Visal Analogue Scale (VAS) in four studies [14, 16–18]. The 3-point Likert-Scale was used in three studies to define pain intensity [14, 19, 20]. The 4-grade Pain-Scale was used in two studies as a measure of pain intensity [21, 22]. One of the authors [23] used the 5-point Likert-Scale to define pain intensity. In another study [24], a combination of the Visual Analogue Scale and the duration and frequency of the pain attacks was used to define pain intensity. One author [25] used the number of hospital admissions for pain during the follow-up period to define pain intensity. The proportion of patients being completely pain free following ESWL was reported in 6 studies [16, 17, 19, 20, 23, 24], showing a pooled proportion of 64.2 % (95 % CI 57.5–70.6) (▶ **Fig. 2**). The test for heterogeneity revealed $P = 0.014$ with a corresponding I^2 of 64.8 % (95 % CI 15.3–85.4). As the definition of partial pain relief was either highly heterogeneous or not defined amongst the respective studies, pooled proportion analysis was not performed on this outcome.

Complete stone fragmentation

A total of 12 studies including 1531 patients assessed complete stone fragmentation by ESWL [15, 18–20, 22, 24, 26–31]. The pooled proportion of patients in whom complete stone fragmentation was achieved was 86.3 % (95 % CI 76.0–94.0) as shown in ▶ **Fig. 3**. As with complete ductal clearance, the studies showed a significant heterogeneity with $P < 0.001$ and corresponding I^2 of 95.9 % (95 % CI 94.2–97.1). As only three studies assessed complete fragmentation rate after first ESWL session [18, 19, 32], pooled analysis was not performed regarding this outcome.

Complications

Pancreatitis as a complication following either ESWL or additional ERCP was reported in 15 studies [14, 15, 18–20, 23, 25, 26, 28, 29, 31–35] (**Supplementary Table 2**). In two studies it was unclear whether there was any overlap in patients with a post-ESWL and a post-ERCP pancreatitis, therefore these studies were excluded from the pooled proportion analysis [21, 22].

▶ **Table 1** Study characteristics.

	Author, year	Country	Design	n (m/f)	Age, y	Pre-ESWL ERCP, n/N (%)	Location stones, n/N (%)	Stone size, mm	MPD strictures, n/N (%)	ESWL equipment
1	Wang et al. 2018 [16]	China	P	49 (NR)[1]	NR	NR	NR	NR	NR	P-ESWL, third-generation electromagnetic lithotripter (Compact Delta II; Dornier Med Tech, Wessling, Germany)
2	Hu et al. 2016 [19]	China	P	214 (156/58)	41.7 ± 13.6	128/214 (60 %)	Head: 162/214 (75.7 %) Head/body: 13/214 (6.1 %) Body: 5/214 (2.3 %) Head/body/tail: 34/214 (15.9 %)	NR	NR	Third-generation electromagnetic lithotripter (Compact Delta II; Dornier Med Tech, Wessling, Germany) with bidimensional fluoroscopic capability
3	Korpela et al. 2016 [14]	Finland	R	83 (59/24)	53 (27–77)[2]	74/83 (89 %)	Head:78/83 (94.0 %) Body: 4/83 (4.8 %) Tail: 1/83 (1.2 %)	10 (5–25)[2]	NR	Electromagnetic lithotripter using fluoroscopic guidance. From 2004–2005: Storz Modulith SLX, Medical AG, Tägerwilen, Switzerland) From 2006–2013: Modulith SLX-F2
4	Lapp et al. 2016 [31]	U.S.A.	R	37 (21/16)	57 ± 13.7	37/37 (100 %)	Head/neck: 29/37 (78.4 %)	10.3 ± 5.5	23/37 (62.2 %)	Piezolith 3000 (Knittlingen, Germany)
5	Li et al. 2016 [20]	China	R	849 (603/246) PPC: 59 (51/8) Non-PPC: 790 (552/238)	PPC: 41.6 ± 13.3 Non-PPC: 41.0 ± 14.2	PPC: 14/59 (23.7 %) Non-PPC: NR	PPC: Head: 14/59 (23.7 %) Tail: 2/59 (3.4 %) Head & at least one other location: 43/59 (72.3 %)	PPC: 5–10mm: 22/59 (37.3 %) 10–20mm: 29/59 (49.2 %) 20–30mm: 6/59 (10.2 %) ≥ 3 0mm: 2/59 (3.4 %)	PPC: 40/59 (67.8 %)	P-ESWL, electromagnetic lithotripter (Compact Delta II; Dornier Med Tech, Wessling, Germany)
6	Vaysse et al. 2016 [35]	France	P	146 (96/50)	51.2 ± 13.4	99/146 (68 %)	NR	< 10 mm: 29/132 (22.0 %) ≥ 1 0mm: 37/132 (28.0 %) Missing: 66/132 (50.0 %)	NR	Third-generation electromagnetic lithotripter (Delta Compact; Dornier Inc., Dornier Medtach, Munich, Germany)

▶ **Table 1** (Continuation)

	Author, year	Country	Design	n (m/f)	Age, y	Pre-ESWL ERCP, n/N (%)	Location stones, n/N (%)	Stone size, mm	MPD strictures, n/N (%)	ESWL equipment
7	Maruyama et al. 2015 [34]	Japan	R	100 (84/16) Chronic AIP: 8 (7/1) Ordinary CP: 92 (77/15)	Chronic AIP: 69 (59–73)[2] Ordinary CP: 56.5 (20–85)[2]	100/100 (100 %)	Chronic AIP: Head: 6/8 (75.0 %) Body: 3/8 (37.5 %) Tail: 0/8 (0.0 %) Ordinary CP: Head: 83/92 (90.2 %) Body: 15/92 (16.3 %) Tail: 1/92 (1.1 %)	NR	NR	Before 2004: Piezolith 2500 lithotriptor (Piezoelectric effect technique; Richard Wolf GmbH, Knittlingen, Germany) After 2004: LITHOSTAR Multiline (Electromagnetic generation technique; Siemens GmbH, Munich, Germany)
8	Ohyama et al. 2015 [21]	Japan	P	128 (99/29)	51.4 ± 15.0	128/128 (100 %)	Head: 98/128 (76.6 %) Body & tail: 30/128 (23.4 %)	12.2 ± 5.5	73/128 (57.0 %)	Piezoelectric lithotripters (LT-01, 02 [EDAP International Inc, Paris, France]) or transportable cylindrical electromagnetic shock wave generator device (Modulith SLZ; Storz Medical AG, Kreuzlingen, Switzerland)
9	Ito et al. 2014 [30]	Japan	R	98 (78/20)	54.8 ± 13	98/98 (100 %)	Single: Head 18/24 (75 %) Body/tail: 6/24 (25.0 %) Multiple: Head 58/74 (78.4 %) Body/tail 16/74 (21.6 %)	> 15: 11/98 (11.2 %) ≤ 15: 87/98 (88.8 %)	62/98 (63.3 %)	Electromagnetic Siemens Lithoskop (Siemens AG, Munich, Germany)
10	Suzuki et al. 2013 [29]	Japan	R	479 (NR)	NR	NR	NR	< 10: 223/479 (46.6 %) ≥ 10, < 20: 162/479 (33.8 %) ≥ 20: 34/479 (7.1 %) Unknown 60/479 (12.5 %)	NR	Electromagnetic system n = 290 (60.5 %) Electrohydraulic spark gap system n = 149 (31.1 %) Piezoelectric generator n = 22 (4.6 %) Unspecified n = 18 (3.8 %)
11	Tandan et al. 2013 [17]	India	R	636 (414/222)	NR	NR	NR	NR	NR	Third generation electromagnetic lithotripter (Delta Compact, Dornier Med Tech., Wessling, Germany)
12	Merrill et al. 2011 [33]	USA	R	30 (20/10)	56.6 (33–71)[3]	30/30 (100 %)	Head: 23/27 (85.2 %) Neck: 1/27 (3.7 %) Body: 2/27 (7.4 %) Tail: 1/27 (3.7 %)	< 5 = 8/27 (29.6 %) 5–10 = 4/27 (14.8 %) 10–20 = 15/27 (55.6 %)	13/30 (43.3 %)	From 2002–2005: Dornier HM3 (Medizintechnik GmbH, Germering, Germany) From 2006–2009: Storz Modulith SLX-F2 (Storz Medical AG, Tagerwilen, Switzerland)

▶ **Table 1** (Continuation)

	Author, year	Country	Design	n (m/f)	Age, y	Pre-ESWL ERCP, n/N (%)	Location stones, n/N (%)	Stone size, mm	MPD strictures, n/N (%)	ESWL equipment
13	Milovic et al. 2011 [23]	Germany	P	32 (24/8)	48 (33–76)[2]	32/32 (100 %)	Head: 15/32 (46.9 %)	NR	NR	Modified mini-lithotripter (Minilith SL 1, Storz, Switzerland)
14	Parsi et al. 2010 [32]	USA	P	10 (3/7)	54 (44–72)[3]	10/10 (100 %)	Head: 4/10 (40 %) Head/body: 2/10 (20 %) Head/body/tail: 4/10 (40 %)	15 (10–20)[3]	NR	Transportable electromagnetic shock wave generator device (Modulith SLX-2; Storz Medical AG, Kreuzlingen, Switzerland)
15	Tadenuma et al. 2005 [22]	Japan	R	117 (85/32)	48 (12–73)[3]	117/117 (100 %)	Head: 100/117 (85.5 %) Body/tail: 17/117 (14.5 %)	11.2 (3–37)[3]	57/117 (48.7 %)	Piezoelectric lithotripter (LT-01, 02; EDAP International Inc., Paris, France) or Piezolith 2500; Richard Wolf, Inc., Knittlingen, Germany)
16	Inui et al. 2005 [28]	Japan	R	555 (465/90)	52.5 (12–79)[3]	NR	NR	NR	NR	Electrohydraulic spark gap system n = 167 Piezoelectric generator n = 109 Electrohydraulic spark gap/electromagnetic system n = 74 Electromagnetic system n = 205
17	Delhaye et al. 2004 [25]	Belgium	R	56 (46/10)	44 ± 12.5	56/56 (100 %)	Distal: 44/56 (78.6 %) Non-distal: 5/56 (8.9 %) Both: 7/56 (12.5 %)	13 ± 5.9	35/56 (62 %)	Electromagnetic lithotripter (Siemens Lithostar, Erlangen, Germany)
18	Farnbacher et al. 2002 [27]	Germany	R	114 (NR)	NR	114/114 (100 %)	NR	NR	NR	Piezoelectric shockwave lithotripter with capability for visualization ultrasonographically (Piezolith 2300, R. Wolf, Knittlingen, Germany) or with alternating ultrasound and radiographic visualization (Piezolith 2500, Piezolith 2501-economy; Wolf)
19	Kozarek et al. 2002 [18]	USA	R	40 (21/19)	53 (23–77)[3]	40/40 (100 %)	NR	13 (4 - 25)[3]	19/40 (47.5 %)	Dornier HM3 lithotriptor (Dornier, Inc., Dornier Medtech, Munich, Germany)
20	Rubenstein et al. 2002 [15]	USA	P	23 (11/12) HM3: 11 (3/8) Lithotron: 12 (9/3)	52.1 (NR) HM3: 52.5 (NR) Lithotron: 51.7 (NR)	23/23 (100 %)	NR	17 (NR) HM3: 21 (NR) Lithotron: 14 (NR)	13/23 (56.5 %) HM3: 6/11 (54.5 %) Lithotron: 7/12 (58.3 %)	HM3 lithotriptor or Lithotron lithotriptor

▶ **Table 1** (Continuation)

	Author, year	Country	Design	n (m/f)	Age, y	Pre-ESWL ERCP, n/N (%)	Location stones, n/N (%)	Stone size, mm	MPD strictures, n/N (%)	ESWL equipment
21	Karasawa et al. 2002 [26]	Japan	R	24 (19/5)	53 ± 18	24/24 (100 %)	Head: 11/24 (45.8 %) Head/body/tail: 13/24 (54.2 %)	10.6 ± 3.7	12/24 (50 %)	Piezoelectric lithotripter (Piezolith 2500; Richard Wolf, Knittlingen, Germany)
22	Brand et al. 2000 [24]	Germany	P	48 (35/13)	51 (14–74)[3]	44/48 (92 %)	Head: 26/48 (54.2 %) Body: 10/48 (20.8 %) Tail: 12/48 (25 %)	12 (4–30)[2]	34/48 (71 %)	Electromagnetic shock-wave lithotripter (modified Lithostar prototype, Siemens, Erlangen, Germany)

AIP, autoimmune pancreatitis; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; f, female; NR, not reported; P, prospective; MPD, main pancreatic duct; m, male; PPC, pancreatic pseudocyst; pts., patients; R, retrospective; SD, standard deviation; y, year

[1] Only matched controls included in analysis

[2] Median with range

[3] Mean with range

The pooled proportion of pancreatitis was 4.0 % (95 % CI 2.5–5.8) (**Supplementary Fig. 5**). The studies showed a significant heterogeneity with $P<0.001$ and corresponding I^2 of 69.1 % (95 % CI 47.5–81.9). A total of 16 studies reported on cholangitis as a complication [14, 15, 18–23, 26, 28, 29, 31, 32, 34, 35]. The pooled proportion of cholangitis was 0.5 % (95 % CI 0.2–0.9) (**Supplementary Fig. 6**). The studies did not show significant heterogeneity with a P-value of 0.055 and corresponding I^2 of 39.1 % (95 % CI 0.0–66.4).

Exocrine deficiency

In total, 10 studies reported on exocrine function following ESWL treatment [14, 17, 19–22, 24–26, 28] (▶ **Table 3**). Four studies measured exocrine function following ESWL using the N-benzoyl-l-tyrosyl-para-aminobenzoic acid (BT-PABA) test [21, 22, 26, 28]. Two studies used fecal elastase to define exocrine deficiency [14, 24]; one of them [14] only measured fecal elastase-1 in case of self-reported diarrhea or steatorrhea. Fecal chymotrypsin was used in two studies as a measure of exocrine deficiency [24, 26]. Two studies [19, 24] used self-reported steatorrhea as a measure for exocrine deficiency, whereas a third study [17] combined this self-reported measure with the amount of pancreatic enzymes required to relieve symptoms. Another study [25] defined exocrine insufficiency as clinical steatorrhea that improved with more than 1 month of treatment with pancreatic enzyme substitution. In the final study [20], it was unknown how exocrine deficiency was defined.

Endocrine deficiency

In total, 10 studies reported on endocrine function following ESWL treatment [14, 17, 19–22, 24–26, 28] (▶ **Table 3**). One study [26] reported on patients requiring antidiabetic treatment after ESWL. Another [25] reported on patients requiring oral antidiabetic drugs or insulin for more than one month. Two of the studies [19, 14] used self-reported diabetes as a measure for endocrine deficiency. Three [17, 24, 28] measured blood glucose, HbA1c, and the required dose of hypoglycemic agents to define endocrine deficiency. Another study [24] further defined endocrine deficiency as a fasting blood glucose level >126 mg/dL and an HbA1c >6.0 %. One author [20] defined endocrine insufficiency as 'patients with diabetes following ESWL, whereas two other authors [21, 22] additionally referred to the American Diabetes Association.

Quality of life

Quality of life was heterogeneously reported among the respective studies [14, 17, 19, 20, 23, 24], therefore, no pooled analysis could be performed for this outcome. Three of the studies used a scale ranging from 1–10 [17, 19, 20], whereas the two others used a 1–5 scale [23] and a European Organization for Research and Treatment of Cancer (EORTC-QLQ) questionnaire with a scale ranging from 0–100 [24], respectively. One study [14] did not report a numeric score but a description of daily activities obtained through telephonic interviews.

Sensitivity analysis

Sensitivity analysis was performed after excluding all studies in which post-ESWL ERCP was not performed (▶ **Table 1**). A total of 12 studies with 1284 (33.2 %) patients were included in the sensitivity analysis. Complete ductal clearance was reached in 71.4 % (95 % CI 61.3–80.5) patients undergoing ESWL with ERCP. Complete pain relief was described in three of the 12 studies with 706 patients. The proportion of patients being completely pain free at follow up after ESWL with ERCP was

▶ **Table 2** Outcomes after ESWL.

	Author, year	Complete stone fragmentation, n/N (%)	Complete stone fragmentation after first session, n/N (%)	Complete ductal clearance after first session, n/N (%)	Post-ESWL ERCP, n/N (%)	Complete ductal clearance, n/N (%)	Method of pain measurement	Pain relief, n/N (%)	Complete pain relief, n/N (%)	Partial pain relief, n/N (%)	Follow-up, m
1	Wang et al. 2018 [16][1]	NR	NR	NR	NR	44/49 (89.8 %)	VAS-score	44/49 (89.8 %)	37/49 (75.5 %)	7/49 (14.3 %)	NR
2	Hu et al. 2016 [19]	214/214 (100 %)	101/214 (47.2 %)	NR	207/214 (96.7 %)	155/214 (72.4 %)	3-point Likert scale	186/195 (95.4 %)	139/195 (71.3 %)	47/195 (24.1 %)	18.5 ± 3.3 (n = 195)
3	Korpela et al. 2016 [14]	NR	NR	50/83 (60.2 %)	83/83 (100 %) 28/83 (100 %) (same day as ESWL)	69/83 (83.1 %)	VAS-score 3-point Likert scale	74/83 (89.2 %)	NR	NR	12 (1–36)[2] (n = 83)
4	Lapp et al. 2016 [31]	22/37 (59.5 %)	NR	NR	36/37 (97.3 %)	29/36 (80.6 %)	NR	14/37 (37.8 %)	NR	NR	NR
5	Li et al. 2016 [20]	PPC: 59/59 (100 %) Non-PPC: NR	NR	NR	PPC: 58/59 (98.3 %) Non-PPC: NR	696/849 (82.0 %) PPC: 39/58 (67.2 %) Non-PPC: 657/790 (83.2 %)	3-point Likert scale	PPC: 49/55 (89.1 %)	PPC: 35/55 (63.6 %)	PPC: 14/55 (25.5 %)	21.9 (12.0–45.1)[2] (n = 55; PPC group)
6	Vaysse et al. 2016 [35]	NR	NR	NR	91/132 (73.5 %)	75/132 (56.8 %)	NR	NR	NR	NR	23 (6–90)[2] (n = 132 with 6-month FU)
7	Maruyama et al. 2015 [34]	NR	NR	NR	100/100 (100 %)	76/100 (76.0 %) Chronic AIP: 5/8 (62.5 %) Ordinary CP: 71/92 (77.2 %)	NR	NR	NR	NR	68 (36–180)[2] (n = 8; chronic AIP)
8	Ohyama et al. 2015 [21]	NR	NR	NR	128/128 (100 %)	66/128 (51.6 %)	4-grade pain scale	115/128 (89.9 %)	NR	NR	42.4 ± 35.8 (n = NR)
9	Ito et al. 2014 [30]	67/98 (100 %)	NR	NR	98/98 (100 %)	72/98 (73.5 %)	NR	81/89 (91.0 %)	NR	NR	NR
10	Suzuki et al. 2013 [29]	186/202 (92.1 %)[3]	NR	NR	255/479 (53.2 %)	356/479 (74.3 %)	NR	435/479 (90.8 %)	NR	NR	31.4 (1–83)[4] (n = 479)

▶ **Table 2** (Continuation)

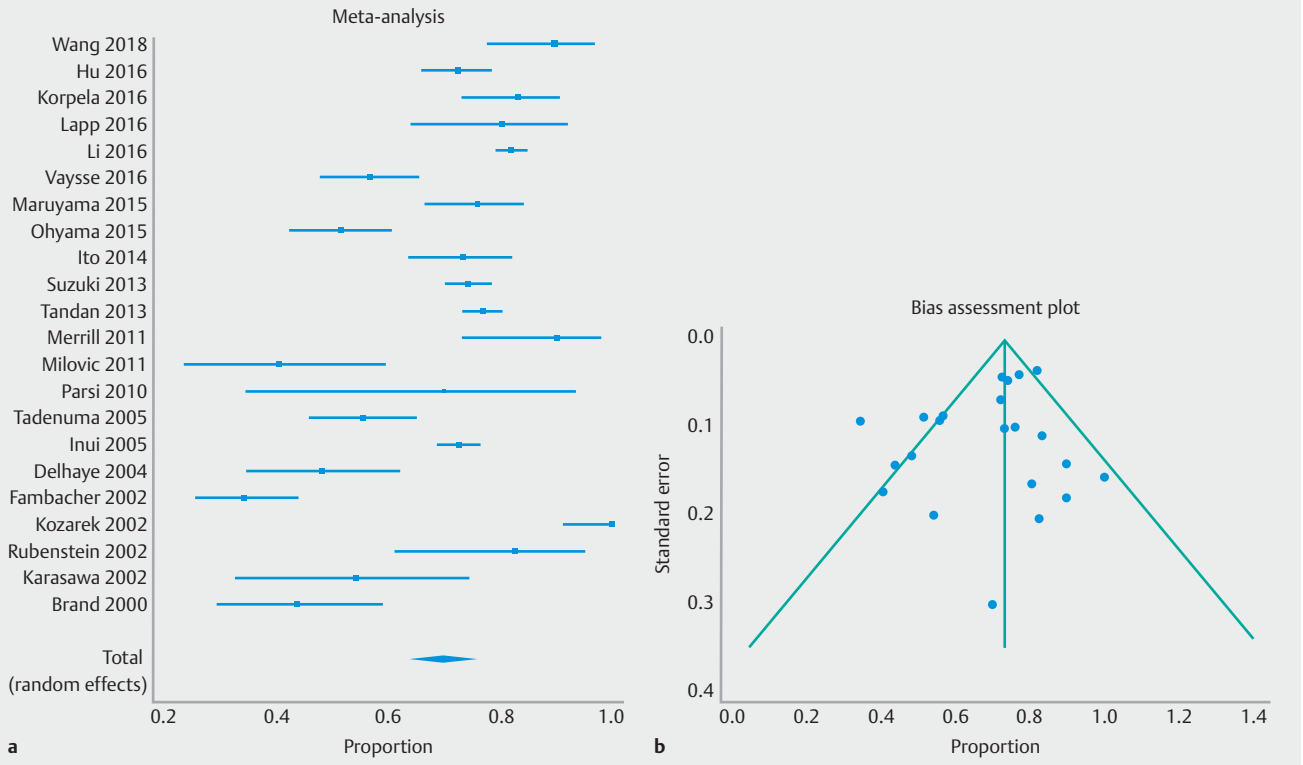
	Author, year	Complete stone fragmentation, n/N (%)	Complete stone fragmentation after first session, n/N (%)	Complete ductal clearance after first session, n/N (%)	Post-ESWL ERCP, n/N (%)	Complete ductal clearance, n/N (%)	Method of pain measurement	Pain relief, n/N (%)	Complete pain relief, n/N (%)	Partial pain relief, n/N (%)	Follow-up, m
11	Tandan et al. 2013 [17]	NR	NR	NR	636/636 (100 %)	489/636 (76.9 %) 282/364 (77.5 %)[5] 207/272 (76.1 %)[7]	VAS-score	NR	414/636 (65.1 %) 250/364 (68.7 %)[5] 164/272 (60.3 %)[6]	NR	Intermediate follow-up 24–60 (n = 364) Long-term follow-up >60 (n = 272)
12	Merrill et al. 2011 [33]	NR	NR	NR	30/30 (100 %)	27/30 (90.0 %) 12/30 (40.0 %)[7]	NR	NR	NR	NR	NR
13	Milovic et al. 2011 [23]	NR	NR	NR	32/32 (100 %)	13/32 (40.6 %)	5-point Likert scale	28/32 (87.5 %) 24/32 (75.0 %)[8]	17/32 (53.1 %) 7/32 (21.9 %)[8]	NR	NR
14	Parsi et al. 2010 [32]	NR	8/10 (80.0 %)	NR	10/10 (100 %)	7/10 (70.0 %)	NR	NR	NR	NR	20 (12–36)[4] (n = 10)
15	Tadenuma et al. 2005 [22]	113/117 (96.6 %)	NR	NR	65/117 (55.6 %)	65/117 (55.6 %)	4-grade pain scale	49/70 (70.0 %) 114/117 (68.2 %)[8]	NR	NR	77.5 ± 30.9 (n = 70)
16	Inui et al. 2005 [28]	513/555 (92.4 %)	NR	NR	237/555 (42.7 %)	403/555 (72.6 %)	NR	428/470 (91.1 %)	NR	428/470 (91.1 %)	44.3 (3–141)[4] (n = 504)
17	Delhaye et al. 2004 [25]	NR	NR	NR	56/56 (100 %)	27/56 (48 %)	Number of hospital admissions for pain during the follow-up period	NR	NR	NR	14.4 ± 0.6 years
18	Farnbacher et al. 2002 [27]	94/114 (82.5 %)	NR	NR	NR	39/114 (34.2 %)	NR	NR	NR	NR	NR
19	Kozarek et al. 2002 [18]	40/40 (100 %)	35/40 (87.5 %)	NR	40/40 (100 %)	40/40 (100 %)	VAS -score	NR	NR	NR	2.4 ± 0.6 years

▶ **Table 2** (Continuation)

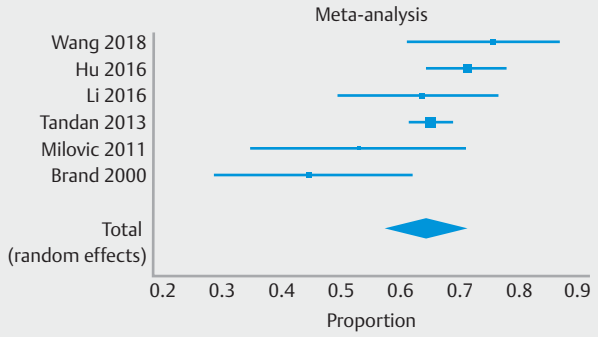
	Author, year	Complete stone fragmentation, n/N (%)	Complete stone fragmentation after first session, n/N (%)	Complete ductal clearance after first session, n/N (%)	Post-ESWL ERCP, n/N (%)	Complete ductal clearance, n/N (%)	Method of pain measurement	Pain relief, n/N (%)	Complete pain relief, n/N (%)	Partial pain relief, n/N (%)	Follow-up, m
20	Rubenstein et al. 2002 [15]	23/23 (100 %)	NR	68 % 64 %[9] 71 %[10]	23/23 (100 %)	19/23 (82.6 %) 9/11 (81.8 %)[9] 10/12 (83.3 %)[10]	NR	NR	NR	NR	NR
21	Karasawa et al. 2002 [26]	3/24 (12.5 %)	NR	NR	14/24 (58.3 %)	13/24 (54.2 %)	NR	11/24 (45.8 %) 19/20 (95.0 %)[8]	NR	NR	NR
22	Brand et al. 2000 [24]	29/48 (60.4 %)	NR	NR	48/48 (100 %)	21/48 (43.8 %)	3 types of pain characteristics	31/38 (82 %)	17/38 (45 %)	14/38 (37 %)	7 (5–9)[2] (n = 38)

ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; m, month; NR, not reported; PPC, pancreatic pseudocyst; SD, standard deviation; VAS, visual analogue scale
[1] Only matched controls included in analysis
[2] Median with range
[3] Only reported for patients who underwent ESWL without additional endoscopy
[4] Mean with range
[5] Intermediate follow-up group
[6] Long-term follow-up group
[7] Ductal clearance rate after ESWL with one additional ERCP
[8] Pain relief immediately after ESWL
[9] HM3
[10] LithoTron
VAS score ranging from 0–10.
3-point Likert-scale = Complete relief, no pain occurred during the follow-up period; partial relief, decreased episodes and intensity of pain; and no relief, no change in the symptom of pain.
4-grade Pain-scale = Ranging from 0 to 3; 0, no pain; 1, mild pain (no use of analgesics, including discomfort); 2, moderate pain (requiring analgesics); 3, severe pain (requiring hospitalization).
5-point Likert-scale = Ranging from 0 to 4; 0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; 4, annihilating pain).
Number of hospital admissions for pain during the follow-up period = compete clinical success, if no further hospital admission for pain was needed during the entire follow-up period; partial clinical success, if 1–5 hospitalizations for pain were recorded during the follow-up period; failure, if patients were admitted to the hospital for pain more than 5 times, or who had undergone any form of surgery related to CP during the follow-up period.
3 types of pain characteristics = Type A is characterized as recurrent short episodes of pain, separated by pain-free episodes of at least months; type B as prolonged periods of either persistent or clusters of recurrent pain for ≥ 2 days/week; and type C as an absence of type A or type B pain. Pain was defined as type A or B when associated with an intensity of > 20 on a visual analog scale (VAS) and as type C when < 20 on VAS (0–100).

56.1 % (95 % CI 42.4–69.4). Stone fragmentation rate was reported in three of the 12 studies with 209 patients, with complete stone fragmentation rate of 86.8 % (95 % CI 61.4–99.5). Post-procedural pancreatitis was described in eight studies with 374 patients and occurred in 3.8 % (95 % CI 1.8–6.6). Cholangitis was described in eight studies with 446 patients and occurred in 1.0 % (95 % CI 0.19–2.3). A second sensitivity analysis was performed after excluding all retrospective studies (▶ **Table 1**). A total of eight studies with 650 (17.1 %) patients were included in the sensitivity analysis. Complete ductal clearance was reached in 63.5 % (95 % CI 51.7–74.5) of the 636 patients undergoing ESWL. Complete pain relief was described in four of eight prospective studies with 314 patients. The proportion of patients being completely pain free after ESWL was 62.5 % (95 % CI 48.9–75.1). Stone fragmentation rate was reported in three of eight prospective studies with 285 patients. Complete stone fragmentation rate was 92.7 % (95 % CI 58.1–97.5). Post-procedural pancreatitis was described in five studies with 418 patients and occurred in 3.1 % (95 % CI 1.7–5.0). Cholangitis was described in six studies with 546 patients and occurred in 0.2 % (95 % CI 0.00–0.79).



▶ **Fig. 1** **a** Pooled proportion of complete ductal clearance. **b** Funnel plot (complete ductal clearance).



▶ **Fig. 2** Pooled proportion of patients being completely pain free after ESWL.

Discussion

This systematic review and meta-analysis on ESWL for pancreatic duct stones in patients with symptomatic chronic pancreatitis reported a pooled complete ductal clearance of 70 %. Complete stone fragmentation was reached in 86 %, with 64 % being completely pain free at follow-up. Post-procedural pancreatitis and cholangitis occurred in 4.0 % and 0.5 %, respectively, with no mortality reported. Sensitivity analysis only including prospective studies reported similar results, with improvement in complete stone fragmentation rate (93 % versus 86 %).

Pain is the most frequent symptom in patients with chronic pancreatitis. Currently, a step-up treatment approach is used, including lifestyle modifications and analgesics, endoscopic, and finally surgical treatment [7, 8]. Treatment goals include pain management, management and prevention of complications (e. g. recurrent flares of cysts), and correction of pancreatic insufficiency.

Conventional endoscopy for the removal of obstructive PD stones with sphincterotomy and basket or balloon extraction, allows for stone extraction in a minority of patients. Conventional endoscopy is regularly limited by factors such as stone size, stone location, and previous gastric surgery [29, 36]. In addition, stone extraction may not be possible if the stone is embedded in the ductal system or when strictures are present [37]. Two retrospective studies reported a 9 % ductal clearance rate after conventional endoscopy in 1041 patients with chronic pancreatitis [27, 29], whereas a survey of 125 hospitals reported a 14 % ductal clearance rate in 1834 patients with chronic pancreatitis [38].

As an alternative, initial stone fragmentation by ESWL was introduced [23]. ESWL is indicated for patients with one or multiple radiopaque obstructive intraductal stones larger than 5 mm located in the head/body of the pancreas, whereas stones that are radiolucent or smaller than 5 mm should be treated with ERCP only [8]. ESWL is contraindicated in patients with non-correctable coagulation disorders, pregnancy, and presence in the shockwave path of bone, calcified vessels, or lung

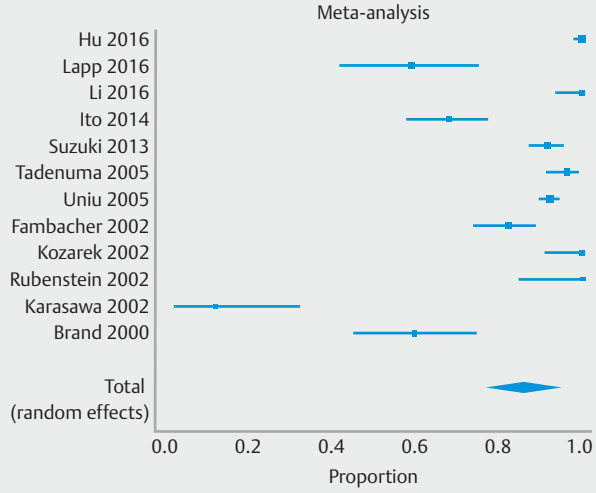
▶ **Table 3** Exocrine and endocrine insufficiency before and after ESWL.

		Exocrine insufficiency			Endocrine insufficiency		
	Author, year	**Method**	**Pre-ESWL**	**Post-ESWL**	**Method**	**Pre-ESWL**	**Post-ESWL**
1	Wang et al. 2018 [16]	NR	NR	NR	NR	NR	NR
2	Hu et al. 2016 [19]	Self-reported steatorrhea	24/195 (12.3 %)	34/195 (17.4 %)	Self-reported diabetes	52/195 (26.7 %)	57/195 (29.2 %)
3	Korpela et al. 2016 [14]	Fecal elastase in case of self-reported diarrhea or steatorrhea	76 µg/g (0-608)[1] (n=25)	38 µg/g (0–573)[1] (n=29)	Self-reported diabetes	22/83 (26.5 %)	29/60 (48.3 %)
4	Lapp et al. 2016 [31]	NR	NR	NR	NR	NR	NR
5	Li et al. 2016 [20]	NR	PPC: 9/55 (16.4 %)	PPC: 11/55 (20 %)	'Patients with diabetes following ESWL'	PPC: 10/55 (18.2 %)	PPC: 11/55 (20.0 %)
6	Vaysse et al. 2016 [35]	NR	NR	NR	NR	NR	NR
7	Maruyama et al. 2015 [34]	NR	NR	NR	NR	NR	NR
8	Ohyama et al. 2015 [21]	BT-PABA test	60.7 ± 18.1 (n = 218)	60.0 ± 21.7 (n = 218)	Definition of American Diabetes Association	28/128 (21.9 %)	28/128 (21.9 %)
9	Ito et al. 2014 [30]	NR	NR	NR	NR	NR	NR
10	Suzuki et al. 2013 [29]	NR	NR	NR	NR	NR	NR
11	Tandan et al. 2013 [17]	Self-reported steatorrhea + required dose of pancreatic enzymes	Intermediate FU: 28/364 (7.7 %) Long-term FU: 23/272 (8.5 %)	Intermediate FU: 28/364 (7.7 %) Long-term FU: 23/272 (8.5 %)	Blood glucose HbA1c Required dose of hypoglycaemic agents	Intermediate FU: 88/364 (24.2 %) Long-term FU: 75/272 (27.6 %)	Intermediate FU: 88/364 (24.2 %) Long-term FU: 139/272 (51.1 %)
12	Merrill et al. 2011 [33]	NR	NR	NR	NR	NR	NR
13	Milovic et al. 2011 [23]	NR	NR	NR	NR	NR	NR
14	Parsi et al. 2010 [32]	NR	NR	NR	NR	NR	NR
15	Tadenuma et al. 2005 [22]	BT-PABA test	64.5 ± 16.1 (n = 30)	56.2 ± 12.9 (n = 30)	Definition of American Diabetes Association	25/70 (35.7 %)	40/70 (57.1 %)
16	Inui et al. 2005 [28]	BT-PABA test	NR	3 months FU: – Improvement: 488/236 (37.3 %) – No change: 103/236 (43.6 %) – Deterioration: 45/236 (19.1 %) 1 year FU: – Improvement: 65/171 (38.0 %) – No change: 49/171 (28.7 %) – Deterioration: 57/171 (33.3 %)	75-g oral glucose tolerance test Blood glucose HbA1c Required dose of hypoglycaemic agents	NR	3 months FU: – Improvement: 52/233 (22.3 %) – No change: 162/233 (69.5 %) – Deterioration: 19/233 (8.2 %) 1 year FU: – Improvement: 44/181 (24.3 %) – No change: 85/181 (47.0 %) – Deterioration: 52/181 (28.7 %)

▶ **Table 3** (Continuation)

		Exocrine insufficiency			Endocrine insufficiency		
	Author, year	**Method**	**Pre-ESWL**	**Post-ESWL**	**Method**	**Pre-ESWL**	**Post-ESWL**
17	Delhaye et al. 2004	Clinical steatorrhea that improved with more than 1 month of treatment with pancreatic enzyme substitution.	16/56 (28.6 %)	34/56 (60.7 %)	Oral antidiabtetic drugs or insulin use for more than 1 month	16/56 (28.6 %)	41/56 (73.2 %)
18	Farnbacher et al. 2002 [27]	NR	NR	NR	NR	NR	NR
19	Kozarek et al. 2002 [18]	NR	NR	NR	NR	NR	NR
20	Rubenstein et al. 2002 [15]	NR	NR	NR	NR	NR	NR
21	Karasawa et al. 2002 [26]	BT-PABA test (at admission) Fecal chymotrypsin	74 ± 22 % 18 ± 12 µU/g	NR 25 ± 16 µU/g	HbA1C	6.6 ± 2.0 %	5.4 ± 0.5 %
22	Brand et al. 2000 [24]	Fecal elastase Fecal chymotrypsin Self-reported steatorrhea	15 mg/g (15–621)[1] 5.4 IU/g (0.7–45.6)[1] 13/48 (27.1 %)	15 mg/g (15–619)[1] 6.6 IU/g (0.2–47.3)[1] Improvement in 10/13 patients (77 %)	Fasting blood glucose HbA1c Required dose of hypoglycemic agents	32/38 (84 %)	27/38 (71 %)

BT-PABA, N-benzoyl-l-tyrosyl-para-aminobenzoic acid; ESWL, extracorporeal shock wave lithotripsy; FU, follow-up; NR, not reported; PPC, pancreatic pseudocyst
[1] Median with range



▶ **Fig. 3** Pooled proportion of stone fragmentation.

tissue [8]. Specific precautions should be taken for patients with implantable defibrillators and pacemakers [39].

A previous meta-analysis on the efficacy and safety of ESWL reported complete ductal clearance in 70.7 % of the pooled patients comparable to the current study, with complete pain relief in 53 % [10]. Post-procedural pancreatitis was reported in 4.2 %, whereas post-procedural cholangitis was not reported. As almost 75 % (20/27) of the included studies was published more than 10 years ago with almost 50 % (13/27) published before the year 2000, the current study provides an important update on the results of ESWL for PD stones.

Factors associated with more ESWL sessions required for complete stone fragmentation are larger stones [40], multiple stones [41] or stones associated with main pancreatic duct strictures [24]. Multicenter surveys have suggested that stone fragmentation is less frequently successful in low-volume centers, while the type of lithotripsy has been controversial [29, 36,38]. Factors associated with successful ductal clearance after ESWL are solitary stones [19, 21, 24, 42, 43], stones located in the pancreatic head [19], stones with lower density at CT scan (<820.5 HU) [21], pancreatic stenting prior to ESWL [14, 44] and pre-ESWL administration of secretin [44].

Endoscopic therapy after ESWL should be restricted to patients with PD strictures or patients with no spontaneous stone clearance after adequate fragmentation with ESWL [8]. The addition of endoscopic therapy to ESWL provided no additional benefit in two studies. Only one randomized controlled trial (RCT) has been published, which showed that combining systematic endoscopy with ESWL adds to the cost of patient care, without improving the outcome of pancreatic pain [11]. This systematic review found similar results.

Intraductal lithotripsy techniques, including laser lithotripsy (LL) and electrohydraulic lithotripsy (EHL), can be attempted either after failure of ESWL or before in an experimental setting. Literature on these lithotripsy techniques in PD stones is scarce, with only one systematic review published showing complete ductal clearance in 43–100 % and adverse events in 0 % to 13.5 % [45]. Large, prospective studies are needed to prove efficiency and safety of these techniques and to compare outcomes with ESWL.

In case of technical or clinical failure of endoscopic therapy, surgical options should be considered [8]. Especially in early-stage chronic pancreatitis, physicians differ in the application of surgical treatment [46]. Currently, multiple RCTs have been published comparing endoscopy with surgery in late-stage chronic pancreatitis. Two recent RCTs on endoscopy versus surgery in late-stage chronic pancreatitis suggested that for pain relief, surgery was superior to endoscopic therapy [47, 48]. The results of both trials, however, should be interpreted with caution. In the first trial [47], pain relief was reached in 15 % versus 34 % treated with endoscopy versus surgery, respectively, showing that neither of these treatment options was entirely satisfactory. The applied endoscopic therapy was suboptimal, as neither ESWL nor cumulative stenting were used. In addition, different surgical procedures were performed [47]. In the second trial, only 39 patients were included; all of them had advanced chronic pancreatitis and most were opioid-dependent [48]. In both trials, only patients with late-stage chronic pancreatitis were included, and therefore the results of the trials cannot been extrapolated to all patients with chronic pancreatitis, especially not to patients with early-stage chronic pancreatitis.

Therefore, the timing of surgical intervention remains matter of debate [49]. Whether early surgery for chronic pancreatitis improves pain control and pancreatic function compared with the current step-up practice should be evaluated in a large multicenter RCT and validated afterwards. A recently published multicenter RCT showed that early surgery compared with an endoscopy-first approach resulted in lower pain scores when integrated over 18 months. In addition, the total number of interventions was lower in the early surgery group (median, 1 vs 3; $P < .001$), altough complications, mortality, pancreatic function and quality of life were comparable [50]. However, further research is needed to assess persistence of differences over time and to replicate the study findings. Despite these results, early surgery strategy may not be easily generalized as most patients and their refering physicians would prefer a non-invasive procedure as first step management.

This study has several limitations. First, each of the included studies were observational with several retrospective studies, potentially leading to selection bias. Furthermore, multiple outcomes were heterogeneously defined among the included studies. For example, meta-analysis on complete ductal clearance revealed an I^2 of 92.6 %. Variation between studies regarding this outcome might be caused by heterogeneity in study protocol, for example, rather than by chance alone. Therefore, the results of the meta-analysis should be interpreted with caution. Furthermore, due to heterogeneity, improvement in quality of life and in endocrine and exocrine insufficiency could not be quantified. In addition, there was a lack of objective means of determining 'complete ductal clearance' and 'complete stone fragmentation', which explains the significant heterogeneity ($I^2 > 90$ %) among the studies. Furthermore, no consensus existed amongst the studies in the grading of gastrointestinal procedure-related complications. As a result, we chose to only report post-procedural pancreatitis and cholangitis. Furthermore, studies were performed in different countries with different patient demographics, various etiologies for chronic pancreatitis and stone formation. Baseline characteristics were not available for all the included studies, and therefore no comparison could be performed. Finally, indications of endoscopic therapy following ESWL were not clearly described in multiple studies. The strength of this study is the extensive, detailed overview of the effects of ESWL for PD stones regarding multiple outcomes and of the heterogeneity that exists in current literature.

Conclusion

This meta-analysis suggests that treatment with ESWL results in complete ductal clearance in 70 % of patients, resulting in absence of pain in over half of patients with symptomatic chronic pancreatitis caused by obstructing pancreatic duct stones. Therefore, ESWL should still be adhered to as a first alternative to conventional endoscopic techniques as long as there are no convincing data about EHL or laser lithotripsy. The available literature, however, is heterogeneous and therefore pragmatic multicenter RCTs in experienced centers are required. In addition, the application of LL and EHL as alternative techniques should be further explored in larger, prospective studies.

Competing interests

The authors declare that they have no conflict of interest.

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