

ORIGINAL ARTICLE

Extracorporeal Shock Wave Lithotripsy in the Management of Chronic Calcific Pancreatitis: A Meta-Analysis

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ABSTRACT

Context Main pancreatic duct stones may contribute to pain in chronic pancreatitis. Extracorporeal shock wave lithotripsy (ESWL) has been used alone or in combination with endoscopic therapy for fragmentation of stones. Published studies have shown mixed efficacy due to small sample size.

Objective Systematic analysis of all published data evaluating ESWL with or without endoscopic therapy in pancreatic duct clearance and symptom relief.

Methods Two investigators independently reviewed the computer databases. 31 potential studies were identified. Only studies using ESWL with or without endoscopic therapy were included. Completeness of the search was confirmed by an expert. Studies were independently coded by two investigators and differences rectified by mutual consent.

Main outcome measures Pain at follow-up and duct clearance.

Results Seventeen studies published between 1989 and 2002 were included. Sixteen had a measure of pain at follow-up and duct clearance. All studies were case series with a total of 588 subjects, and included varying

number of subjects undergoing endoscopic pancreatic sphincterotomy and stone extraction. The mean effect size (weighted correlation coefficient) for pain was 0.6215 and for duct clearance was 0.7432; thus indicating a large effect. All studies showed homogeneity suggesting similar effect size irrespective of the combinations of therapy.

Conclusions ESWL is effective in clearance of stones from the pancreatic duct and in relief of pain. Published studies showed homogeneity of the effect size of ESWL both in pancreatic duct clearance and relief of pain.

INTRODUCTION

Chronic pancreatitis is a clinical entity most often characterized by recurrent or persistent episodes of abdominal pain. There are many etiologies including alcohol, hereditary, and idiopathic [1]. Whether removal of the offending agent might positively alter the natural history of the disease in obstructive forms is still debated [2, 3, 4].

Presence of pancreatic calcifications is considered to be pathognomonic of chronic pancreatitis and can be seen in up to 90% of the patients with alcoholic pancreatitis at long term follow-up [5]. Pancreatic duct calculi are generally considered to be a consequence of chronic pancreatitis and not the cause [5, 6].

Pancreatic duct calculi can lead to outflow obstruction of the pancreatic zymogens with subsequent atrophy of the acinar cells and progressive fibrosis of the pancreatic gland. Outflow obstruction of the main pancreatic duct is thought to cause recurrent attacks of pancreatitis or chronic abdominal pain [7, 8]. Restitution of the pancreatic duct flow has shown to improve the physiological function of the pancreas [2, 3].

Pancreatic duct obstruction in chronic pancreatitis due to pancreatic duct calculi, strictures or both can be relieved by surgical techniques. However, these are invasive and are associated with significant morbidity and occasional mortality. Endoscopic drainage procedures including endoscopic pancreatic sphincterotomy, dilation of pancreatic strictures and the placement of pancreatic stents have been successfully performed [9, 10, 11, 12, 13]. These procedures are less invasive compared to surgery and carry a lower rates of morbidity. However, less than 70% of the stones can be removed by endoscopic techniques alone, and is most likely to be successful when the stone burden is small (3 or less stones, with a diameter less than or equal to 10 mm), and stones are confined to the head and or body of the pancreas. Presence of a downstream stricture or stone impaction are unfavorable for endoscopic drainage [14].

The problem of delivering a large stone through the pancreatic duct can potentially be overcome by reducing the stone size. There are limited data regarding chemical dissolution of pancreatic duct calculi. Mechanical lithotripsy using a through the scope mechanical lithotripter is technically challenging and successful only with few floating stones [15], while intraductal lithotripsy techniques are cumbersome and require highly specialized equipment. Fragmentation of pancreatic stones using extracorporeal shock wave lithotripsy (ESWL) serves as another alternative. Use of ESWL for gallstones was first reported by Sauerbruch *et al.* in Germany in 1987 [16], and has since been reported by several investigators for fragmentation of pancreatic

stones [17, 18, 19, 20, 21, 22]. Data from these studies have been divergent. Most studies were observational in nature and included limited numbers of patients to evaluate the efficacy of ESWL on stone clearance and clinical outcomes. A meta-analysis of these published studies is hence performed to evaluate the heterogeneity and clinical outcomes with ESWL therapy for chronic calcific pancreatitis.

METHODS

Two investigators independently reviewed the computer databases Healthstar, MEDLINE and PreMEDLINE. Search words used were: "extracorporeal shockwave lithotripsy" and "chronic pancreatitis" or "pancreatic ducts" or "pancreatitis". Thirty potential studies were identified. Abstracts were reviewed and criteria used for inclusion were: i) ESWL as the only method of treatment or if treatment modalities were mixed, results were separated; ii) pancreatic ducts the only site treated or if treatment targets were mixed results were separated; iii) more than five cases reported in the study; and iv) some measure of pain at follow-up or duct clearance. In addition, an expert in the field reviewed the identified studies to make sure the search was complete.

Coding

Two investigators independently coded the studies and entered them into an Excel (Microsoft Co., Washington, DC, USA) spreadsheet. In addition to pain at follow-up and duct clearance potential moderators were coded; these included year of the study, country, age of subjects, gender, etiology of pancreatitis, presence of strictures, stent placement, length of follow-up, number of ESWL sessions, mean number of shockwaves, stone size, presence of multiple stones, type of lithotripter, and, finally, if sphincterotomy was performed. Findings were compared and disagreements in variable coding between the investigators were identified. Studies were reviewed again by

each investigator and mutual agreement reached on appropriate coding. A large number of variables were included as possible modifiers when the articles were abstracted, so that this data would be available if needed. When the analysis was performed, it was determined that the studies were homogeneous with respect to the two outcomes: pain and duct clearance. Modifier analysis was not needed to explain lack of homogeneity, which is what they are used for in a meta-analysis.

STATISTICS

Two fixed effect model meta-analyses were conducted. One model was constructed on the effect of ESWL on pain at follow-up and one on the effect of ESWL on duct clearance. Statistical methods were based on those recommended by Cooper and Hedges [23]. The effect size is the degree of association between two variables. In this analysis it is the degree of association between ESWL treatment for chronic pancreatitis and pain at follow-up and duct clearance. The measure of effect for each study was converted into a correlation coefficient and this was used as the common metric for effect size. Values close to zero indicate very little effect and those larger and smaller than zero indicate a greater magnitude of effect size. A correlation coefficient of 0-0.10 indicates a small effect size, values ranging 0.11-0.30 indicate a medium effect size and values greater than 0.50 indicate a large effect size [24]. Any effect in between 0.31 and 0.50 may be considered medium to large using these numbers as a bench mark. The relationship can be either negative or positive. A standard error was computed for each measure. Correlation coefficients were weighted by the study size and a weighted average correlation coefficient was computed by combining correlation coefficients directly. Homogeneity of effect size (Q) was computed to determine if the study effect sizes were uniform across all the studies. If the Q statistic exceeds the critical level of the chi square distribution at alpha equal to 0.05 it

indicates the presence of variability that is due to factors other than sampling error. Outliers were detected by using a previously described procedure based on the Q statistic [25].

Since there are no validated tools to measure the relief of pain and to assess the duct clearance outcomes, data were coded as reported in the original work, and were highly varied. While most of them were dichotomous outcomes, others were rated using scales (as in last two pain items below). All were converted to effect size (r) in order to render them comparable.

Duct clearance:

- successful vs. not successful;
- no clearance vs. partial/complete clearance;
- stone free vs. fragments present in duct;
- poor clearance vs. adequate/good clearance.

Pain:

- no pain vs. pain recurrence;
- no pain vs. pain;
- continued pain vs. pain relief;
- mean of pain score pre vs. mean of pain score post;
- pain attacks per month pre vs. pain attacks per month post.

RESULTS

There were 17 studies included in the meta-analyses. These studies were performed between 1989 and 2002 and included diverse population across the globe. Six studies were from Germany, 4 from the United States, 2 from Japan and the remaining 5 from European countries other than Germany. The outcomes measured were variable. However, all studies included two major outcomes: duct clearance and pain relief. Sixteen studies had a measure of pain at follow-up and 16 studies had a measure of duct clearance, although one was excluded as an outlier. The Q statistic was not significant for pain ($Q=11.38$), while it was significant for duct clearance (it was 39.34 prior to eliminating the outlier and it was equal to 8.86 after eliminating the

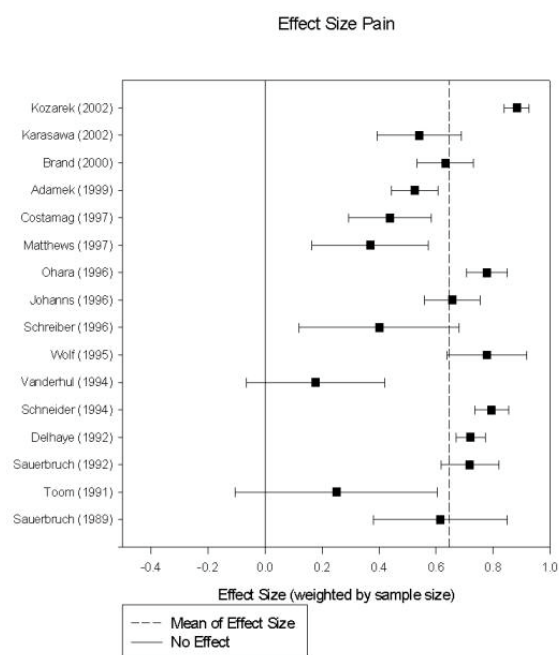


Figure 1. Effect size ($r \pm SE$) for measurement of effect of ESWL for pain relief. The solid line represents no effect and the dashed line the mean of effect size over all of the studies.

outlier); therefore, the effect size of one study was determined to be an outlier and excluded from further analysis [25]. Because the meta-analyses sets exhibited homogeneity of effect size when the outlier was removed from the analysis, moderator analysis was not conducted.

Table 1. Correlation coefficients effect of ESWL on pain at follow-up.

Study	Year	N pain	r pain (SE)
Sauerbruch [35]	1989	8	0.6149 (0.2351)
Den Toom [27]	1991	8	0.2500 (0.3543)
Sauerbruch [36]	1992	24	0.7179 (0.1011)
Delhaye [30]	1992	88	0.7208 (0.0515)
Schneider [37]	1994	39	0.7949 (0.0597)
Van der Hul [33]	1994	17	0.1764 (0.2422)
Wolf [22]	1995	9	0.7777 (0.1397)
Schreiber [38]	1996	10	0.4000 (0.2800)
Johans [31]	1996	35	0.6571 (0.0974)
Ohara [32]	1996	32	0.7778 (0.0709)
Matthews [18]	1997	19	0.3684 (0.2037)
Costamagna [34]	1997	32	0.4375 (0.1452)
Adamek [25]	1999	80	0.5250 (0.0815)
Brand [29]	2000	38	0.6316 (0.0988)
Karasawa [39]	2002	24	0.5400 (0.1477)
Kozarek [17]	2002	28	0.8823 (0.0426)
Overall*	-	491	0.6215 (0.1716)

* $df=15$; $Q=11.38$

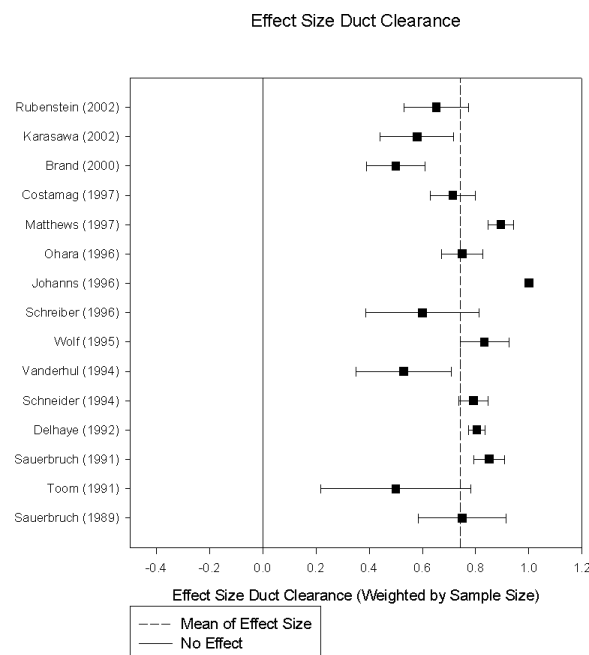


Figure 2. Effect size ($r \pm SE$) for measurement of effect of ESWL for duct clearance of pancreatic duct stones. The solid line represents no effect and the dashed line the mean of effect size over all of the studies.

All of the studies were case reports and included a total of 588 subjects. The mean effect size for pain was 0.6215 (Table 1, Figure 1). The mean effect size for duct clearance was 0.7432 (Table 2, Figure 2). Available data indicate that both analyses exhibited homogeneity of effect size. Mean

Table 2. Correlation coefficients effect of ESWL on duct clearance.

Study	Year	N duct	r duct (SE)
Sauerbruch [35]	1989	8	0.7500 (0.1654)
Den Toom [27]	1991	8	0.5000 (0.2835)
Sauerbruch [36]	1992	24	0.8506 (0.0576)
Delhaye [30]	1992	123	0.8049 (0.0319)
Schneider [37]	1994	48	0.7917 (0.0544)
Van der Hul [33]	1994	17	0.5294 (0.1799)
Wolf [22]	1995	12	0.8333 (0.0921)
Schreiber [38]	1996	10	0.6000 (0.2133)
Johans [31]	1996	35	1.0000 (0.0000)
Ohara [32]	1996	32	0.7500 (0.0786)
Matthews [18]	1997	19	0.8948 (0.0470)
Costamagna [34]	1997	35	0.7143 (0.0840)
Brand [29]	2000	48	0.5000 (0.1094)
Karasawa [39]	2002	24	0.5800 (0.1384)
Rubenstein [20]	2002	23	0.6522 (0.1225)
Overall*	-	491	0.7432 (0.0175)

* $df=14$; $Q=8.86$

effect size measures for both the duct clearance and pain improvement indicate a large effect of EWSL, suggesting that ESWL is clinically useful in reducing the stone burden in the main pancreatic duct and also for improvement of pain. Since most studies included a combination of endoscopic therapies including pancreatic sphincterotomy, stent placement and endoscopic removal of the pancreatic stones following lithotripsy it is difficult to ascertain the individual role of endoscopic therapy. Data from this study also show a significant homogeneity which precludes us from performing any secondary analysis.

DISCUSSION

In chronic calcific pancreatitis, the main goals of therapy have been to relieve pain by decompression of the main pancreatic duct, primarily by removing stones or treating strictures. Endoscopic decompression has been shown to be effective by some nonrandomized studies [11, 12, 26]. Endoscopic stone extraction and duct decompression is limited by the size of the pancreatic calculi and presence of strictures [14]. ESWL overcomes the problem of the stone size by fragmenting the stones and reducing the stone burden, thus facilitating endoscopic clearance of the duct. Though ESWL has been performed at various centers the results of clearance of the main pancreatic duct has ranged from 37.5% [27] to 100% [28]. Moreover, most studies have not shown any direct correlation between the stone fragmentation and duct clearance rates. Most patients with chronic pancreatitis complain of pain and this appears to be the most clinically important outcome, although a subjective outcome that is difficult to measure. The results of our meta-analysis indicate that ESWL has a significant impact on the improvement of pain, and that the effect of ESWL on pain relief is large. The potential mechanism for this improvement in pain is possibly due to main pancreatic duct decompression and relief of obstruction by stone fragmentation. Reasons for failure to

relieve pain are many and may include incomplete stone clearance, persistent strictures, or parenchymal pancreatic pain due to a diseased organ and not related to ductal hypertension.

Although various studies have looked at a spectrum of other outcomes including improvement in the endocrine and exocrine function, weight gain etc., following clearance of the main pancreatic duct calculi [25, 29, 30, 31, 32] the outcome measures were inconsistent and data not sufficiently homogenous to allow meaningful interpretation.

In the studies reviewed, ESWL was tolerated well by patients, with no mortality, but some morbidity including pancreatitis [33], sepsis from biliary or pancreatic origin, pancreatic fluid collection, and gastric submucosal hematoma [34].

Outcomes of therapy are best studied in randomized, placebo controlled trials. Meta-analyses typically include data from randomized controlled trials to calculate the effect size. Unfortunately, there are no randomized trials of therapy for pancreatic duct stones. All reported literature is that of institutional experience based on case series. We have attempted to overcome this limitation by performing a two-way fixed model of meta-analysis and checking for the homogeneity of the studies included in this analysis.

In summary, this study is the first meta-analysis of the effect of ESWL on main pancreatic duct clearance and the relief of pain in patients with chronic calcific pancreatitis. Combining data from multiple centers may overcome the limitations of small case series from single centers with varied expertise. ESWL appears to be effective in both relief of main pancreatic duct obstruction and alleviation of pain in chronic calcific pancreatitis in combination with endoscopic therapy.

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Keywords Endoscopy; Lithotripsy; Pancreatitis

Abbreviations ESWL: extracorporeal shock wave lithotripsy

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